

Ton J. Cleophas · Aeilko H. Zwinderman

# Statistics Applied to Clinical Studies

*Fifth Edition*

 Springer

# Statistics Applied to Clinical Studies



Ton J. Cleophas • Aeilko H. Zwinderman

# Statistics Applied to Clinical Studies

Fifth Edition

With the help from

Toine F. Cleophas, Eugene P. Cleophas,  
and Henny I. Cleophas-Allers



Springer

Ton J. Cleophas  
Past-President American  
College of Angiology  
Co-Chair Module Statistics  
Applied to Clinical Trials  
European Interuniversity College  
of Pharmaceutical Medicine, Lyon  
France  
  
Department of Medicine  
Albert Schweitzer Hospital, Dordrecht  
Netherlands

Aeilko H. Zwinderman  
President-Elect International  
Society of Biostatistics  
Co-Chair Module Statistics  
Applied to Clinical Trials  
European Interuniversity College  
of Pharmaceutical Medicine, Lyon  
France  
  
Department of Biostatistics  
and Epidemiology, Academic Medical  
Center, Amsterdam  
Netherlands

ISBN 978-94-007-2862-2                      e-ISBN 978-94-007-2863-9  
DOI 10.1007/978-94-007-2863-9  
Springer Dordrecht Heidelberg London New York

Library of Congress Control Number: 2012931360

© Springer Science+Business Media B.V. 2012

No part of this work may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without written permission from the Publisher, with the exception of any material supplied specifically for the purpose of being entered and executed on a computer system, for exclusive use by the purchaser of the work.

Printed on acid-free paper

Springer is part of Springer Science+Business Media ([www.springer.com](http://www.springer.com))

# Foreword

In clinical medicine appropriate statistics has become indispensable to evaluate treatment effects. Randomized controlled trials are currently the only trials that truly provide evidence-based medicine. Evidence based medicine has become crucial to optimal treatment of patients. We can define randomized controlled trials by using Christopher J. Bulpitt's definition "a carefully and ethically designed experiment which includes the provision of adequate and appropriate controls by a process of randomization, so that precisely framed questions can be answered". The answers given by randomized controlled trials constitute at present the way how patients should be clinically managed. In the setup of such randomized trial one of the most important issues is the statistical basis. The randomized trial will never work when the statistical grounds and analyses have not been clearly defined beforehand. All endpoints should be clearly defined in order to perform appropriate power calculations. Based on these power calculations the exact number of available patients can be calculated in order to have a sufficient quantity of individuals to have the predefined questions answered. Therefore, every clinical physician should be capable to understand the statistical basis of well performed clinical trials. It is therefore a great pleasure that Drs. T. J. Cleophas, A. H. Zwinderman, and T. F. Cleophas have published a book on statistical analysis of clinical trials. The book entitled "Statistics Applied to Clinical Trials" is clearly written and makes complex issues in statistical analysis transparent. Apart from providing the classical issues in statistical analysis, the authors also address novel issues such as interim analyses, sequential analyses, and meta-analyses. The book is composed of 18 chapters, which are nicely structured. The authors have deepened our insight in the applications of statistical analysis of clinical trials. We would like to congratulate the editors on this achievement and hope that many readers will enjoy reading this intriguing book.

Professor of Cardiology, President Netherlands  
Association of Cardiology, Leiden, Netherlands

E.E. van der Wall, M.D., Ph.D.



## Preface to First Edition

The European Interuniversity Diploma of Pharmaceutical Medicine is a postacademic course of 2–3 years sponsored by the Socrates program of the European Community. The office of this interuniversity project is in Lyon and the lectures are given there. The European Community has provided a building and will remunerate lecturers. The institute which provides the teaching is called the European College of Pharmaceutical Medicine, and is affiliated with 15 universities throughout Europe, whose representatives constitute the academic committee. This committee supervises educational objectives. Start lectures February 2000.

There are about 20 modules for the first 2 years of training, most of which are concerned with typically pharmacological and clinical pharmacological matters including pharmacokinetics, pharmacodynamics, phase III clinical trials, reporting, communication, ethics and, any other aspects of drug development. Subsequent training consists of practice training within clinical research organisations, universities, regulatory bodies etc., and finally of a dissertation. The diploma, and degree are delivered by the Claude Bernard University in Lyon as well as the other participating universities.

The module “Statistics applied to clinical trials” will be taught in the form of a 3–6 day yearly course given in Lyon and starting February 2000. Lecturers have to submit a document of the course (this material will be made available to students). Three or four lecturers are requested to prepare detailed written material for students as well as to prepare examination of the students. The module is thus an important part of a postgraduate course for physicians and pharmacists for the purpose of obtaining the European diploma of pharmaceutical medicine. The diploma should make for leading positions in pharmaceutical industry, academic drug research, as well as regulatory bodies within the EC. This module is mainly involved in the statistics of randomized clinical trials.

The Chaps. 1–9, 11, 17, and 18 of this book are based on the module “Medical statistics applied to clinical trials” and contain material that should be mastered by the students before their exams. The remaining chapters are *capita selecta* intended for excellent students and are not included in the exams.



The authors believe that this book is innovative in the statistical literature because, unlike most introductory books in medical statistics, it provides an explanatory rather than mathematical approach to statistics, and, in addition, emphasizes non-classical but increasingly frequently used methods for the statistical analyses of clinical trials, e.g., equivalence testing, sequential analyses, multiple linear regression analyses for confounding, interaction, and synergism. The authors are not aware of any other work published so far that is comparable with the current work, and, therefore, believe that it does fill a need.

August 1999  
Dordrecht, Leiden  
Delft

# Preface to Second Edition

In this second edition the authors have removed textual errors from the first edition. Also seven new chapters (Chaps. 8, 10, 13, 15–18) have been added. The principles of regression analysis and its resemblance to analysis of variance was missing in the first edition, and have been described in Chap. 8. Chapter 10 assesses curvilinear regression. Chapter 13 describes the statistical analyses of crossover data with binary response. The latest developments including statistical analyses of genetic data and quality-of-life data have been described in Chaps. 15 and 16. Emphasis is given in Chaps. 17 and 18 to the limitations of statistics to assess non-normal data, and to the similarities between commonly-used statistical tests. Finally, additional tables including the Mann-Whitney and Wilcoxon rank sum tables have been added in the Appendix.

December 2001  
Dordrecht, Amsterdam  
Delft



# Preface to the Third Edition

The previous two editions of this book, rather than having been comprehensive, concentrated on the most relevant aspects of statistical analysis. Although well-received by students, clinicians, and researchers, these editions did not answer all of their questions. This called for a third, more comprehensive, rewrite. In this third edition the 18 chapters from the previous edition have been revised, updated, and provided with a conclusions section summarizing the main points. The formulas have been re-edited using the Formula-Editor from Windows XP 2004 for enhanced clarity. Thirteen new chapters (Chaps. 8–10, 14, 15, 17, 21, 25–29, 31) have been added. The Chaps. 8–10 give methods to assess the problems of multiple testing and data testing closer to expectation than compatible with random. The Chaps. 14 and 15 review regression models using an exponential rather than linear relationship including logistic, Cox, and Markow models. Chapter 17 reviews important interaction effects in clinical trials and provides methods for their analysis. In Chap. 21 study designs appropriate for medicines from one class are discussed. The Chaps. 25–29 review respectively (1) methods to evaluate the presence of randomness in the data, (2) methods to assess variabilities in the data, (3) methods to test reproducibility in the data, (4) methods to assess accuracy of diagnostic tests, and (5) methods to assess random rather than fixed treatment effects. Finally, Chap. 31 reviews methods to minimize the dilemma between sponsored research and scientific independence. This updated and extended edition has been written to serve as a more complete guide and reference-text to students, physicians, and investigators, and, at the same time, preserves the common sense approach to statistical problem-solving of the previous editions.

August 2005  
Dordrecht, Amsterdam  
Delft



# Preface to Fourth Edition

In the past few years many important novel methods have been applied in published clinical research. This has made the book again rather incomplete after its previous edition. The current edition consists of 16 new chapters, and updates of the 31 chapters from the previous edition. Important methods like Laplace transformations, log likelihood ratio statistics, Monte Carlo methods, and trend testing have been included. Also novel methods like superiority testing, pseudo-R<sup>2</sup> statistics, optimism corrected c-statistic, I-statistics, and diagnostic meta-analyses have been addressed.

The authors have given special efforts for all chapters to have their own introduction, discussion, and references section. They can, therefore, be studied separately and without need to read the previous chapters first.

September 2008

Dordrecht, Amsterdam, Gorinchem, and Delft



# Preface to Fifth Edition

Thanks to the omnipresent computer, current statistics can include data files of many thousands of values, and can perform any exploratory analysis in less than seconds. This development, however fascinating, generally does not lead to simple results. We should not forget that clinical studies are, mostly, for confirming prior hypotheses based on sound arguments, and the simplest tests provide the best power and are adequate for such purposes. In the past few years the authors of this 5th edition, as teachers and research supervisors in academic and top-clinical facilities, have been able to closely observe the latest developments in the field of clinical data analysis, and they have been able to assess their performance. In this 5th edition the 47 chapters of the previous edition have been maintained and upgraded according to the current state of the art, and 20 novel chapters have been added after strict selection of the most valuable and promising novel methods. The novel methods are explained using practical examples and step-by-step analyses readily accessible not only to statisticians but also to non-mathematicians.

In order to keep up with the forefront of statistical analysis it was unavoidable to also include more complex data modeling and computationally intensive statistical methods. These methods include, e.g., multistage regression, neural networks, fuzzy modeling, mixed linear and non linear models, item response modeling, non linear regression methods, propensity score matching, Bhattacharya modeling and various regression models with multiple outcome variables. However, the authors have given every effort to review these methods in an explanatory rather than mathematical manner.

We should add that the authors are well-qualified in their field. Professor Zwinderman is president-elect of the International Society of Biostatistics, and Professor Cleophas is past-president of the American College of Angiology. From their expertise they should be able to make adequate selections of modern methods for clinical data analysis for the benefit of physicians, students, and investigators. The authors have been working and publishing together for over 10 years, and their research of statistical methodology can be characterized as a continued effort to demonstrate that statistics is not mathematics but rather a discipline at the interface of biology and mathematics.

September 2011  
Dordrecht, Amsterdam, Lyon





# Contents

<b>1 Hypotheses, Data, Stratification .....</b>	<b>1</b>
1 General Considerations.....	1
2 Two Main Hypotheses in Drug Trials: Efficacy and Safety.....	2
3 Different Types of Data: Continuous Data.....	3
4 Different Types of Data: Proportions, Percentages and Contingency Tables.....	8
5 Different Types of Data: Correlation Coefficient.....	10
6 Stratification Issues .....	12
7 Randomized Versus Historical Controls .....	13
8 Factorial Designs .....	13
9 Conclusions.....	14
References.....	14
<b>2 The Analysis of Efficacy Data .....</b>	<b>15</b>
1 Overview .....	15
2 The Principle of Testing Statistical Significance .....	16
3 The t-Value = Standardized Mean Result of Study.....	18
4 Unpaired t-Test.....	19
5 Null-Hypothesis Testing of Three or More Unpaired Samples .....	21
6 Three Methods to Test Statistically a Paired Sample.....	22
6.1 First Method.....	22
6.2 Second Method .....	23
6.3 Third Method .....	24
7 Null-Hypothesis Testing of Three or More Paired Samples .....	26
8 Null-Hypothesis Testing with Complex Data.....	27
9 Paired Data with a Negative Correlation.....	28
9.1 Studies Testing Significance of Differences .....	28
9.2 Studies Testing Equivalence.....	32
10 Rank Testing .....	33
10.1 Paired Test: Wilcoxon Signed Rank Test.....	34
10.2 Unpaired Test: Mann-Whitney Test.....	35

- 11 Rank Testing for Three or More Samples..... 36
  - 11.1 The Friedman Test for Paired Observations..... 36
  - 11.2 The Kruskal-Wallis Test for Unpaired Observations..... 37
- 12 Conclusions..... 38
- References..... 38
- 3 The Analysis of Safety Data ..... 41**
  - 1 Introduction, Summary Display..... 41
  - 2 Four Methods to Analyze Two Unpaired Proportions ..... 42
    - 2.1 Method 1 ..... 42
    - 2.2 Method 2 ..... 44
    - 2.3 Method 3 ..... 47
    - 2.4 Method 4 ..... 47
  - 3 Chi-square to Analyze More Than Two Unpaired Proportions ..... 48
  - 4 McNemar’s Test for Paired Proportions..... 51
  - 5 Multiple Paired Binary Data (Cochran’s Q Test)..... 52
  - 6 Survival Analysis ..... 54
    - 6.1 Survival Analysis ..... 54
    - 6.2 Testing Significance of Difference Between  
Two Kaplan-Meier Curves ..... 55
  - 7 Odds Ratio Method for Analyzing Two Unpaired Proportions ..... 56
  - 8 Odds Ratios for One Group, Two Treatments ..... 59
  - 9 Conclusions..... 59
- 4 Log Likelihood Ratio Tests for Safety Data Analysis ..... 61**
  - 1 Introduction..... 61
  - 2 Numerical Problems with Calculating Exact Likelihoods..... 61
  - 3 The Normal Approximation and the Analysis of Clinical Events ... 62
  - 4 Log Likelihood Ratio Tests and the Quadratic Approximation..... 64
  - 5 More Examples ..... 66
  - 6 Discussion ..... 67
  - 7 Conclusions..... 67
- References..... 68
- 5 Equivalence Testing ..... 69**
  - 1 Introduction..... 69
  - 2 Overview of Possibilities with Equivalence Testing..... 70
  - 3 Calculations..... 72
  - 4 Equivalence Testing, a New Gold Standard?..... 72
  - 5 Validity of Equivalence Trials..... 73
  - 6 Special Point: Level of Correlation  
in Paired Equivalence Studies..... 73
  - 7 Conclusions..... 74
- 6 Statistical Power and Sample Size ..... 77**
  - 1 What Is Statistical Power ..... 77
  - 2 Emphasis on Statistical Power Rather  
Than Null-Hypothesis Testing ..... 78

- 3 Power Computations ..... 80
  - 3.1 For t-Distributions of Continuous Data..... 80
  - 3.2 For Proportions..... 80
  - 3.3 For Equivalence Testing of Samples  
with t-Distributions and Continuous Data..... 81
- 4 Examples of Power Computation Using the t-Table..... 81
  - 4.1 First Example ..... 81
  - 4.2 Second Example..... 83
  - 4.3 Third Example..... 83
- 5 Calculation of Required Sample Size, Rationale ..... 86
- 6 Calculations of Required Sample Size, Methods..... 87
  - 6.1 A Simple Method ..... 87
  - 6.2 A More Accurate Method Is the Power Index Method ..... 87
  - 6.3 Power Calculation for Parallel-Group Studies ..... 89
  - 6.4 Required Sample Size Equation  
for Studies with Proportions..... 89
  - 6.5 Required Sample Size Formula for Equivalence Testing..... 90
- 7 Testing Inferiority of a New Treatment (Type III Error)..... 91
- 8 Conclusions ..... 93
- Reference ..... 93
- 7 Interim Analyses ..... 95**
  - 1 Introduction..... 95
  - 2 Monitoring ..... 95
  - 3 Interim Analysis..... 96
  - 4 Group-Sequential Design of Interim Analysis..... 99
  - 5 Continuous Sequential Statistical Techniques ..... 99
  - 6 Conclusions..... 101
  - References..... 101
- 8 Controlling the Risk of False Positive Clinical Trials ..... 103**
  - 1 Introduction..... 103
  - 2 Bonferroni Test ..... 103
  - 3 Least Significant Difference (LSD) Test..... 105
  - 4 Other Tests for Adjusting the p-Values ..... 105
  - 5 Composite Endpoint Procedures..... 106
  - 6 No Adjustments at all, and Pragmatic Solutions ..... 107
  - 7 Conclusions..... 107
  - References..... 107
- 9 Multiple Statistical Inferences ..... 109**
  - 1 Introduction..... 109
  - 2 Multiple Comparisons..... 109
  - 3 Multiple Variables..... 113
  - 4 Conclusions..... 116
  - References..... 117

**10 The Interpretation of the p-Values** ..... 119

    1 Introduction..... 119

    2 Renewed Attention to the Interpretation  
    of the Probability Levels, Otherwise Called the p-Values ..... 119

    3 Standard Interpretation of p-Values ..... 120

    4 Common Misunderstandings of the p-Values ..... 122

    5 Renewed Interpretations of p-Values,  
    Little Difference Between  $p=0.06$  and  $p=0.04$ ..... 122

    6 The Real Meaning of Very Large p-Values Like  $p>0.95$  ..... 123

    7 p-Values Larger than 0.95, Examples (Table 10.2)..... 124

    8 The Real Meaning of Very Small p-Values Like  $p<0.0001$  ..... 124

    9 p-Values Smaller than 0.0001, Examples (Table 10.3)..... 126

    10 Discussion ..... 127

    11 Recommendations..... 128

    12 Conclusions..... 129

References..... 130

**11 Research Data Closer to Expectation  
than Compatible with Random Sampling** ..... 133

    1 Introduction..... 133

    2 Methods and Results ..... 134

    3 Discussion ..... 135

    4 Conclusions..... 138

References..... 138

**12 Statistical Tables for Testing Data Closer  
to Expectation than Compatible with Random Sampling**..... 139

    1 Introduction..... 139

    2 Statistical Tables of Unusually High p-Values..... 141

    3 How to Calculate the p-Values Yourself ..... 141

        3.1 t-Test ..... 141

        3.2 Chi-square Test ..... 141

        3.3 F-Test ..... 142

    4 Additional Examples Simulating Real Practice,  
    Multiple Comparisons..... 144

    5 Discussion ..... 146

    6 Conclusions..... 146

References..... 147

**13 Data Dispersion Issues**..... 149

    1 Introduction..... 149

    2 Data Without Measure of Dispersion..... 150

        2.1 Numbers Needed to Treat in Clinical Trials ..... 150

        2.2 Reproducibility of Quantitative Diagnostic Tests ..... 151

        2.3 Sensitivity and Specificity..... 152

        2.4 Markov Predictors..... 153

        2.5 Risk Profiles from Multiple Logistic Models ..... 154

- 3 Data with Over-Dispersion ..... 155
- 4 Discussion ..... 157
- 5 Conclusions ..... 158
- References ..... 159
- 14 Linear Regression, Basic Approach ..... 161**
  - 1 Introduction ..... 161
  - 2 More on Paired Observations ..... 162
  - 3 Using Statistical Software for Simple Linear Regression ..... 164
  - 4 Multiple Linear Regression ..... 166
  - 5 Multiple Linear Regression, Example ..... 168
  - 6 Purposes of Linear Regression Analysis ..... 171
  - 7 Another Real Data Example of Multiple  
Linear Regression (Exploratory Purpose) ..... 173
  - 8 It May Be Hard to Define What Is Determined  
by What, Multiple and Multivariate Regression ..... 174
  - 9 Limitations of Linear Regression ..... 176
  - 10 Conclusions ..... 176
- 15 Linear Regression for Assessing Precision,  
Confounding, Interaction, Basic Approach ..... 177**
  - 1 Introduction ..... 177
  - 2 Example ..... 178
  - 3 Model ..... 178
  - 4 (I.) Increased Precision of Efficacy ..... 180
  - 5 (II.) Confounding ..... 181
  - 6 (III.) Interaction and Synergism ..... 182
  - 7 Estimation, and Hypothesis Testing ..... 183
  - 8 Goodness-of-Fit ..... 183
  - 9 Selection Procedures ..... 185
  - 10 Main Conclusions ..... 185
  - References ..... 185
- 16 Curvilinear Regression ..... 187**
  - 1 Introduction ..... 187
  - 2 Methods, Statistical Model ..... 188
    - 2.1 Reproducibility of Means of the Population ..... 189
    - 2.2 Reproducibility of Individual Data ..... 189
  - 3 Results ..... 190
    - 3.1 Reproducibility of Means of Population ..... 190
    - 3.2 Reproducibility of Individual Data ..... 193
  - 4 Discussion ..... 194
  - 5 Conclusions ..... 196
  - References ..... 196

**17 Logistic and Cox Regression, Markov Models, Laplace Transformations** ..... 199

1 Introduction ..... 199

2 Linear Regression ..... 199

3 Logistic Regression ..... 203

    3.1 Logistic Regression Analysis for Predicting the Probability of an Event ..... 203

    3.2 Logistic Regression for Efficacy Data Analysis ..... 207

4 Cox Regression ..... 209

5 Markov Models ..... 212

6 Regression-Analysis with Laplace Transformations ..... 213

7 Discussion ..... 216

8 Conclusions ..... 217

References ..... 218

**18 Regression Modeling for Improved Precision** ..... 219

1 Introduction ..... 219

2 Regression Modeling for Improved Precision of Clinical Trials, the Underlying Mechanism ..... 220

3 Regression Model for Parallel-Group Trials with Continuous Efficacy Data ..... 220

4 Regression Model for Parallel-Group Trials with Proportions or Odds as Efficacy Data ..... 222

5 Discussion ..... 224

6 Conclusions ..... 225

References ..... 225

**19 Post-hoc Analyses in Clinical Trials, A Case for Logistic Regression Analysis** ..... 227

1 Multiple Variables Methods ..... 227

2 Examples ..... 228

3 Logistic Regression Equation ..... 230

4 Conclusions ..... 231

References ..... 231

**20 Multistage Regression** ..... 233

1 Introduction ..... 233

2 An Example, Usual Linear Regression Modeling ..... 234

3 Path Analysis ..... 234

4 Multistage Least Squares Method ..... 237

5 Bivariate Analysis Using Path Analysis ..... 238

6 Discussion ..... 239

7 Conclusions ..... 240

References ..... 241

- 21 Categorical Data**..... 243
  - 1 Introduction..... 243
  - 2 Races as a Categorical Variable ..... 244
  - 3 Numbers of Co-medications as a Categorical Variable ..... 248
  - 4 Discussion ..... 250
    - 4.1 Multinomial Logistic Regression..... 251
  - 5 Conclusions..... 251
  - References..... 252
- 22 Missing Data**..... 253
  - 1 Introduction..... 253
  - 2 Current Methods for Missing Data Imputation..... 254
  - 3 A Proposed Novel Approach to Regression-Substitution..... 254
  - 4 Example ..... 255
  - 5 Discussion ..... 258
  - 6 Conclusions..... 262
  - Appendix ..... 262
  - References..... 265
- 23 Poisson Regression** ..... 267
  - 1 Introduction..... 267
  - 2 Example 1 ..... 267
  - 3 Example 2 ..... 272
  - 4 Discussion ..... 273
  - 5 Conclusions..... 274
  - References..... 275
- 24 More on Non Linear Relationships, Splines** ..... 277
  - 1 Introduction..... 277
  - 2 Logit or Probit Transformation ..... 278
  - 3 “Trial and Error” Method, Box Cox Transformation, ACE/AVAS Packages ..... 280
  - 4 Curvilinear Data..... 281
  - 5 Spline Modeling..... 282
  - 6 Discussion ..... 285
  - 7 Conclusions..... 286
  - Appendix ..... 287
  - References..... 288
- 25 Multivariate Analysis**..... 289
  - 1 Introduction..... 289
  - 2 Multivariate Regression Analysis Using Path Analysis..... 290
  - 3 Multiple Analysis of Variance, First Example..... 292
  - 4 Multiple Analysis of Variance, Second Example ..... 294
  - 5 Multivariate Probit Regression ..... 296
  - 6 Discussion ..... 297
  - 7 Conclusions..... 298
  - References..... 299



<b>26</b>	<b>Bhattacharya Modeling</b> .....	301
1	Introduction .....	301
2	Unmasking Normal Values .....	302
3	Improving the p-Values of Data Testing .....	304
4	Objectively Searching Subsets in the Data .....	307
5	Discussion .....	309
6	Conclusions .....	310
	References .....	311
<b>27</b>	<b>Trend-Testing</b> .....	313
1	Introduction .....	313
2	Binary Data, the Chi-Square-Test-for-Trends .....	314
3	Continuous Data, Linear-Regression-Test-for-Trends .....	315
4	Discussion .....	316
5	Conclusions .....	318
	References .....	318
<b>28</b>	<b>Confounding</b> .....	319
1	Introduction .....	319
2	First Method for Adjustment of Confounders: Subclassification on One Confounder .....	320
3	Second Method for Adjustment of Confounders: Regression Modeling .....	321
4	Third Method for Adjustment of Confounders: Propensity Scores .....	323
5	Discussion .....	325
6	Conclusions .....	326
	References .....	327
<b>29</b>	<b>Propensity Score Matching</b> .....	329
1	Introduction .....	329
2	Calculation of Propensity-Scores .....	329
3	Propensity-Scores for Adjusting Covariates .....	331
4	Propensity-Scores for Matching .....	332
5	Discussion .....	333
6	Conclusions .....	334
	Appendix .....	335
	References .....	336
<b>30</b>	<b>Interaction</b> .....	337
1	Introduction .....	337
2	What Exactly Is Interaction, a Hypothesized Example .....	337
3	How to Test Interaction Statistically, a Real Data Example with a Concomitant Medication as Interacting Factor: Incorrect Method .....	339

- 4 Three Analysis Methods ..... 340
  - 4.1 First Method, t-Test ..... 341
  - 4.2 Second Method, Analysis of Variance (ANOVA)..... 341
  - 4.3 Third Method, Regression Analysis..... 342
- 5 Using a Regression Model for Testing  
Interaction, Another Real Data Example ..... 343
- 6 Analysis of Variance for Testing Interaction,  
Other Real Data Examples ..... 345
  - 6.1 Parallel-Group Study with Treatment  $\times$  Health  
Center Interaction..... 345
  - 6.2 Crossover Study with Treatment  $\times$  Subjects Interaction..... 347
- 7 Discussion ..... 349
- 8 Conclusions ..... 350
- References ..... 351
- 31 Time-Dependent Factor Analysis ..... 353**
  - 1 Introduction ..... 353
  - 2 Cox Regression Without Time-Dependent Predictors ..... 354
  - 3 Cox Regression with a Time-Dependent Predictor..... 356
  - 4 Cox Regression with a Segmented Time-Dependent Predictor ..... 359
  - 5 Multiple Cox Regression with a Time-Dependent Predictor ..... 361
  - 6 Discussion ..... 362
  - 7 Conclusions ..... 363
  - References ..... 364
- 32 Meta-analysis, Basic Approach..... 365**
  - 1 Introduction ..... 365
  - 2 Examples..... 366
  - 3 Clearly Defined Hypotheses ..... 367
  - 4 Thorough Search of Trials ..... 368
  - 5 Strict Inclusion Criteria..... 368
  - 6 Uniform Data Analysis ..... 368
    - 6.1 Individual Data ..... 369
    - 6.2 Continuous Data, Means and Standard  
Errors of the Mean (SEMs) ..... 369
    - 6.3 Proportions: Relative Risks (RRs), Odds Ratios (ORs),  
Differences Between Relative Risks (RDs) ..... 369
    - 6.4 Publication Bias ..... 371
    - 6.5 Heterogeneity ..... 372
    - 6.6 Robustness..... 375
  - 7 Discussion, Where Are We Now?..... 376
  - 8 Conclusions ..... 377
  - References ..... 377

<b>33</b>	<b>Meta-analysis, Review and Update of Methodologies .....</b>	<b>379</b>
1	Introduction.....	379
2	Four Scientific Rules.....	380
2.1	Clearly Defined Hypothesis .....	380
2.2	Thorough Search of Trials.....	380
2.3	Strict Inclusion Criteria.....	380
2.4	Uniform Data Analysis .....	381
3	General Framework of Meta-analysis.....	381
4	Pitfalls of Data Analysis .....	383
4.1	Publication Bias .....	383
4.2	Heterogeneity .....	384
4.3	Investigating the Cause for Heterogeneity .....	385
4.4	Lack of Robustness .....	386
5	New Developments .....	386
6	Conclusions.....	388
	References.....	388
<b>34</b>	<b>Meta-regression.....</b>	<b>391</b>
1	Introduction.....	391
2	An Example of a Heterogeneous Meta-analysis.....	391
3	Discussion.....	394
4	Conclusions.....	395
	References.....	396
<b>35</b>	<b>Crossover Studies with Continuous Variables.....</b>	<b>397</b>
1	Introduction.....	397
2	Mathematical Model .....	398
3	Hypothesis Testing.....	399
4	Statistical Power of Testing.....	400
5	Discussion.....	403
5.1	Analysis of Covariance (ANCOVA) .....	403
6	Conclusion .....	404
	References.....	405
<b>36</b>	<b>Crossover Studies with Binary Responses .....</b>	<b>407</b>
1	Introduction.....	407
2	Assessment of Carryover and Treatment Effect .....	408
3	Statistical Model for Testing Treatment and Carryover Effects.....	409
4	Results.....	409
4.1	Calculation of $p_c$ Values Just Yielding a Significant Test for Carryover Effect.....	409
4.2	Power of Paired Comparison for Treatment Effect.....	410
5	Examples.....	410
6	Discussion.....	412
7	Conclusions.....	413
	References.....	413

<b>37</b>	<b>Cross-Over Trials Should Not Be Used to Test Treatments with Different Chemical Class</b> .....	415
1	Introduction .....	415
2	Examples from the Literature in Which Cross-Over Trials Are Correctly Used.....	417
3	Examples from the Literature in Which Cross-Over Trials Should Not Have Been Used.....	417
4	Estimate of the Size of the Problem by Review of Hypertension Trials Published.....	419
5	Discussion .....	421
6	Conclusions.....	421
	References.....	422
<b>38</b>	<b>Quality-Of-Life Assessments in Clinical Trials</b> .....	423
1	Introduction.....	423
2	Some Terminology.....	423
3	Defining QOL in a Subjective or Objective Way?.....	425
4	The Patients' Opinion Is an Important Independent-Contributor to QOL.....	425
5	Lack of Sensitivity of QOL-Assessments.....	426
6	Odds Ratio Analysis of Effects of Patient Characteristics on QOL Data Provides Increased Precision.....	427
7	Discussion .....	429
8	Conclusions.....	430
	References.....	430
<b>39</b>	<b>Item Response Modeling</b> .....	433
1	Introduction.....	433
2	Item Response Modeling, Principles .....	434
3	Quality Of Life Assessment.....	435
4	Clinical and Laboratory Diagnostic-Testing .....	438
5	Discussion .....	439
6	Conclusions.....	442
	References.....	442
<b>40</b>	<b>Statistical Analysis of Genetic Data</b> .....	445
1	Introduction.....	445
2	Some Terminology.....	446
3	Genetics, Genomics, Proteonomics, Data Mining .....	447
4	Genomics .....	448
5	Conclusions.....	452
	References.....	453
<b>41</b>	<b>Relationship Among Statistical Distributions</b> .....	455
1	Introduction.....	455
2	Variances.....	456
3	The Normal Distribution.....	456

4	Null-Hypothesis Testing with the Normal or t-Distribution .....	458
5	Relationship Between the Normal Distribution and Chi-Square Distribution, Null-Hypothesis Testing with Chi-Square Distribution .....	459
6	Examples of Data Where Variance Is More Important Than Mean .....	462
7	Chi-Square Can Be Used for Multiple Samples of Data .....	462
7.1	Contingency Tables .....	462
7.2	Pooling Relative Risks or Odds Ratios in a Meta-analysis of Multiple Trials .....	463
7.3	Analysis of Variance (ANOVA) .....	463
8	Discussion .....	465
9	Conclusions .....	466
	Reference .....	467
<b>42</b>	<b>Testing Clinical Trials for Randomness .....</b>	<b>469</b>
1	Introduction .....	469
2	Individual Data Available .....	470
2.1	Method 1: The Chi-Square Goodness of Fit Test .....	470
2.2	Method 2: The Kolmogorov-Smirnov Goodness of Fit Test .....	471
2.3	Randomness of Survival Data .....	472
3	Individual Data Not Available .....	473
3.1	Studies with Single Endpoints .....	473
3.2	Studies with Multiple Endpoints .....	475
4	Discussion .....	476
5	Conclusions .....	477
	References .....	478
<b>43</b>	<b>Clinical Trials Do Not Use Random Samples Anymore .....</b>	<b>479</b>
1	Introduction .....	479
2	Non-normal Sampling Distributions, Giving Rise to Non-normal Data .....	479
3	Testing the Assumption of Normality .....	481
4	What to Do in case of Non-normality .....	482
5	Discussion .....	483
6	Conclusions .....	484
	References .....	485
<b>44</b>	<b>Clinical Data Where Variability Is More Important Than Averages .....</b>	<b>487</b>
1	Introduction .....	487
2	Examples .....	488
2.1	Testing Drugs with Small Therapeutic Indices .....	488
2.2	Testing Variability in Drug Response .....	488
2.3	Assessing Pill Diameters or Pill Weights .....	488

- 2.4 Comparing Different Patient Groups  
for Variability in Patient Characteristics ..... 488
- 2.5 Assessing the Variability in Duration  
of Clinical Treatments ..... 489
- 2.6 Finding the Best Method for Patient Assessments ..... 489
- 3 An Index for Variability in the Data ..... 489
- 4 How to Analyze Variability, One Sample ..... 490
  - 4.1  $\chi^2$  Test ..... 490
  - 4.2 Confidence Interval ..... 491
  - 4.3 Equivalence Test ..... 491
- 5 How to Analyze Variability, Two Samples ..... 492
  - 5.1 F Test ..... 492
  - 5.2 Confidence Interval ..... 492
  - 5.3 Equivalence Test ..... 493
- 6 How to Analyze Variability, Three or More Samples ..... 493
  - 6.1 Bartlett’s Test ..... 493
  - 6.2 Levene’s Test ..... 494
- 7 Discussion ..... 495
- 8 Conclusions ..... 496
- References ..... 496
- 45 Testing Reproducibility ..... 499**
  - 1 Introduction ..... 499
  - 2 Testing Reproducibility of Quantitative  
Data (Continuous Data) ..... 500
    - 2.1 Method 1, Duplicate Standard  
Deviations (Duplicate SDs) ..... 500
    - 2.2 Method 2, Repeatability Coefficients ..... 500
    - 2.3 Method 3, Intraclass Correlation Coefficients (ICCS) ..... 501
  - 3 Testing Reproducibility of Qualitative  
Data (Proportions and Scores) ..... 502
    - 3.1 Cohen’s Kappas ..... 502
  - 4 Incorrect Methods to Assess Reproducibility ..... 503
    - 4.1 Testing the Significance of Difference  
Between Two or More Sets of Repeated Measures ..... 503
    - 4.2 Calculating the Level of Correlation Between  
Two Sets of Repeated Measures ..... 504
  - 5 Additional Real Data Examples ..... 504
    - 5.1 Reproducibility of Ambulatory  
Blood Pressure Measurements (ABPM) ..... 504
    - 5.2 Two Different Techniques to Measure  
the Presence of Hypertension ..... 506
  - 6 Discussion ..... 507
  - 7 Conclusions ..... 508
  - References ..... 508