Ton J. Cleophas · Aeilko H. Zwinderman

Statistics Applied to Clinical Studies

Fifth Edition

Springer

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With the help from

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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-R2 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

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