

# Developments in Statistical Evaluation of Clinical Trials



Kees van Montfort • Johan Oud •  
Wendimagegn Ghidey  
Editors

# Developments in Statistical Evaluation of Clinical Trials

 Springer

*Editors*

Kees van Montfort  
Department of Biostatistics  
Erasmus Medical Center  
Rotterdam  
The Netherlands

Johan Oud  
Behavioural Science Institute  
University of Nijmegen  
Nijmegen  
The Netherlands

Wendimagegn Ghidey  
Department of Hematology  
Erasmus Medical Center  
Rotterdam  
The Netherlands

ISBN 978-3-642-55344-8

ISBN 978-3-642-55345-5 (eBook)

DOI 10.1007/978-3-642-55345-5

Springer Heidelberg New York Dordrecht London

Library of Congress Control Number: 2014951708

© Springer-Verlag Berlin Heidelberg 2014

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed. Exempted from this legal reservation are brief excerpts in connection with reviews or scholarly analysis or material supplied specifically for the purpose of being entered and executed on a computer system, for exclusive use by the purchaser of the work. Duplication of this publication or parts thereof is permitted only under the provisions of the Copyright Law of the Publisher's location, in its current version, and permission for use must always be obtained from Springer. Permissions for use may be obtained through RightsLink at the Copyright Clearance Center. Violations are liable to prosecution under the respective Copyright Law.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

While the advice and information in this book are believed to be true and accurate at the date of publication, neither the authors nor the editors nor the publisher can accept any legal responsibility for any errors or omissions that may be made. The publisher makes no warranty, express or implied, with respect to the material contained herein.

Printed on acid-free paper

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

# Preface

Over the last few decades the role of statistics in the evaluation and interpretation of clinical data has become more and more important. As a result the standards of clinical study design, conduct and interpretation have been advanced. In this book statistical considerations in data analysis as a basis for deriving an accurate clinical interpretation are elaborated.

Most often it is the physician who decides whether to prescribe a specific drug for a specific patient in a specific situation. The decisions of the physicians are largely based on the interpretation of data they have read and heard. This book describes various ways of approaching and interpreting the data that result from a clinical trial study.

The book reemphasizes the essential role that biostatistics plays in clinical trials. The book contains 18 carefully reviewed chapters on recent developments in trials and statistics. The chapters in this book are generally autonomous and may be read in any order. Each chapter is written by one or more experts in the specific approach. Starting from (a) some background information about the specific approach (short history and main publications), the chapter (b) describes the type of research questions the approach is able to answer and the kind of data to be collected, (c) gives the statistical and mathematical explanation of the model(s) used in the analysis of the data, (d) discusses the input and output of the software used in the analysis, and (e) provides one or more examples with typical data sets enabling the readers to apply the programs themselves. The chapters are worked out in a homogeneous style to enhance comparability between the approaches. The data sets and the computer code for the analysis with various softwares are a very important component of the book. They are available upon request (by emailing the authors of the chapters).

Each chapter is self-contained in this edited volume. The chapters are written and reviewed by experts in the specific approach. Although an authored volume could have advantages, because of the rapid changes in the field, an edited book written by people who are in the middle of the latest developments in the specific approach

is preferable. In addition, the authors of the chapters use a shared notation to enable the reader to compare methods more easily.

The book addresses the great majority of researchers in the field of clinical trials. Included are biostatisticians, medical researchers and physicians. It is meant as a reference work for all those actually doing and using research in the field of clinical trials. To reach this vast audience, knowledge of statistics as taught at master degree level in medical and biomedical sciences is required. However, the restricted number of chapters gives each of the chapters the opportunity to go into sufficient details to enable the readers to understand and apply the methods. In addition, the book addresses biostatisticians and physicians, who are professionally dealing with research in the field of clinical trials, to provide standards for state-of-the-art practices. Furthermore, the book offers researchers new ideas about the use of biostatistical analysis in solving their research problems. Finally the book is suitable as obligated literature for courses in clinical trial evaluation given at university medical and epidemiological research schools.

We thank the authors of the chapters for their willingness to contribute to the book, the anonymous reviewers for their expertise and time invested and Springer Publishers for their decision to publish the book in their Statistics book program.

Rotterdam, The Netherlands  
Nijmegen, The Netherlands  
Rotterdam, The Netherlands

Kees van Montfort  
Johan Oud  
Wendimagegn Ghidey

# Contents

<b>1</b>	<b>Statistical Models and Methods for Incomplete Data in Randomized Clinical Trials</b> .....	1
	Michael A. McIsaac and Richard J. Cook	
<b>2</b>	<b>Bayesian Decision Theory and the Design and Analysis of Randomized Clinical Trials</b> .....	29
	Andrew R. Willan	
<b>3</b>	<b>Designing Multi-arm Multi-stage Clinical Studies</b> .....	51
	Thomas Jaki	
<b>4</b>	<b>Statistical Approaches to Improving Trial Efficiency and Conduct</b> .....	71
	Janice Pogue, P.J. Devereaux, and Salim Yusuf	
<b>5</b>	<b>Competing Risks and Survival Analysis</b> .....	85
	Kees van Montfort, Peter Fennema, and Wendimagegn Ghidey	
<b>6</b>	<b>Recent Developments in Group-Sequential Designs</b> .....	97
	James M.S. Wason	
<b>7</b>	<b>Statistical Inference for Non-inferiority of a Diagnostic Procedure Compared to an Alternative Procedure, Based on the Difference in Correlated Proportions from Multiple Raters</b> .....	119
	Hiroyuki Saeki and Toshiro Tango	
<b>8</b>	<b>Design and Analysis of Clinical Trial Simulations</b> .....	139
	Kazuhiko Kuribayashi	
<b>9</b>	<b>Causal Effect Estimation and Dose Adjustment in Exposure-Response Relationship Analysis</b> .....	153
	Jixian Wang	

<b>10</b>	<b>Different Methods to Analyse the Results of a Randomized Controlled Trial with More Than One Follow-Up Measurement</b> .....	177
	Jos W.R. Twisk	
<b>11</b>	<b>Statistical Methods for the Assessment of Clinical Relevance</b> .....	195
	Meinhard Kieser	
<b>12</b>	<b>Statistical Considerations in the Use of Composite Endpoints in Time to Event Analyses</b> .....	209
	Richard J. Cook and Ker-Ai Lee	
<b>13</b>	<b>Statistical Validation of Surrogate Markers in Clinical Trials</b> .....	227
	Ariel Alonso, Geert Molenberghs, and Gerard van Breukelen	
<b>14</b>	<b>Biomarker-Based Designs of Phase III Clinical Trials for Personalized Medicine</b> .....	247
	Shigeyuki Matsui, Takahiro Nonaka, and Yuki Choai	
<b>15</b>	<b>Dose-Finding Methods for Two-Agent Combination Phase I Trials</b> .....	265
	Akihiro Hirakawa and Shigeyuki Matsui	
<b>16</b>	<b>Multi-state Models Used in Oncology Trials</b> .....	283
	Birgit Gaschler-Markefski, Karin Schiefele, Julia Hocke, and Frank Fleischer	
<b>17</b>	<b>Review of Designs for Accommodating Patients' or Physicians' Preferences in Randomized Controlled Trials</b> .....	305
	Afisi S. Ismaila and Stephen D. Walter	
<b>18</b>	<b>Dose Finding Methods in Oncology: From the Maximum Tolerated Dose to the Recommended Phase II Dose</b> .....	335
	Xavier Paoletti and Adélaïde Doussau	



# List of Contributors

**Ariel Alonso** Department of Methodology and Statistics, Maastricht University, Maastricht, The Netherlands

**Gerard van Breukelen** Department of Methodology and Statistics, Maastricht University, Maastricht, The Netherlands

**Yuki Choai** Department of Statistical Science, School of Multidisciplinary Sciences, The Graduate University for Advanced Studies, Tachikawa, Tokyo, Japan

**Richard J. Cook** Department of Statistics and Actuarial Science, University of Waterloo, Waterloo, ON, Canada

**P. J. Devereaux** Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada

**Adélaïde Doussau** USMR, Bordeaux University-Hospital, ISPED Centre INSERM U897-Epidemiologie-Biostatistique, Bordeaux, France

**Peter Fennema** Advanced Medical Research, Männedorf, Switzerland

**Frank Fleischer** Department of Biostatistics, Boehringer Ingelheim Pharma GmbH and Co. KG, Biberach, Germany

**Birgit Gaschler-Markefski** Department of Biostatistics, Boehringer Ingelheim Pharma GmbH and Co. KG, Biberach, Germany

**Wendimagegn Ghidey** Department of Hematology, Erasmus Medical Center, The Netherlands

**Akihiro Hirakawa** Center for Advanced Medicine and Clinical Research, Nagoya University Graduate School of Medicine, Showa-ku, Nagoya, Japan

**Julia Hocke** Department Biostatistics, Boehringer Ingelheim Pharma GmbH and Co. KG, Biberach, Germany

**Afisi S. Ismaila** Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada

**Thomas Jaki** Medical and Pharmaceutical Statistics Research Unit, Department of Mathematics and Statistics, Lancaster University, Lancaster, United Kingdom

**Meinhard Kieser** Institute of Medical Biometry and Informatics, University of Heidelberg, Heidelberg, Germany

**Kazuhiko Kuribayashi** Pfizer Japan Inc., Tokyo, Japan

**Ker-Ai Lee** Department of Statistics and Actuarial Science, University of Waterloo, Waterloo, ON, Canada

**Shigeyuki Matsui** Department of Biostatistics, Graduate School of Medicine, Nagoya University, Showa-ku, Nagoya, Japan

**Michael A. McIsaac** Department of Public Health Sciences, Queen's University, Kingston, ON, Canada

**Geert Molenberghs** I-BioStat, Universiteit Hasselt, Diepenbeek, Belgium  
KU Leuven, Leuven, Belgium

**Kees van Montfort** Department of Biostatistics, Erasmus Medical Center, Rotterdam, The Netherlands

**Takahiro Nonaka** Pharmaceuticals and Medical Devices Agency, Chiyoda-ku, Tokyo, Japan

**Johan H.L. Oud** Behavioural Science Institute, Radboud University Nijmegen, Nijmegen, The Netherlands

**Xavier Paoletti** Department of Biostatistics/INSERM U900, Institut Curie, Paris, France

**Janice Pogue** Department of Clinical Epidemiology and Biostatistics and Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada

**Hiroyuki Saeki** FUJIFILM RI Pharma Co. LTD., Chuo-ku, Tokyo, Japan

**Karin Schiefele** Department of Epidemiology and Medical Biometry, University Ulm, Ulm, Germany

**Toshiro Tango** Center for Medical Statistics, Minato-ku, Tokyo, Japan

**Jos W.R. Twisk** Department of Epidemiology and Biostatistics, VU Medical Centre, Amsterdam, The Netherlands

**Stephen D. Walter** Department of Medicine, McMaster University, Hamilton, ON, Canada

**Jixian Wang** Novartis Pharma AG, Basel, Switzerland

**James M.S. Wason** MRC Biostatistics Unit Hub for Trials Methodology Research, Institute of Public Health, Cambridge, United Kingdom

**Andrew R. Willan** SickKids Research Institute, Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

**Salim Yusuf** Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada