

# Dose Finding in Drug Development

*Series Editor*

M. Gail, K. Krickeberg, J. Samet, A. Tsiatis, W. Wong

# Statistics for Biology and Health

---

- Borchers/Buckland/Zucchini*: Estimating Animal Abundance: Closed Populations.
- Burzykowski/Molenberghs/Buyse*: The Evaluation of Surrogate Endpoints
- Everitt/Rabe-Hesketh*: Analyzing Medical Data Using S-PLUS.
- Ewens/Grant*: Statistical Methods in Bioinformatics: An Introduction, 2<sup>nd</sup> ed.
- Gentleman/Carey/Huber/Izarrry/Dudoit*: Bioinformatics and Computational Biology Solutions Using R and Bioconductor
- Hougaard*: Analysis of Multivariate Survival Data.
- Keyfitz/Caswell*: Applied Mathematical Demography, 3rd ed.
- Klein/Moeschberger*: Survival Analysis: Techniques for Censored and Truncated Data, 2nd ed.
- Kleinbaum/Klein*: Survival Analysis: A Self-Learning Text, 2<sup>nd</sup> ed.
- Kleinbaum/Klein*: Logistic Regression: A Self-Learning Text, 2<sup>nd</sup> ed.
- Lange*: Mathematical and Statistical Methods for Genetic Analysis, 2nd ed.
- Manton/Singer/Suzman*: Forecasting the Health of Elderly Populations.
- Martinussen/Scheike*: Dynamic Regression Models for Survival Data
- Moyé*: Multiple Analyses in Clinical Trials: Fundamentals for Investigators.
- Nielsen*: Statistical Methods in Molecular Evolution
- Parmigiani/Garrett/Irizarry/Zeger*: The Analysis of Gene Expression Data: Methods and Software.
- Salsburg*: The Use of Restricted Significance Tests in Clinical Trials.
- Simon/Korn/McShane/Radmacher/Wright/Zhao*: Design and Analysis of DNA Microarray Investigations.
- Sorensen/Gianola*: Likelihood, Bayesian, and MCMC Methods in Quantitative Genetics.
- Stallard/Manton/Cohen*: Forecasting Product Liability Claims: Epidemiology and Modeling in the Manville Asbestos Case.
- Therneau/Grambsch*: Modeling Survival Data: Extending the Cox Model.
- Ting*: Dose Finding in Drug Development
- Vittinghoff/Glidden/Shiboski/McCulloch*: Regression Methods in Biostatistics: Linear, Logistic, Survival, and Repeated Measures Models.
- Zhang/Singer*: Recursive Partitioning in the Health Sciences.

Naitee Ting

Editor

# Dose Finding in Drug Development

With 48 Illustrations



Springer

Naitee Ting  
Pfizer  
New London, CT 06320  
naitee.ting@pfizer.com

*Series Editors:*

M. Gail  
National Cancer Institute  
Rockville, MD 20892  
USA

K. Krickeberg  
Le Chatelet  
F-63270 Manglieu  
France

J. Samet  
Department of Epidemiology  
School of Public Health  
Johns Hopkins University  
615 Wolfe Street  
Baltimore, MD 21205-2103  
USA

A. Tsiatis  
Department of Statistics  
North Carolina State University  
Raleigh, NC 27695  
USA

W. Wong  
Sequoia Hall  
Department of Statistics  
Stanford University  
390 Serra Mall  
Stanford, CA 94305-4065  
USA

Library of Congress Control Number: 2005935288

ISBN-10: 0-387-29074-5

ISBN-13: 978-0387-29074-4

Printed on acid-free paper.

© 2006 Springer Science+Business Media, Inc.

All rights reserved. This work may not be translated or copied in whole or in part without the written permission of the publisher (Springer Science+Business Media, Inc., 233 Spring Street, New York, NY 10013, USA), except for brief excerpts in connection with reviews or scholarly analysis. Use in connection with any form of information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed is forbidden.

The use in this publication of trade names, trademarks, service marks, and similar terms, even if they are not identified as such, is not to be taken as an expression of opinion as to whether or not they are subject to proprietary rights.

Printed in the United States of America. (TB/MVY)

9 8 7 6 5 4 3 2 1

springer.com

# Preface

This book emphasizes dose selection issues from a statistical point of view. It presents statistical applications in the design and analysis of dose–response studies. The importance of this subject can be found from the International Conference on Harmonization (ICH) E4 Guidance document.

Establishing the dose–response relationship is one of the most important activities in developing a new drug. A clinical development program for a new drug can be broadly divided into four phases – namely Phases I, II, III, and IV. Phase I clinical trials are designed to study the clinical pharmacology. Information obtained from these studies will help in designing Phase II studies. Dose–response relationships are usually studied in Phase II. Phase III clinical trials are large-scale, long-term studies. These studies serve to confirm findings from Phases I and II. Results obtained from Phases I, II, and III clinical trials would then be documented and submitted to regulatory agencies for drug approval. In the United States, reviewers from Food and Drug Administration (FDA) review these documents and make a decision to approve or to reject this New Drug Application (NDA). If the new drug is approved, then Phase IV studies can be started. Phase IV clinical trials are also known as postmarketing studies.

Phase II is the key phase to help find doses. At this point, dose-ranging studies and dose-finding studies are designed and carried out sequentially. These studies usually include several dose groups of the study drug, plus a placebo treatment group. Sometimes an active control treatment group may also be included. If the Phase II program is successful, then one or several doses will be considered for the Phase III clinical development. In certain life-threatening diseases, flexible-dose designs are desirable. Various proposals about design and analysis of these studies are available in the statistical and medical literature.

Statistics is an important science in drug development. Statistical methods can be applied to help with study design and data analysis for both preclinical and clinical studies. Evidences of drug efficacy and drug safety in human subjects are mainly established on the findings from randomized double-blind controlled clinical trials. Without statistics, there would be no such trials. Descriptive statistics are frequently used to help understand various characteristics of a drug. Inferential

statistics helps quantify probabilities of successes, risks in drug discovery and development, as well as variability around these probabilities. Statistics is also an important decision-making tool throughout the entire drug development process. In clinical trials of all phases, studies are designed using statistical principles. Clinical data are displayed and analyzed using statistical models.

This book introduces the drug development process and the design and analysis of clinical trials. Much of the material in the book is based on applications of statistical methods in the design and analysis of dose-response studies. In general, there are two major types of dose-response concerns in drug development—concerns regarding drugs developed for nonlife-threatening diseases and those for life-threatening diseases. Most of the drug development programs in the pharmaceutical industry and the ICH E4 consider issues of nonlife-threatening diseases. On the other hand, many of the NIH/NCI sponsored studies and some of the pharmaceutical industry-sponsored studies deal with life-threatening diseases. Statistical and medical concerns in designing and analyzing these two types of studies can be very different. In this book, both types of clinical trials will be covered to a certain depth.

Although the book is prepared primarily for statisticians and biostatisticians, it also serves as a useful reference to a variety of professionals working for the pharmaceutical industry. Nonetheless, other professions – pharmacokineticists, clinical scientists, clinical pharmacologists, pharmacists, project managers, pharmaceutical scientists, clinicians, programmers, data managers, regulatory specialists, and study report writers can also benefit from reading this book. This book can also be a good reference for professionals working in a drug regulatory environment, for example, the FDA. Scientists and reviewers from both U.S. and foreign drug regulatory agencies can benefit greatly from this book. In addition, statistical and medical professionals in academia may find this book helpful in understanding the drug development process, and the practical concerns in selecting doses for a new drug.

The purpose of this book is to introduce the dose-selection process in drug development. Although it includes many preclinical experiments, most of dose-finding activities occur during the Phase II/III clinical stage. Therefore, the emphasis of this book is mostly about design and analysis of Phase II/III dose-response clinical trials. Chapter 1 offers an overview of drug development process. Chapter 2 covers dose-finding in preclinical studies, and Chapter 3 details Phase I clinical trials. Chapters 4 to 8 discuss issues relating to design, and Chapters 9 to 13 discuss issues relating to analysis of dose-response clinical trials. Chapter 14 introduces power and sample size estimation for these studies. For readers who are interested in designs involving life-threatening diseases such as cancer, Chapters 4 and 5 provide a good overview from both the nonparametric and the parametric points. In planning dose-response trials, researchers are likely to find PK/PD and trial simulation useful tools to help with study design. Hence Chapters 6 to 8 cover these and other general design issues for Phase II studies. In data analysis of dose-response results, the two major approaches are modeling approaches and multiple comparisons. Chapters 9 and 10 cover the

modeling approach while Chapters 11 and 12 cover the multiple comparison methods. Chapter 13 discusses the analysis of categorical data in dose-finding clinical trials.

Naitee Ting  
Pfizer Global Research and Development  
New London  
Connecticut  
[Naitee.ting@pfizer.com](mailto:Naitee.ting@pfizer.com)

# Contents

|                                                                                     |           |
|-------------------------------------------------------------------------------------|-----------|
| <b>Preface</b>                                                                      | <b>v</b>  |
| <b>1 Introduction and New Drug Development Process</b>                              | <b>1</b>  |
| 1.1 Introduction .....                                                              | 1         |
| 1.2 New Drug Development Process .....                                              | 4         |
| 1.3 Nonclinical Development .....                                                   | 5         |
| 1.3.1 Pharmacology .....                                                            | 5         |
| 1.3.2 Toxicology/Drug Safety .....                                                  | 6         |
| 1.3.3 Drug Formulation Development .....                                            | 7         |
| 1.4 Premarketing Clinical Development .....                                         | 8         |
| 1.4.1 Phase I Clinical Trials .....                                                 | 8         |
| 1.4.2 Phase II/III Clinical Trials .....                                            | 10        |
| 1.4.3 Clinical Development for Life-Threatening Diseases .....                      | 12        |
| 1.4.4 New Drug Application .....                                                    | 12        |
| 1.5 Clinical Development Plan .....                                                 | 13        |
| 1.6 Postmarketing Clinical Development .....                                        | 14        |
| 1.7 Concluding Remarks .....                                                        | 16        |
| <b>2 Dose Finding Based on Preclinical Studies</b>                                  | <b>18</b> |
| 2.1 Introduction .....                                                              | 18        |
| 2.2 Parallel Line Assays .....                                                      | 20        |
| 2.3 Competitive Binding Assays .....                                                | 20        |
| 2.4 Anti-infective Drugs .....                                                      | 25        |
| 2.5 Biological Substances .....                                                     | 25        |
| 2.6 Preclinical Toxicology Studies .....                                            | 26        |
| 2.7 Extrapolating Dose from Animal to Human .....                                   | 28        |
| <b>3 Dose-Finding Studies in Phase I and Estimation of Maximally Tolerated Dose</b> | <b>30</b> |
| 3.1 Introduction .....                                                              | 30        |
| 3.2 Basic Concepts .....                                                            | 30        |
| 3.3 General Considerations for FIH Studies .....                                    | 32        |



|          |                                                                            |           |
|----------|----------------------------------------------------------------------------|-----------|
| 3.3.1    | Study Designs .....                                                        | 33        |
| 3.3.2    | Population.....                                                            | 35        |
| 3.4      | Dose Selection.....                                                        | 37        |
| 3.4.1    | Estimating the Starting Dose in Phase I.....                               | 37        |
| 3.4.2    | Dose Escalation.....                                                       | 40        |
| 3.5      | Assessments.....                                                           | 42        |
| 3.5.1    | Safety and Tolerability.....                                               | 42        |
| 3.5.2    | Pharmacokinetics.....                                                      | 43        |
| 3.5.3    | Pharmacodynamics.....                                                      | 43        |
| 3.6      | Dose Selection for Phase II.....                                           | 46        |
| <b>4</b> | <b>Dose-Finding in Oncology—Nonparametric Methods</b>                      | <b>49</b> |
| 4.1      | Introduction .....                                                         | 49        |
| 4.2      | Traditional or 3 + 3 Design.....                                           | 50        |
| 4.3      | Basic Properties of Group Up-and-Down Designs.....                         | 51        |
| 4.4      | Designs that Use Random Sample Size: Escalation<br>and A + B Designs ..... | 52        |
| 4.4.1    | Escalation and A + B Designs .....                                         | 52        |
| 4.4.2    | The 3 + 3 Design as an A + B Design.....                                   | 53        |
| 4.5      | Designs that Use Fixed Sample Size .....                                   | 53        |
| 4.5.1    | Group Up-and-Down Designs.....                                             | 54        |
| 4.5.2    | Fully Sequential Designs for Phase I Clinical<br>Trials .....              | 54        |
| 4.5.3    | Estimation of the MTD After the Trial .....                                | 54        |
| 4.6      | More Complex Dose-Finding Trials.....                                      | 55        |
| 4.6.1    | Trials with Ordered Groups.....                                            | 55        |
| 4.6.2    | Trials with Multiple Agents.....                                           | 56        |
| 4.7      | Conclusion.....                                                            | 56        |
| <b>5</b> | <b>Dose Finding in Oncology—Parametric Methods</b>                         | <b>59</b> |
| 5.1      | Introduction .....                                                         | 59        |
| 5.2      | Escalation with Overdose Control Design.....                               | 61        |
| 5.2.1    | EWOC Design.....                                                           | 61        |
| 5.2.2    | Example .....                                                              | 62        |
| 5.3      | Adjusting for Covariates.....                                              | 63        |
| 5.3.1    | Model .....                                                                | 63        |
| 5.3.2    | Example .....                                                              | 66        |
| 5.4      | Choice of Prior Distributions.....                                         | 68        |
| 5.4.1    | Independent Priors.....                                                    | 69        |
| 5.4.2    | Correlated Priors.....                                                     | 69        |
| 5.4.3    | Simulations .....                                                          | 70        |
| 5.5      | Concluding Remarks .....                                                   | 70        |
| <b>6</b> | <b>Dose Response: Pharmacokinetic–Pharmacodynamic Approach</b>             | <b>73</b> |
| 6.1      | Exposure Response .....                                                    | 73        |

|          |                                                                                                     |           |
|----------|-----------------------------------------------------------------------------------------------------|-----------|
| 6.1.1    | How Dose Response and Exposure Response Differ                                                      | 73        |
| 6.1.2    | Why Exposure Response is More Informative .....                                                     | 73        |
| 6.1.3    | FDA Exposure Response Guidance .....                                                                | 73        |
| 6.2      | Time Course of Response.....                                                                        | 74        |
| 6.2.1    | Action, Effect, and Response.....                                                                   | 74        |
| 6.2.2    | Models for Describing the Time Course of Response                                                   | 74        |
| 6.3      | Pharmacokinetics.....                                                                               | 75        |
| 6.3.1    | Review of Basic Elements of Pharmacokinetics .....                                                  | 75        |
| 6.3.2    | Why the Clearance/Volume Parameterization<br>is Preferred.....                                      | 76        |
| 6.4      | Pharmacodynamics .....                                                                              | 77        |
| 6.4.1    | Review of Basic Elements of Pharmacodynamics...                                                     | 77        |
| 6.5      | Delayed Effects and Response.....                                                                   | 77        |
| 6.5.1    | Two Main Mechanism Classes for Delayed Effects.                                                     | 78        |
| 6.6      | Cumulative Effects and Response.....                                                                | 80        |
| 6.6.1    | The Relevance of Considering Integral of Effect<br>as the Outcome Variable.....                     | 80        |
| 6.6.2    | Why Area Under the Curve of Concentration is<br>not a Reliable Predictor of Cumulative Response ... | 80        |
| 6.6.3    | Schedule Dependence.....                                                                            | 81        |
| 6.6.4    | Predictability of Schedule Dependence.....                                                          | 82        |
| 6.7      | Disease Progress.....                                                                               | 82        |
| 6.7.1    | The Time Course of Placebo Response and<br>Disease Natural History .....                            | 82        |
| 6.7.2    | Two Main Classes of Drug Effect .....                                                               | 83        |
| 6.8      | Modeling Methods.....                                                                               | 84        |
| 6.8.1    | Analysis .....                                                                                      | 84        |
| 6.8.2    | Mixed Effect Models.....                                                                            | 85        |
| 6.8.3    | Simulation.....                                                                                     | 85        |
| 6.8.4    | Clinical Trial Simulation .....                                                                     | 85        |
| 6.9      | Conclusion.....                                                                                     | 86        |
| <b>7</b> | <b>General Considerations in Dose–Response Study Designs</b>                                        | <b>89</b> |
| 7.1      | Issues Relating to Clinical Development Plan.....                                                   | 89        |
| 7.2      | General Considerations for Designing Clinical Trials.....                                           | 90        |
| 7.2.1    | Subject Population and Endpoints.....                                                               | 91        |
| 7.2.2    | Parallel Designs versus Crossover Designs .....                                                     | 93        |
| 7.2.3    | Selection of Control .....                                                                          | 93        |
| 7.2.4    | Multiple Comparisons .....                                                                          | 94        |
| 7.2.5    | Sample Size Considerations .....                                                                    | 95        |
| 7.2.6    | Multiple Center Studies .....                                                                       | 96        |
| 7.3      | Design Considerations for Phase II Dose–Response Studies ..                                         | 96        |
| 7.3.1    | Frequency of Dosing .....                                                                           | 97        |
| 7.3.2    | Fixed-Dose versus Dose-Titration Designs .....                                                      | 99        |
| 7.3.3    | Range of Doses to be Studied .....                                                                  | 100       |

|           |                                                                                                     |            |
|-----------|-----------------------------------------------------------------------------------------------------|------------|
| 7.3.4     | Number of Doses to be Tested .....                                                                  | 101        |
| 7.3.5     | Dose Allocation, Dose Spacing .....                                                                 | 102        |
| 7.3.6     | Optimal Designs .....                                                                               | 103        |
| 7.4       | Concluding Remarks .....                                                                            | 103        |
| <b>8</b>  | <b>Clinical Trial Simulation—A Case Study Incorporating Efficacy and Tolerability Dose Response</b> | <b>106</b> |
| 8.1       | Clinical Development Project Background .....                                                       | 106        |
| 8.1.1     | Clinical Trial Objectives .....                                                                     | 107        |
| 8.1.2     | Uncertainties Affecting Clinical Trial Planning .....                                               | 107        |
| 8.2       | The Clinical Trial Simulation Project .....                                                         | 108        |
| 8.2.1     | Clinical Trial Objectives Used for the CTS Project ..                                               | 109        |
| 8.2.2     | The Simulation Project Objective .....                                                              | 111        |
| 8.2.3     | Simulation Project Methods 1: Data Models and Design Options .....                                  | 111        |
| 8.2.4     | Simulation Project Methods 2: Analysis and Evaluation Criteria .....                                | 117        |
| 8.3       | Simulation Results and Design Recommendations .....                                                 | 120        |
| 8.3.1     | Objective 1: Power for Confirming Efficacy .....                                                    | 120        |
| 8.3.2     | Objective 2: Accuracy of Target Dose Estimation ...                                                 | 121        |
| 8.3.3     | Objective 3: Estimation of a Potentially Clinically Noninferior Dose Range .....                    | 121        |
| 8.3.4     | Trial Design Recommendations .....                                                                  | 124        |
| 8.4       | Conclusions .....                                                                                   | 125        |
| <b>9</b>  | <b>Analysis of Dose–Response Studies—<math>E_{\max}</math> Model</b>                                | <b>127</b> |
| 9.1       | Introduction to the $E_{\max}$ Model .....                                                          | 127        |
| 9.2       | Sensitivity of the $E_{\max}$ Model Parameters .....                                                | 129        |
| 9.2.1     | Sensitivity of the $E_0$ and $E_{\max}$ Parameters .....                                            | 129        |
| 9.2.2     | Sensitivity of the $ED_{50}$ Parameter .....                                                        | 130        |
| 9.2.3     | Sensitivity of the $N$ Parameter .....                                                              | 131        |
| 9.2.4     | Study Design for the $E_{\max}$ Model .....                                                         | 131        |
| 9.2.5     | Covariates in the $E_{\max}$ Model .....                                                            | 133        |
| 9.3       | Similar Models .....                                                                                | 134        |
| 9.4       | A Mixed Effects $E_{\max}$ Model .....                                                              | 134        |
| 9.5       | Examples .....                                                                                      | 135        |
| 9.5.1     | Oral Artesunate Dose–Response Analysis Example                                                      | 135        |
| 9.5.2     | Estimation Methodology .....                                                                        | 137        |
| 9.5.3     | Initial Parameter Values for the Oral Artesunate Dose–Response Analysis Example .....               | 138        |
| 9.5.4     | Diastolic Blood Pressure Dose–Response Example ..                                                   | 139        |
| 9.6       | Conclusions .....                                                                                   | 141        |
| <b>10</b> | <b>Analysis of Dose–Response Studies—Modeling Approaches</b>                                        | <b>146</b> |
| 10.1      | Introduction .....                                                                                  | 146        |

|           |                                                                                 |            |
|-----------|---------------------------------------------------------------------------------|------------|
| 10.2      | Some Commonly Used Dose–Response Models.....                                    | 149        |
| 10.2.1    | $E_{\max}$ Model.....                                                           | 150        |
| 10.2.2    | Linear in Log-Dose Model.....                                                   | 151        |
| 10.2.3    | Linear Model.....                                                               | 151        |
| 10.2.4    | Exponential (Power) Model.....                                                  | 151        |
| 10.2.5    | Quadratic Model.....                                                            | 152        |
| 10.2.6    | Logistic Model.....                                                             | 152        |
| 10.3      | Estimation of Target Doses.....                                                 | 153        |
| 10.3.1    | Estimating the MED in Dose-Finding Example.....                                 | 155        |
| 10.4      | Model Uncertainty and Model Selection.....                                      | 156        |
| 10.5      | Combining Modeling Techniques and Multiple Testing.....                         | 160        |
| 10.5.1    | Methodology.....                                                                | 160        |
| 10.5.2    | Proof-of-Activity Analysis in the<br>Dose-Finding Example.....                  | 162        |
| 10.5.3    | Simulations.....                                                                | 163        |
| 10.6      | Conclusions.....                                                                | 169        |
| <b>11</b> | <b>Multiple Comparison Procedures in Dose Response Studies</b>                  | <b>172</b> |
| 11.1      | Introduction.....                                                               | 172        |
| 11.2      | Identifying the Minimum Effective Dose (MinED).....                             | 172        |
| 11.2.1    | Problem Formulation.....                                                        | 172        |
| 11.2.2    | Review of Multiple Test Procedures.....                                         | 174        |
| 11.2.3    | Simultaneous Confidence Intervals.....                                          | 176        |
| 11.3      | Identifying the Maximum Safe Dose (MaxSD).....                                  | 177        |
| 11.4      | Examples.....                                                                   | 177        |
| 11.5      | Extensions.....                                                                 | 180        |
| 11.6      | Discussion.....                                                                 | 181        |
| <b>12</b> | <b>Partitioning Tests in Dose–Response Studies with<br/>Binary Outcomes</b>     | <b>184</b> |
| 12.1      | Motivation.....                                                                 | 184        |
| 12.2      | Comparing Two Success Probabilities in a Single Hypothesis                      | 185        |
| 12.3      | Comparison of Success Probabilities in<br>Dose–Response Studies.....            | 188        |
| 12.3.1    | Predetermined Step-Down Method.....                                             | 188        |
| 12.3.2    | Sample-Determined Step-Down Method.....                                         | 190        |
| 12.3.3    | Hochberg’s Step-up Procedure.....                                               | 194        |
| 12.4      | An Example Using Partitioning Based Stepwise Methods.....                       | 195        |
| 12.5      | Conclusion and Discussion.....                                                  | 197        |
| <b>13</b> | <b>Analysis of Dose–Response Relationship Based<br/>on Categorical Outcomes</b> | <b>200</b> |
| 13.1      | Introduction.....                                                               | 200        |
| 13.2      | When the Response is Ordinal.....                                               | 201        |
| 13.2.1    | Modeling Dose–Response.....                                                     | 201        |

|           |        |                                                                       |            |
|-----------|--------|-----------------------------------------------------------------------|------------|
|           | 13.2.2 | Testing for a Monotone Dose–Response Relationship.....                | 203        |
| 13.3      |        | When the Response is Binary.....                                      | 207        |
| 13.4      |        | Multiple Comparisons.....                                             | 210        |
|           | 13.4.1 | Bonferroni Adjustment.....                                            | 211        |
|           | 13.4.2 | Bonferroni–Holm Procedure.....                                        | 211        |
|           | 13.4.3 | Hochberg Procedure.....                                               | 212        |
|           | 13.4.4 | Gate-Keeping Procedure.....                                           | 212        |
|           | 13.4.5 | A Special Application of Dunnett’s Procedure for Binary Response..... | 213        |
| 13.5      |        | Discussion.....                                                       | 213        |
| <b>14</b> |        | <b>Power and Sample Size for Dose Response Studies</b>                | <b>220</b> |
|           | 14.1   | Introduction.....                                                     | 220        |
|           | 14.2   | General Approach to Power Calculation.....                            | 221        |
|           | 14.3   | Multiple-Arm Dose Response Trial.....                                 | 223        |
|           |        | 14.3.1 Normal Response.....                                           | 224        |
|           |        | 14.3.2 Binary Response.....                                           | 227        |
|           |        | 14.3.3 Time-to-Event Endpoint.....                                    | 230        |
|           | 14.4   | Phase I Oncology Dose Escalation Trial.....                           | 233        |
|           |        | 14.4.1 The A + B Escalation without Dose De-Escalation.....           | 234        |
|           |        | 14.4.2 The A + B Escalation with Dose De-Escalation.....              | 236        |
|           | 14.5   | Concluding Remarks.....                                               | 238        |
|           |        | <b>Index</b>                                                          | <b>243</b> |