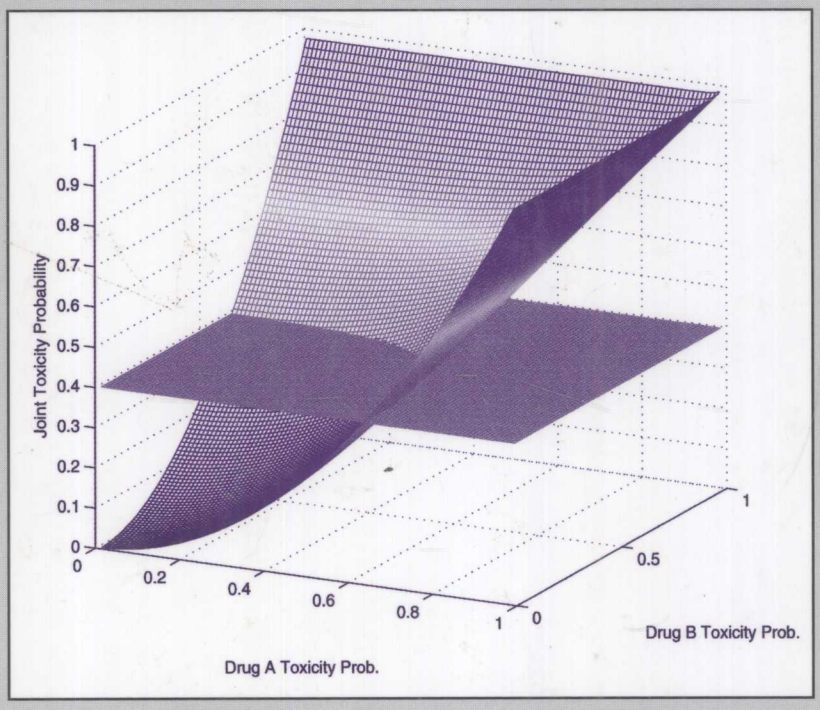
Handbook of Adaptive Designs in Pharmaceutical and Clinical Development



Edited by
Annpey Pong
Shein-Chung Chow

CRC Press
Taylor & Francis Group
A CHAPMAN & HALL BOOK

Handbook of Adaptive Designs in Pharmaceutical and Clinical Development

Edited by
Annpey Pong
Shein-Chung Chow

CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group an **informa** business
A CHAPMAN & HALL BOOK

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number: 978-1-4398-1016-3 (Hardback)

Library of Congress Cataloging-in-Publication Data

Handbook of adaptive designs in pharmaceutical and clinical development / edited by Annpey Pong, Shein-Chung Chow.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-4398-1016-3 (hardcover : alk. paper)
1. Clinical trials--Handbooks, manuals, etc. 2. Drugs--Research--Methodology--Handbooks, manuals, etc. I. Pong, Annpey. II. Chow, Shein-Chung, 1955-
[DNLM: 1. Clinical Trials as Topic--methods. 2. Research Design. 3. Statistics as Topic--methods. QV 771]

R853.C55H355 2011
615.5072'4--dc22 2010037121

Visit the Taylor & Francis Web site at
http://www.taylorandfrancis.com

and the CRC Press Web site at
http://www.crcpress.com

Handbook of Adaptive Designs in Pharmaceutical and Clinical Development

Preface

In recent years, as motivated by the U.S. Food and Drug Administration (FDA) *Critical Path Initiative*, the use of innovative adaptive design methods in clinical trials has attracted much attention from clinical investigators and regulatory agencies. Pharmaceutical Research Manufacturer Association (PhRMA) Working Group on Adaptive Design defines an adaptive design as a clinical trial design that uses accumulating data to decide how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial. Adaptive designs are attractive to clinical scientists for several reasons. First, it does reflect medical practice in the real world. Second, it is ethical with respect to both efficacy and safety (toxicity) of the test treatment under investigation. Third, it provides an opportunity for a flexible and an efficient study design in the early phase of clinical development. However, there are some major obstacles when applying adaptive design methods in clinical development. These obstacles include (i) operational biases are inevitable to avoid, (ii) it is difficult to preserve the overall Type I error when many adaptations are applied, (iii) statistical methods and software packages are not well established, (iv) current infrastructure and clinical trial processes may not be ready for implementation of adaptive design methods in clinical trials, and (v) little regulatory guidelines or guidances are available.

The purpose of this book is to provide a comprehensive and unified presentation of the principles and methodologies (up-to-date) in adaptive design and analysis with respect to modifications (changes or adaptations) made to trial procedures and/or statistical methods based on accrued data of on-going clinical trials. In addition, this book is intended to give a well-balanced summary of current regulatory perspectives in this area. It is our goal to provide a complete, comprehensive, and updated reference book in the area of adaptive design and analysis in clinical research.

Chapter 1 gives an overview for the use of adaptive design methods in clinical trials. Chapter 2 provides fundamental theory behind adaptive trial design for the unplanned design change with blind data. Chapter 3 focuses on the application of the Bayesian approach in adaptive designs. The impact of potential population shift due to protocol amendments is studied in Chapter 4. Statistical methods from group sequential design to adaptive designs are reviewed in Chapter 5. Sample-size calculation for classical design is summarized in Chapter 6, while methodologies for flexible sample-size reestimation and adaptive interim analysis are discussed in Chapters 7 and 8, respectively. In Chapters 9 through 11, basic philosophy and methodology of dose finding and statistical methods for classical and adaptive dose finding trials are explored. Chapters 12 and 13 discuss statistical methods and issues that are commonly encountered when applying Phase I/II and Phase II/III seamless adaptive designs in clinical development, respectively. The sample-size estimation/allocation for multiple (two) stage seamless adaptive trial designs is studied in Chapter 14. Chapters 15 through 18 deal with various types of adaptive designs including adaptive randomization trial (Chapter 15), hypotheses-adaptive design (Chapter 16), treatment-adaptive designs (Chapter 17), and predictive biomarker diagnostics for new drug development (Chapter 18). Chapter 19 provides some insight regarding clinical strategies for endpoint selection in translational research. Chapters 20 through 21 provide useful information regarding infrastructure and independent data monitoring committee when implementing adaptive design methods in clinical

trials. Chapter 22 provides an overview of the enrichment process in targeted clinical trials for personalized medicine. Applications of adaptive designs utilizing genomic or genetic information are given in Chapter 23. Chapter 24 provides detailed information regarding adaptive clinical trial simulation, which is often considered a useful tool for evaluation of the performances of the adaptive design methods applied. The issue regarding the efficiency of adaptive design is discussed in Chapter 25. Some case studies are presented in Chapter 26. Chapter 27 concludes the book with standard operating procedures for good adaptive practices.

We sincerely express our thanks to all of the contributors that made this book possible. They are the opinion leaders in the area of clinical research at the pharmaceutical industry, academia, or regulatory agencies. Their knowledge and experience will provide complete, comprehensive, and updated information to the readers who are involved or interested in the area of adaptive design and analysis in clinical research.

From Taylor & Francis, we would like to thank David Grubbs and Sunil Nair for providing us the opportunity to edit this book. We would like to thank colleagues from Merck Research Laboratories and the Department of Biostatistics and Bioinformatics and Duke Clinical Research Institute (DCRI) of Duke University School of Medicine for their constant support during the preparation of this book. In addition, we wish to express our gratitude to the following individuals for their encouragement and support: Roberts Califf, MD; Ralph Corey, MD; and John McHutchison, MD of Duke Clinical Research Institute and Duke University Medical Center; Greg Campbell, PhD of the U.S. FDA; and many friends from the academia, the pharmaceutical industry, and regulatory agencies.

Finally, we are solely responsible for the contents and errors of this book. Any comments and suggestions will be very much appreciated.

Annpey Pong
Shein-Chung Chow

Editors

Annpey Pong, PhD, is currently a manager at the Department of Biostatistics and Research Decision Sciences, Merck Research Laboratories, Rahway, New Jersey. Dr. Pong is the Associate Editor of the *Journal of Biopharmaceutical Statistics*, as well as the Guest Editor of the special issues on "Adaptive Design and Analysis in Clinical Development" (2004), "Recent Development of Adaptive Design in Clinical Trials" (2007), and the Organizer and Section Chair for "Recent Development of Design and Analysis in Clinical Trials" in the 17th Annual ICSA Applied Statistics Symposium (2008). Dr. Pong is the author or co-author of numerous publications in the field of pharmaceutical research. Dr. Pong received a BS in mathematics from Providence University, Taiwan, an MS in biostatistics from the University of Michigan–Ann Arbor, another MS in mathematics from Eastern Michigan University–Ypsilanti, and a PhD in statistics from Temple University–Philadelphia, Pennsylvania.

Shein-Chung Chow, PhD, is currently a professor at the Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, North Carolina, and a professor of clinical sciences, Duke–National University of Singapore Graduate Medical School, Singapore. Dr. Chow is currently the Editor-in-Chief of the *Journal of Biopharmaceutical Statistics.* He was elected Fellow of the American Statistical Association in 1995 and became a member of the International Statistical Institute in 1999. Dr. Chow is the author or co-author of over 200 methodology papers and 18 books, which include *Design and Analysis of Bioavailability and Bioequivalence Studies* (Marcel Dekker, 1992); *Sample Size Calculations in Clinical Research* (Marcel Dekker, 2003); *Encyclopedia of Biopharmaceutical Statistics* (Marcel Dekker, 2000); *Adaptive Design Methods in Clinical Trials* (Taylor & Francis, 2006); *Translational Medicine* (Taylor & Francis, 2008); and *Design and Analysis of Clinical Trials* (John Wiley & Sons, 1998). Dr. Chow received his BS in mathematics from National Taiwan University, Taiwan, and his PhD in statistics from the University of Wisconsin–Madison.

Contributors

Kwangmi Ahn
Department of Public Health Sciences
Pennsylvania State College of Medicine
Hershey, Pennsylvania

Arthur Berg
Department of Public Health Sciences
Pennsylvania State College of Medicine
Hershey, Pennsylvania

Rahul Bhattacharya
Department of Statistics
West Bengal State University
Barasat, Kolkata, India

Atanu Biswas
Applied Statistics Unit
Indian Statistical Institute
Kolkata, India

Björn Bornkamp
Department of Statistics
TU Dortmund University
Dortmund, Germany

Frank Bretz
Statistical Methodology
Integrated Information Sciences
Novartis Pharma AG
Basel, Switzerland

Carl-Fredrik Burman
Statistics and Informatics
AstraZeneca R&D
Mölndal, Sweden

Bill Byrom
Perceptive Informatics
Nottingham, United Kingdom

Mark Chang
Biostatistics and Data Management
AMAG Pharmaceuticals Inc.
Lexington, Massachusetts

George Y. H. Chi
Statistical Science
J&J Global Development Organization
Raritan, New Jersey

Shein-Chung Chow
Department of Biostatistics and Bioinformatics
Duke University School of Medicine
Durham, North Carolina

Christy Chuang-Stein
Statistical Research and Consulting Center
Pfizer, Inc.
Kalamazoo, Michigan

Lu Cui
Biostatistics
Eisai Inc.
Woodcliff Lake, New Jersey

Kiranmoy Das
Department of Statistics
Pennsylvania State University
University Park, Pennsylvania

Vladimir Dragalin
Center for Statistics in Drug Development
Quintiles Innovation
Morrisville, North Carolina

Tim Friede
Abteilung Medizinische Statistik
Universitätsmedizin Göttingen
Göttingen, Germany

Paul Gallo
Novartis Pharmaceuticals
East Hanover, New Jersey

Yonghong Gao
Division of Biostatistics/CDRH
U. S. Food and Drug Administration
Rockville, Maryland

Gerhard Hommel
Institut für Medizinische Biometrie, Epidemiologie und Informatik
Universitätsmedizin Mainz
Mainz, Germany

Christopher Jennison
Department of Mathematical Sciences
University of Bath
Bath, United Kingdom

Qi Jiang
Global Biostatistics & Epidemiology
Amgen, Inc.
Thousand Oaks, California

Simon Kirby
Statistical Research and Consulting Center
Pfizer, Inc.
Sandwich, Kent, United Kingdom

Shiowjen Lee
Office of Biostatistics and Epidemiology/CBER
U.S. Food and Drug Administration
Rockville, Maryland

Jiahan Li
Department of Statistics
Pennsylvania State University
University Park, Pennsylvania

Ning Li
Department of Regulatory and Medical Policy, China
Sanofi-aventis
Bridgewater, New Jersey

Yao Li
Department of Statistics
West Virginia University
Morgantown, West Virginia

Jen-Pei Liu
Division of Biometry
Department of Agronomy
Institute of Epidemiology
National Taiwan University
Taipei, Taiwan, Republic of China

and

Division of Biostatistics and Bioinformatics
Institute of Population Health Sciences
National Health Research Institutes
Zhunan, Taiwan, Republic of China

Qing Liu
Statistical Science
J&J Global Development Organization
Raritan, New Jersey

Qingshu Lu
Department of Statistics and Finance
University of Science and Technology of China
Anhui, People's Republic of China

Jiangtao Luo
Department of Mathematics
University of Florida
Gainesville, Florida

and

Department of Public Health Sciences
Pennsylvania State College of Medicine
Hershey, Pennsylvania

Jeff Maca
Statistical Methodology Group
Novartis Pharmaceuticals
East Hanover, New Jersey

Damian McEntegart
Perceptive Informatics
Nottingham, United Kingdom

Frank Miller
Statistics and Informatics
AstraZeneca R&D
Södertälje, Sweden

Graham Nicholls
Perceptive Informatics
Nottingham, United Kingdom

José Pinheiro
Statistical Methodology
Integrated Information Sciences
Novartis Pharmaceuticals
East Hanover, New Jersey

Annpey Pong
Department of BARDS
Merck Research Laboratories
Rahway, New Jersey

William Rosenberger
Department of Statistics
George Mason University
Fairfax, Virginia

Richard Simon
Biometric Research Branch
National Cancer Institute
Bethesda, Maryland

Steven Snapinn
Department of Global Biostatistics & Epidemiology
Amgen, Inc.
Thousand Oaks, California

Nigel Stallard
Warwick Medical School
The University of Warwick
Coventry, United Kingdom

Naitee Ting
Department of Biometrics and Data Management
Boehringer-Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut

Siu Keung Tse
Department of Management Sciences
City University of Hong Kong
Hong Kong, People's Republic of China

Bruce W. Turnbull
Department of Statistical Science
Cornell University,
Ithaca, New York

Marc Vandemeulebroecke
Translational Sciences Biostatistics
Integrated Information Sciences
Novartis Pharma AG
Basel, Switzerland

Zhong Wang
Department of Public Health Sciences
Pennsylvania State College of Medicine
Hershey, Pennsylvania

Gernot Wassmer
University of Cologne
Cologne, Germany

and

ADDPLAN GmbH
Cologne, Germany

Kiat Wee Wong
Statistics and Informatics
AstraZeneca R&D
Södertälje, Sweden

Rongling Wu
Department of Public Health Sciences
Pennsylvania State College of Medicine
Hershey, Pennsylvania

and

Department of Statistics
Pennsylvania State University
University Park, Pennsylvania

and

Department of Biotechnology
Beijing Forestry University
Beijing, People's Republic of China

Xiaoru Wu
Department of Statistics
Columbia University
New York City, New York

Guosheng Yin
Department of Statistics and Actuarial Science
The University of Hong Kong
Hong Kong, People's Republic of China

Ying Yuan
Department of Biostatistics
M. D. Anderson Cancer Center
The University of Texas
Houston, Texas

Lanju Zhang
MedImmune LLC
Gaithersberg, Maryland

Contents

1

Overview of Adaptive Design Methods in Clinical Trials

Annpey Pong
Merck Research Laboratories

Shein-Chung Chow
Duke University School of Medicine

1.1 Introduction

In the past several decades, as pointed out by Woodcock (2005), increasing spending of biomedical research does not reflect an increase in the success rate of pharmaceutical/clinical research and development. The low success rate of pharmaceutical development could be due to (i) a diminished margin for improvement that escalates the level of difficulty in proving drug benefits, (ii) genomics and other new science have not yet reached their full potential, (iii) mergers and other business arrangements have decreased candidates, (iv) easy targets are the focus as chronic diseases are harder to study, (v) failure rates have not improved, and (vi) rapidly escalating costs and complexity decreases willingness/ability to bring many candidates forward into the clinic (Woodcock 2005). As a result, the U.S. Food and Drug Administration (FDA) kicked off a *Critical Path Initiative* to assist the sponsors in identifying the scientific challenges underlying the medical product pipeline problems. In 2006, the FDA released a *Critical Path Opportunities List* that calls for advancing innovative trial designs by using prior experience or accumulated information in trial design. Many researchers interpret it as the encouragement of using innovative adaptive design methods in clinical trials, while some researchers believe it is the recommendation for using the Bayesian approach. The purpose of adaptive design methods in clinical trials is to provide the flexibility to the investigator for identifying best (optimal) clinical benefit of the test treatment under study in a timely and efficient fashion without undermining the validity and integrity of the intended study.

The concept of adaptive design can be traced back to the 1970s when adaptive (play-the-winner) randomization and a class of designs for sequential clinical trials were introduced (Wei 1978). As a result, most adaptive design methods in clinical research and development are referred to as adaptive randomization (see, e.g., Efron 1971; Lachin 1988; Atkinson and Donev 1992; Rosenberger et al. 2001; Hardwick

and Stout 2002; Rosenberger and Lachin 2002), group sequential designs with the flexibility for stopping a trial early due to safety, futility, and/or efficacy (see, e.g., Lan and DeMets 1987; Wang and Tsiatis 1987; Lehmacher and Wassmer 1999; Posch and Bauer 1999; Liu, Proschan, and Pledger 2002), and sample size reestimation at interim for achieving the desired statistical power (see, e.g., Cui, Hung, and Wang 1999; Chung-Stein et al. 2006; Chow, Shao, and Wang 2007). The use of adaptive design methods for modifying the trial procedures and/or statistical procedures of on-going clinical trials based on accrued data has been practiced for years in clinical research and development. Adaptive design methods in clinical research are very attractive to clinical scientists for several reasons. First, it reflects medical practice in real world. Second, it is ethical with respect to both efficacy and safety (toxicity) of the test treatment under investigation. Third, it is not only flexible, but also efficient in the early phase of clinical development. However, it is a concern whether the p-value or confidence interval regarding the treatment effect obtained after the modification is correct or reliable. In addition, it is also a concern that the use of adaptive design methods in a clinical trial may lead to a totally different trial that is unable to address scientific/medical questions that the trial is intended to answer.

In recent years, the potential use of adaptive design methods in clinical trials have attracted much attention. For example, the Pharmaceutical Research and Manufacturers of America (PhRMA) and Biotechnology Industry Organization (BIO) have established adaptive design working groups and proposed/published white papers regarding strategies, methodologies, and implementations for regulatory consideration (see, e.g., Gallo et al. 2006; Chang 2007a). However, there are no universal agreement in terms of definition, methodologies, applications, and implementations. In addition, many journals have also published special issues on adaptive design for evaluating the potential use of adaptive trial design methods in clinical research and development. These scientific journals include, but are not limited to, *Biometrics* (Vol. 62, No. 3), *Statistics in Medicine* (Vol. 25, No. 19), *Journal of Biopharmaceutical Statistics* (Vol. 15, No. 4 and Vol. 17, No. 6), *Biometrical Journal* (Vol. 48, No. 4), and *Pharmaceutical Statistics* (Vol. 5, No. 2). In addition, many professional conferences/meetings have devoted special sessions for discussion of the feasibility, applicability, efficiency, validity, and integrity of the potential use of the innovative adaptive design methods in clinical trials in the past several years. For example, the FDA/Industry Statistics Workshop has offered adaptive sessions and workshops from industrial, academic, and regulatory perspectives consecutively between 2006 and 2009. More details regarding the use of adaptive design methods in clinical trials can be found in the books by Chow and Chang (2006) and Chang (2007a).

The purpose of this handbook is not only to provide a comprehensive summarization of the issues that are commonly encountered when applying/implementing the adaptive design methods in clinical trials, but also to include recently development such as the role of the independent data safety monitoring board and sample size estimation/allocation, justification, and adjustment when implementing a much more complicated adaptive design in clinical trials. In the next section, commonly employed adaptations and the resultant adaptive designs are briefly described. Also included in this section are regulatory and statistical perspectives regarding the use of adaptive design methods in clinical trials. The impact of protocol amendments, challenges of *by design* adaptations, and obstacles of retrospective adaptations when applying adaptive design methods in clinical trials are described in Section 1.3. Some trial examples and strategies for clinical development are discussed in Sections 1.4 and 1.5, respectively. The aim and scope of the book are given in the last section.

1.2 What is Adaptive Design?

It is not uncommon to modify trial procedures and/or statistical methods during the conduct of clinical trials based on the review of accrued data at interim. The purpose is not only to efficiently identify clinical benefits of the test treatment under investigation, but also to increase the probability of success for the intended clinical trial. Trial procedures are referred to as the eligibility criteria, study dose, treatment duration, study endpoints, laboratory testing procedures, diagnostic procedures, criteria for evaluability, and assessment of clinical responses. Statistical methods include a randomization scheme, study design

selection, study objectives/hypotheses, sample size calculation, data monitoring and interim analysis, statistical analysis plan (SAP), and/or methods for data analysis. In this chapter, we will refer to the adaptations (changes or modifications) made to the trial and/or statistical procedures as the adaptive design methods. Thus, an adaptive design is defined as a design that allows adaptations to trial and/or statistical procedures of the trial after its initiation without undermining the validity and integrity of the trial (Chow, Chang, and Pong 2005). In one of their publications, with the emphasis of the feature by design adaptations only (rather than ad hoc adaptations), the PhRMA Working Group on Adaptive Design refers to an adaptive design as a clinical trial design that uses accumulating data to decide on how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial (Gallo et al. 2006). The FDA defines an adaptive design as a study that includes a *prospectively* planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study (FDA, 2010). In many cases, an adaptive design is also known as a flexible design (EMEA 2002, 2006).

1.2.1 Adaptations

An adaptation is referred to as a modification or a change made to trial procedures and/or statistical methods during the conduct of a clinical trial. By definition, adaptations that are commonly employed in clinical trials can be classified into the categories of prospective adaptation, concurrent (or ad hoc) adaptation, and retrospective adaptation. Prospective adaptations include, but are not limited to, adaptive randomization, stopping a trial early due to safety, futility, or efficacy at interim analysis, dropping the losers (or inferior treatment groups), sample size reestimation, and so on. Thus, prospective adaptations are usually referred to by design adaptations as described in the PhRMA white paper (Gallo et al. 2006). Concurrent adaptations are usually referred to as any ad hoc modifications or changes made as the trial continues. Concurrent adaptations include, but are not limited to, modifications in inclusion/exclusion criteria, evaluability criteria, dose/regimen and treatment duration, changes in hypotheses and/or study endpoints, and so on. Retrospective adaptations are usually referred to as modifications and/or changes made to a SAP prior to database lock or unblinding of treatment codes. In practice, prospective, ad hoc, and retrospective adaptations are implemented by study protocols, protocol amendments, and statistical analysis plans with regulatory reviewer's consensus, respectively.

1.2.2 Type of Adaptive Designs

Based on the adaptations employed, commonly considered adaptive designs in clinical trials include, but are not limited to: (i) an adaptive randomization design, (ii) a group sequential design, (iii) an N-adjustable (or flexible sample size reestimation) design, (iv) a drop-the-loser (or pick-the-winner) design, (v) an adaptive dose finding design, (vi) a biomarker-adaptive design, (vii) an adaptive treatment-switching design, (viii) a adaptive-hypothesis design, (ix) an adaptive seamless (e.g., phase I/II or phase II/III) trial design, and (x) a multiple-adaptive design. These adaptive designs are all briefly described below.

1.2.2.1 Adaptive Randomization Design

An adaptive randomization design allows modification of randomization schedules based on varied and/or unequal probabilities of treatment assignment in order to increase the probability of success. As a result, an adaptive randomization design is sometimes referred to as a play-the-winner design since it will increase the probability of success. Commonly applied adaptive randomization procedures include treatment-adaptive randomization (Efron 1971; Lachin 1988), covariate-adaptive randomization, and response-adaptive randomization (Rosenberger et al. 2001; Hardwick and Stout 2002).

Although an adaptive randomization design could increase the probability of success, it may not be feasible for a large trial or a trial with a relatively longer treatment duration because the randomization of a given subject depends on the response of the previous subject. A large trial or a trial with a relatively

longer treatment duration utilizing adaptive randomization design will take a much longer time to complete. Besides, a randomization schedule may not be available prior to the conduct of the study. Moreover, statistical inference on treatment effect is often difficult to obtain due to the complexity of the randomization scheme. In practice, a statistical test is often difficult to obtain—if not impossible—due to complicated probability structure as the result of adaptive randomization, which has also limited the potential use of adaptive randomization design in practice.

1.2.2.2 Group Sequential Design

A group sequential design allows for prematurely stopping a trial due to safety, futility/efficacy, or both with options of additional adaptations based on results of interim analysis. Many researchers refer to a group sequential design as a typical adaptive design because some adaptations may be applied after the review of interim results of the study such as stopping the trial early due to safety, efficacy and/or futility. In practice, various stopping boundaries based on different boundary functions for controlling an overall type I error rate are available in the literature (see, e.g., Lan and DeMets 1987; Wang and Tsiatis 1987; Jennison and Turnbull 2000, 2005; Rosenberger et al. 2001; Chow and Chang 2006). In recent years, the concept of two-stage adaptive design has led to the development of the adaptive group sequential design (e.g., Cui, Hung, and Wang 1999; Posch and Bauer 1999; Lehmacher and Wassmer 1999; Liu, Proschan, and Pledger 2002).

It should be noted that when additional adaptations such as adaptive randomization, dropping the losers, and/or adding additional treatment arms (in addition to the commonly considered adaptations) are applied to a typical group sequential design after the review of the interim results, the resultant group sequential design is usually referred to as an adaptive group sequential design. In this case, the standard methods for the typical group sequential design may not be appropriate. In addition, it may not be able to control the overall type I error rate at the desired level of 5% if (i) there are additional adaptations (e.g., changes in hypotheses and/or study endpoints), and/or (ii) there is a shift in target patient population due to additional adaptations or protocol amendments.

1.2.2.3 Flexible Sample Size Reestimation Design

A flexible sample size reestimation (or N-adjustable) design allows for sample size adjustment or reestimation based on the observed data at interim. Sample size adjustment or reestimation could be done in either a blinding or unblinding fashion based on the criteria of treatment effect-size, variability, conditional power, and/or reproducibility probability (see, e.g., Proschan and Hunsberger 1995; Cui, Hung, and Wang 1999; Posch and Bauer 1999; Liu and Chi 2001; Friede and Kieser 2004; Chung-Stein et al. 2006; Chow, Shao, and Wang 2007). Sample size reestimation suffers from the same disadvantage as the original power analysis for sample size calculation prior to the conduct of the study because it is performed by treating *estimates* of the study parameters, which are obtained based on data observed at interim, as true values.

In practice, it is not a good clinical/statistical practice to start with a small number and then perform sample size reestimation (adjustment) at interim by ignoring the clinically meaningful difference that one wishes to detect for the intended clinical trial. It should be noted that the observed difference at interim based on a small number of subjects may not be of statistically significance (i.e., it may be observed by chance alone). In addition, there is variation associated with the observed difference that is an estimate of the true difference. Thus, standard methods for sample size reestimation based on the observed difference with a limited number of subjects may be biased and misleading. To overcome these problems in practice, a sensitivity analysis (with respect to variation associated with the observed results at interim) for sample size reestimation design is recommended.

1.2.2.4 Drop-the-Losers Design

A drop-the-losers design allows dropping the inferior treatment groups. This design also allows adding additional (promising) arms. A drop-the-losers design is useful in the early phase of clinical development

especially when there are uncertainties regarding the dose levels (Bauer and Kieser 1999; Brannath, Koening, and Bauer 2003; Posch et al. 2005; Sampson and Sill 2005). The selection criteria (including the selection of initial dose, the increment of the dose, and the dose range) and decision rules play important roles for this design. Dose groups that are dropped may contain valuable information regarding dose response of the treatment under study. Typically, drop-the-losers design is a two-stage design. At the end of the first stage, the inferior arms will be dropped based on some prespecified criteria. The winners will then proceed to the next stage. In practice, the study is often powered for achieving a desired power at the end of the second stage (or at the end of the study). In other words, there may not be any statistical power for the analysis at the end of the first stage for dropping the losers (or picking up the winners).

In practice, it is not uncommon to drop the losers or pick up the winners based on so-called *precision analysis* (see, e.g., Chow, Shao, and Wang 2007). The precision approach is an approach based on the confidence level for achieving *statistical significance*. In other words, the decision will be made (i.e., to drop the losers) if the confidence level for observing a statistical significance (i.e., the observed difference is not by chance alone or it is reproducible with the prespecified confidence level) exceeds a prespecified confidence level. Note that in a drop-the-losers design, a general principle is to drop the inferior treatment groups or add promising treatment arms but at the same time it is suggested that the control group be retained for a fair and reliable comparison at the end of the study. It should be noted that dose groups that are dropped may contain valuable information regarding dose response of the treatment under study. In practice, it is also suggested that subjects who are assigned in the inferior dose groups should be switched to the better dose group for ethical consideration. Treatment switching in a drop-the-losers design could complicate statistical evaluation in the dose selection process. Note that some clinical scientists prefer the term *pick-the-winners* rather than drop-the-losers.

1.2.2.5 Adaptive Dose Finding Design

The purpose of an adaptive dose finding (e.g., escalation) design is multifold, which includes (i) the identification whether there is a dose response, (ii) the determination of the minimum effective dose (MED) and/or the maximum tolerable dose (MTD), (iii) the characterization of dose response curve, and (iv) the study of dose ranging. The information obtained from an adaptive dose finding experiment is often used to determine the dose level for the next phase of clinical development (see, e.g., Bauer and Rohmel 1995; Whitehead 1997; Zhang, Sargent, and Mandrekar 2006). For adaptive dose finding design, the method of continual reassessment method (CRM) in conjunction with the Bayesian approach is usually considered (O'Quigley, Pepe, and Fisher 1990; O'Quigley and Shen 1996; Chang and Chow 2005). Mugno, Zhus, and Rosenberger (2004) introduced a nonparametric adaptive urn design approach for estimating a dose-response curve. For more details regarding PhRMA's proposed statistical methods, the reader should consult with a special issue recently published in the *Journal of Biopharmaceutical Statistics* (Vol. 17, No. 6).

Note that according to the ICH E4 guideline on *Dose-Response Information to Support Drug Registration*, there are several types of dose-finding (response) designs, which are (i) randomized parallel dose-response designs, (ii) crossover dose-response design, (iii) forced titration design (dose-escalation design), and (iv) optimal titration design (placebo-controlled titration to endpoint). Some commonly asked questions for an adaptive dose finding design include, but are not limited to (i) how to select the initial dose, (ii) how to select the dose range under study, (iii) how to achieve statistical significance with a desired power with a limit number of subjects, (iv) what are selection criteria and decision rules if one would like to make a decision based on safety, tolerability, efficacy, and/or pharmacokinetic information, and (v) what is the probability of achieving the optimal dose. In practice, a clinical trial simulation and/or sensitivity analysis is often recommended to evaluate or address the above questions.

1.2.2.6 Biomarker-Adaptive Design

A biomarker-adaptive design allows for adaptations based on the response of biomarkers such as genomic markers. An adaptive biomarker design involves biomarker qualification and standard, optimal screening design, and model selection and validation. It should be noted that there is a gap between