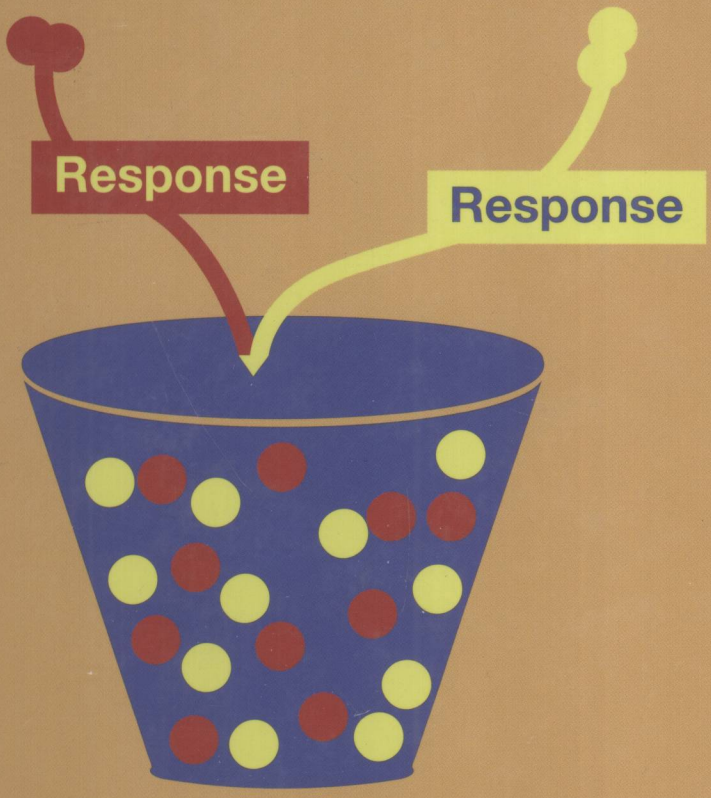
Mark Chang

Classical and Adaptive Clinical Trial Designs

Using ExpDesign Studio™



Includes the Professional Version 5.0 of ExpDesign Studio™ software

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CLASSICAL AND ADAPTIVE CLINICAL TRIAL DESIGNS USING EXPDESIGN STUDIO™

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PREFACE

Drug development is shifting from the classical approaches to more dynamic or adaptive approaches. The pharmaceutical industry and the U.S. Food and Drug Administration (FDA) has been seeking efficient methods of drug development as indicated in the FDA's critical path document. Many people believe that the innovative approach of adaptive design is a major pathway to success in drug development in today's challenging drug development environment.

In a book that I co-authored, *Adaptive Design Methods in Clinical Trials* (Chow and Chang, 2006), various adaptive design methods were introduced. Six months later I authored a second book, *Adaptive Design Theory and Implementation Using SAS and R* (Chang, 2007a), which provided in-depth and unified theory regarding adaptive designs and implementations, with many trial examples. These two books require a strong statistical background and clinical trial experience.

However, based on feedback from recent adaptive design workshops and conferences, I realize that there are many practitioners who are very good at strategic thinking and solution of practical problems but little interested in or lacking time to study the theory. Although I have kept the SAS and R program units as small as possible, with a clear logic flow from my previous books, there are still minimal requirements for knowledge of SAS or R. Also, many statisticians who are familiar with SAS would prefer to have software with a graphic user interface that can provide user-friendly tools for both classical and adaptive designs and monitoring. Among other options, I believe that ExpDesign Studio® fits the practical needs and provides a one-stop-shopping experience (CTriSoft, www.CTriSoft.net). This book, which avoids dealing with theory, is complementary to the two books mentioned earlier. Readers can jump-start to adaptive design without difficulty if they have one or two years of clinical trial design experience. However, for readers interested in the mathematical details, the mathematical notes at the end of each chapter will provide the key formulations for each method, or they can review *Adaptive Design Theory and Implementation Using SAS and R* (Chang, 2007a) for an in-depth understanding of the theory and algorithms for computer implementation.

ExpDesign is commercial software used by major pharmaceutical companies, universities, and research institutes worldwide. With ExpDesign you can design a classical or adaptive design literately in two minutes if you have the parameters ready. The ExpDesign enterprise version can also generate SAS and R code for an adaptive design.

The book has been written with practitioners in mind. It is not intended to teach adaptive design theory nor to function as a simple software user manual. The objective of the book is to demonstrate the use of ExpDesign in trial design, to assist strategic decision making, and to help solve issues related to classical and adaptive trials. It is written as a tutorial, a self-learning textbook (see the Self-Study and Practice Guide following the preface). Readers are expected to master the basic adaptive trial techniques in about one week. The book, together with the software, makes learning easy and fun. The accompanying software is a fully professional version of ExpDesign Studio 5.0, not a typical trial version. The book and the software, covering both classical and adaptive designs, can be used to leverage drug development in such a way that statisticians and other parties have more freedom and time to focus on the real issues, not the calculation or theory. The book is organized as follows:

In Chapter 1 we present an overview of the software ExpDesign Studio, provide a feeling for what it can do in trial designs, demonstrate simple design examples from classical, group sequential, adaptive, and other trials with ExpDesign Studio, and explain the basic operation of the software.

Chapter 2 provides an overview of a variety of clinical trial designs, their advantages and disadvantages, and when different classical and adaptive designs can be used.

Chapter 3 focuses on classical designs. After a discussion as to how sample size should be determined and on the variety of factors that affect the decision as to what sample size to use in a trial, examples are given on how to utilize ExpDesign to calculate sample size. Among nearly 150 sample-size calculation methods available in ExpDesign, the examples are carefully chosen to include a variety of designs, types of endpoints, and phases of clinical trials.

In Chapter 4 we discuss group sequential design (GSD), a commonly used and probably the simplest adaptive design. Starting with an overview of group sequential design, how to design and monitor a GSD trial using ExpDesign Studio is discussed. Finally, the key mathematic formulations for GSD are summarized for those interested in the mathematical details.

In Chapter 5 we discuss adaptive trial designs and introduce the stagewise test statistic and stopping rules. Interim analysis and trial monitor tools such as conditional power are described. We also discuss how to use ExpDesign Studio to design sample-size reestimation, drop-loser, biomarker-adaptive, response-adaptive randomization, and adaptive dose-finding trials. The mathematic formulations are summarized in the final section.

In Chapter 6 we discuss the specific design of early-phase oncology trials, because of its uniqueness. It includes multiple-stage single-arm design and dose-escalation design for maximum tolerated dose and show how to use ExpDesign to design oncology trials and how to compare and evaluate different designs based on their operating characteristics.

In Chapter 7 we focus on adaptive trial monitoring. The importance of trial monitoring and mathematic tools for monitoring is discussed, and how to use

the trial monitor in ExpDesign to monitor an adaptive trial is described in detail using real-world examples.

In Chapter 8 we present a computer simulation approach in which the test statistic is the same as the classical design. The simulation module in ExpDesign allows for any combinations of the following adaptations: early futility and/or efficacy stopping, sample-size reestimation, drop-loser, and response-adaptive randomization based on the dose–response relationship. Step-by-step instructions are presented with trial examples.

In Chapter 9 we discuss how to get further assistance from ExpDesign. ExpDesign provides many toolkits for design, monitoring, and analysis of trials: the graphical calculator, which allows you to plot complicated mathematical expressions, the probability calculator for probability and percentile calculations, and the confidence interval calculator for exact confidence interval calculations. For advanced users, we also discuss how to use ExpDesign to generate univariate and multivariate data that can be used for various purposes of trial design, monitoring, and risk assessment.

In Chapter 10 we present notes on technique for nearly 100 methods for sample-size calculation, grouped by the number of arms, the trial endpoint, and the analysis basis. We describe the purpose of each method, information about the methods, such as when and how to use each one, the formula and/or references, and the assumptions or limitations of the methods.

Appendix A is about validation of ExpDesign. Several reviewers have indicated the importance of software validation and suggested including the validation information in the book. The validation document is also meant to support pharmaceutical end users to meet FDA 21 CFR part 11 requirements.

Installation instructions for the software CD and the license agreement appear at the end of the pages.

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Lexington, Massachusetts
Winter 2007
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SELF-STUDY AND PRACTICE GUIDE

Day 1

- ExpDesign Studio 5.0 Installation (10 minutes)
- Chapter 1: ExpDesign Studio (30 minutes of reading and practice)
- Chapter 2: Clinical Trial Design (3 hours of reading)
- Chapter 3: Classical Trial Design (4 hours of reading and practice)
- Chapter 10: Classical Design Method Reference (15 minutes of reading)
- Appendix A: Validation of ExpDesign Studio (15 minutes of reading)

Day 2

- Chapter 4: Group Sequential Trial Design (8 hours of reading and practice) The classical group sequential design and simplest adaptive design are discussed. Make sure you understand the basic concepts of group sequential design, such as the notion of early stopping, error inflation due to multiple looks, different types of stopping boundaries, and different scales for stopping boundaries. Go through all the trial examples using ExpDesign; it helps you get "hands-on" experience. Trial monitoring requires your effort, which will give you the feeling of running an actual group sequential trial.

Days 3

- Chapter 5: Adaptive Trial Design (8 hours of reading and practice)
- You will learn various adaptive designs. Make sure that you understand the three commonly used statistical methods. Again, go through the trial practice using ExpDesign for hands-on experiences. The practices are straightforward and should take no more than 20 minutes each.

Day 4

- Chapter 6: Adaptive Trial Monitoring (8 hours of reading and practice) Adaptive trial monitoring can be considered as the most challenging part

of this book. It is about how you make actual adaptations for an ongoing trial based on the design without undermining the validity and integrity of the trial. Play around with the trial examples using ExpDesign, and spend extra time if needed.

Day 5

- Chapter 7: Oncology Adaptive Trial Design (5 hours of reading and practice)
- Chapter 8: Adaptive Trial Simulator (2 hours of optional reading and practice)
- Chapter 9: Further Assistance with ExpDesign Studio (1 hour of reading and practice)

The mathematical notes in Chapters 3, 4, and 7 are not meant to be studied in your first reading; rather, they are for future reference. Similarly, Chapter 10 and Appendix A can be read as needed.

CONTENTS

1 ExpDesign Studio

1.1 INTRODUCTION

ExpDesign Studio (ExpDesign) is an integrated environment for designing experiments or clinical trials. It is a powerful and user-friendly statistical software product that has seven integrated main components: classical design (CD), sequential design (SD), multistage design (MSD), dose-escalation design (DED), adaptive design (AD), adaptive trial monitoring (ATM), and dose-escalation trial monitoring (DTM) modules. In addition, the ExpDesign randomizor can generate random variates from a variety of distributions. The ExpDesign toolkit provides features for distributional calculation, confidence intervals, and function and data plotting (Figure 1.1).

Classical trials are the most commonly used in practice. ExpDesign provides nearly 150 methods for sample-size calculations in CD for different trial designs. It includes methods for single-, two-, and multiple-group designs, and for superiority, noninferiority, and equivalence designs with various endpoints. See the list of classical design methods in Appendix B.

Group sequential trials are advanced designs with multiple analyses. A group sequential trial is usually a cost-effective design compared to a classical design. SD covers a broad range of sequential trials with different endpoints and different types of stopping boundaries.

A multistage design is an exact method for group sequential trials with a binary response, whereas group sequential design uses an asymptotic approach. MSD provides three optimal designs among others: MinMax, MinExp, and MaxUtility, which minimize the maximum sample size, minimize the expected sample size, and maximize the utility index, respectively.

A dose-escalation trial in aggressive disease areas such as oncology has unique characteristics. Due to the toxicity of the testing drug, researchers are allowed to use fewer patients to obtain as much information as possible about the toxicity profile or maximum tolerable dose. By means of computer simulations, DED provides researchers with an efficient way to search for an optimal design for dose-escalation trials with a variety of criteria. It includes traditional escalation rules, restricted escalation rules, two-stage

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