

# Preface

A great deal of progress has been made in the past couple of decades with regard to research and publications focused on technical and methodological aspects of planning and analyzing adaptive design. The major impetus behind the interest in the use of adaptive designs is the increased efficiency they offer, resulting in savings of cost and time, ultimately getting drugs to patients sooner. However, the adoption of adaptive designs in clinical development has been relatively low, approximately 20 % in recent years, according to a survey conducted by Tufts Center for the Study of Drug Development. One of the chief reasons for this has been the increased complexity of adaptive trials compared to traditional trials. Barriers, some perceived and some real, to the use of clinical trials with adaptive features still persist, and these may include, but are not limited to, the concerns about the integrity of study design and conduct, the risk of regulatory acceptance, the need for an advanced infrastructure for complex randomization and clinical supply scenarios, change management for process and behavior modifications, extensive resource requirements for the planning and design of adaptive trials, and the potential to relegate key decision makings to outside entities (such as Data Monitoring Committees). There have been limited publications on practical considerations and recommendations on adaptive trial designs and suggestions regarding best practices and solutions on implementation to address these real or perceived barriers.

This book aims to fill this publication void and serves as a resource for trialists who wish to consider adaptive trials in their clinical development programs, providing them with guidance on practical considerations for adaptive trial design and implementation. The target audience is anyone involved, or with an interest, in the planning and execution of clinical trials, in particular, statisticians, clinicians, pharmacometricians, clinical operation specialists, drug supply managers, infrastructure providers working in academic or contract research organizations, government, and industry. Our goal for this book is to provide, to the extent possible, a balanced and comprehensive coverage of practical considerations for adaptive trial design and implementation.

This book is comprised of three parts: Part I focuses on practical considerations from a design perspective, Part II delineates practical considerations related to the implementation of adaptive trials, and Part III presents a rich collection of practical case studies.

Part I includes a total of ten chapters. Chapter 1 discusses the need for and the future of adaptive designs in clinical development. Regulatory guidance documents on adaptive designs have been released by the European Medicines Agency (EMA) and US Food and Drug Administration (US FDA). Chapters 2 and 3 discuss key points in these two guidance documents from industry and regulatory perspectives, respectively. Improving clinical development efficiency starts at the program level. To provide trialists with the tools to strategically consider their clinical development plans, Chap. 4 describes adaptive program concepts and illustrates the efficiency of complex strategies for clinical program development through a case study, while Chap. 5 provides optimal Go/No Go decisions for clinical development. To provide guidance to practitioners on key issues associated with interim analyses, Chap. 6 presents a comprehensive and balanced discussion on optimal timing and frequency of interim analyses, including logistic and regulatory considerations. Adaptive design approaches provide greater efficiency, as compared to traditional design approaches, with regard to dose finding and optimal dose selection. The main statistical methods available for planning and analysis of adaptive designs in Phase I, II, and III are covered in Chap. 7. Chapter 8 provides a review of currently available simulation software tools, discussing detailing their specific features. Often evaluation of an adaptive design approach for a trial requires careful examination of randomization needs. Randomization challenges in adaptive design trials, and randomization techniques that help addressing these challenges, are described in Chap. 9. Chapter 10 discusses response-adaptive randomization, including regulatory concerns and recommendations for the path forward.

As reported in the DIA Adaptive Design Scientific Working Group (ADSWG) 2012 survey, the key barriers for the broader adoption of adaptive trials in clinical development include the lack of experience with and knowledge in the implementation of adaptive designs, along with a lack of appropriate processes and infrastructure to support efficient trial execution. Part II of the book deals with these issues in Chaps. 11 through 16. Chapter 11 highlights operational challenges that must be taken into consideration when conducting an adaptive trial and provides strategies for efficient execution of an adaptive design trial. Similarly, Chap. 12 illustrates various operational challenges via a case study, while Chap. 13 discusses logistic and operational challenges with a focus on IT and infrastructure improvement. A particularly critical issue for adaptive clinical trials, with potentially great impact on how large a role this type of studies will play in confirmatory stages of clinical development, involves the processes by which accruing data are collected and analyzed, and adaptation decisions are made and implemented. Chapter 14 discusses who should be involved in data review for adaptation decisions, how the data flow and access to results should be controlled, and the specific role that Data Monitoring Committees might play in this process. Drug supply and patient recruitment play critical roles in the ultimate success of adaptive trial execution. Chapters 14, 15, and 16 cover,

respectively, the roles that modeling and simulation may play in successfully planning and carrying out clinical supply and patient recruitment strategies.

Putting it all together, Part III, featuring Chaps. 17 through 20, presents four illustrative case studies ranging from description and discussion of various specific adaptive trial design considerations to the logistic and regulatory issues faced in trial implementation. The solutions to practical challenges and recommended best practices, along with the rest of the chapters in the book, should equip clinical trialists with the much needed toolkit to embark on their journey to efficient adaptive trial design and implementation.

We would like to express our sincerest gratitude to all of the contributors who made this book possible. They are the leading experts in adaptive trial design and implementation from industry, regulatory and academia. Their in-depth discussions, thought-provoking considerations, and abundant advice based on a wealth of experience make this book unique and valuable for a wide range of audiences. We hope that you will find this book helpful as well. We would also like to thank Marc Strauss of Springer Science and Business Media for giving us the idea for this book and for providing us with the opportunity for publication. Thanks also go to Jonathan Gurstelle and Hannah Bracken, both of Springer Science and Business Media, for their patience and help in guiding us through the production phase of the book. Finally, our immense thanks go out to our families for their unfailing support.

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