Introduction to Adaptive Trial Designs and Master Protocols
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Preface

When we think of clinical trials, we mostly imagine ‘one shot’ two-arm trials. These conventional trials evaluating a single intervention against placebo or some standard-of-care as a control group are designed with a fixed sample size that is predetermined at the design stage based on a variety of assumptions, and the statistical analysis occurs once after the recruitment reaches this predetermined target. There are other approaches to clinical trials that can broadly be classified into two methods of ‘adaptive trial designs’ and ‘master protocols’.

Adaptive trial designs refer to a type of design that allows for pre-specified modifications to trial designs during the trial in response to accumulated trial data. For many research questions, by being able to respond to the trial data mid-trial, adaptive trial design can have important efficiencies over fixed sample trial designs. Master protocols refer to a single overarching protocol designed to answer multiple interventional questions. The framework of master protocols aims to create a common trial infrastructure in which multiple interventions can be evaluated using the standardised rules that are outlined in the protocol. Instead of two-arm conventional trials, the master protocol framework aims to reduce the need for redundant clinical trials and enable multiple interventions and hypotheses to be tested by bringing a collaborative approach to clinical trial research.

In this book, we hope to assist investigators to gain confidence and a clear understanding of adaptive trial designs and master protocols. This book is intended for those with minimal background in clinical trial research and to help readers grasp strengths and limitations of these novel designs and apply them to their own areas of research and clinical practice. For those who plan to conduct clinical trial research over a long period of time, this book is intended to be read before tackling other technically oriented books or papers for further methodological development and implementation.

Introduction to Adaptive Trial Designs and Master Protocols is divided into five parts. In Part I, we define the concepts of clinical research, clinical trial phases, and randomisation and summarise conventional approaches to clinical trials research. The concept of exploratory research (hypothesis-generating research) and confirmatory research (hypothesis-confirming research) is discussed, since the appropriateness of a specific research design depends on the type of research question that is being asked. Before more detailed discussion of adaptive trial designs and master protocols occurs, it is important that the reader gain an understanding of concepts including p-values, statistical power, and other relevant concepts in frequentist and Bayesian statistics. An overview is given in the first chapter to help bridge the gap for readers less familiar with any of these topics.

Part II introduces the reader to the basic ingredients of adaptive trial designs. Before having a more elaborate discussion of how adaptive trial designs in trials being conducted under the master protocol framework, it is important to understand the principles of adaptive trial designs and their common types. As more planning is required in adaptive trial designs relative to traditional trial designs through extensive clinical trial simulations, it is important for the reader to understand how simulations work and are used to come up with decision rules and other features of adaptive clinical trials.
In Part III, the key attributes of the concept of master protocols and their sub-categories (basket trials, umbrella trials, and platform trials) are introduced and differentiated from adaptive trial designs for the reader. Some master protocol trials may be designed with fixed sample designs, so it is important to distinguish the concept of master protocols from adaptive trial designs. Basket trials and umbrella trials are compared and contrasted, as students often mistake one for the other. Adaptive platform randomised trials, also known as multi-arm, multi-stage designs, are introduced and compared to other types of adaptive trial designs.

Part IV is intended to improve the reader’s ability to comprehend and critically appraise published results of clinical trials that are designed using adaptive trial designs and master protocols. Thus, this section is dedicated to the discussion of published case studies of adaptive clinical trials, basket trials, umbrella trials, and platform trials. In this section, general guidelines on what to look for when reading results or a proposal of adaptive clinical trials and master protocols is provided as well as specific guidelines for common types of adaptive trial designs and master protocols.

Part V introduces the reader to common misconceptions and practical considerations for adaptive trial designs and master protocols. Common misconceptions about adaptive trial designs and master protocols are discussed here to differentiate and clarify the issues that are specific to these novel designs as opposed to those that apply to any clinical research. The practical considerations regarding funding and implementation of clinical trials using adaptive trial designs and master protocol frameworks are drawn from the authors’ personal professional experience.

Each chapter is written to be as self-contained as possible. There are introductory summaries of the chapter mission statement and chapter goals. Where applicable, there are three to five bullet point summaries of the material provided in each chapter.
About the Authors

Jay J. H. Park is a trained Clinical Trialist with expertise in adaptive trial designs and master protocols. He holds a faculty position in the Department of Health Research Methods, Evidence, and Impact within the Faculty of Health Sciences at McMaster University. At McMaster University, he teaches HRM 732, the first available graduate-level course on adaptive clinical trial design and master protocols.

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