
Planning Clinical Research

This book teaches how to choose the best design for your question. Planning a clinical study is much more than deciding on the basic study design. Who will you be studying? How do you plan to recruit your study participants? How do you plan to retain them in the study? What data do you plan to collect? How will you obtain this data? How will you minimize bias? All these decision must be consistent with the ethical considerations of studying people.

Drawing on their many years working in clinical research, Robert A. Parker and Nancy Greene Berman guide readers through the essential elements of study planning to help get them started. The authors offer numerous examples to illustrate the key decisions needed, describing what works and what does not work, and why. Written specifically for junior investigators beginning their research careers, this guide will also be useful to senior investigators needing to review specific topics.

Dr. Robert A. Parker has been a consulting biostatistician for nearly 40 years. He has worked in academia, medicine, industry (a Top 25 global pharmaceutical company), and government (World Health Organization; US Centers for Disease Control). In industry, he was the arbiter of statistical methods for more than 100 statisticians at the company that employed him. Having worked with junior investigators for most of his professional life, he is dedicated to mentoring the next generation of medical researchers. This book reflects his passion to train junior investigators in the art of clinical research.

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To Laurie, for everything (R.A.P)
To my family (N.G.B)

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Preface

This book is entitled *Planning Clinical Research*. We call it “planning” because much of what we do is not the design – in the strict statistical sense – but the overall planning of a study. This includes, of course, the actual design of the study, but planning begins much earlier, with the initial decision: What questions will you ask and how will you ask them? The questions you ask have an impact on the basic design – can you do an interventional study or not? What type of interventional study are you using? Or must you do some type of observational study? But planning a study is much more than choosing the basic design. So even if you have decided on the design (say, a randomized, double-blind, placebo-controlled parallel group study [see Chapter 5 for more about this]), you still need to plan all the details of the study. Who will you be studying? How do you plan to recruit them? How do you plan to retain them in the study? What data do you plan to collect? How will you obtain this data? How will you minimize bias in all aspects of the study? All these decisions must be consistent with the ethics of studying people. This book will help you understand these questions, gain insight into approaches to making these decisions, and understand some of the ethical problems involved in clinical research.

This book is intended to provide the essential concepts and elements of study planning to help you get started. Although we occasionally mention analysis techniques, our focus is on what to do before you have started collecting data. We tried to anticipate the needs of junior investigators who are beginning their research careers, but we hope the book will also be useful for more senior investigators needing to review a specific topic.

To do this, we have used a lot of examples. Often examples are presented multiple times, with refinements or additional information, reflecting how we actually plan a real study. We consider options and keep refining them as we develop the study. We have found that it is best to sketch out options rather than to write out a detailed plan. It seems that once a lot of effort has been put into writing the detailed plan, it becomes an anchor, and making changes to the basic plan becomes very difficult – even when other alternatives are better. We urge you to limit your plan to a single page – preferably a bulleted list – to keep your mind open about possible changes until you really have fully defined the study and have obtained critiques on the idea, so that you are open when a suggestion is made for a radical revision. If you remember nothing else from this book but that you need to always be thinking about refining your design and sharing the plan with your colleagues and (most importantly) actually considering the suggestions they make, we have helped you.

The book is organized in 6 parts containing a total of 30 chapters and 2 appendixes. The organization of the book reflects the basic organization of the research protocol for a study. A study is any systematic investigation intended to answer a question. Since our focus in this book is on clinical research, the questions answered will involve people. However, much of the material, particularly for the design of interventional studies and control of bias, applies to all biological research, whether molecular pathways, cell cultures, or animal studies. The book is not intended to be read cover-to-cover, but rather for you to dip into it as needed.

Clinical studies can only begin after approval by your local Institutional Review Board (IRB), also called an Institutional Ethics Committee (IEC). Thus, Part I of the book (Chapters 1–3) is an introduction to both the fundamental questions you should be asking yourself and ethics and consent issues in clinical research. Some readers may feel that Chapter 1 is quite pretentious. Most statisticians feel that this is the heart of what we do. We discuss ethical issues at length in Chapters 2 and 3. These issues are so fundamental to clinical research that we end each subsequent chapter with a brief discussion of the ethical issues that are relevant to the technical material in the chapter.

The research protocol provides the IRB with the information it needs to decide whether to approve your study. There are many components of the protocol, including the aims of the study, background as to why the study is needed, and the basic study design. Part II of the book (Chapters 4–10) is intended to help you determine the appropriate design for your study. We recommend that all readers read Chapter 4, which provides an overview of all the designs discussed. Then, if you think you are doing an interventional study (meaning that you are doing something to the participants and seeing what happens), you would probably want to go to Chapter 5 for more details of the different types of interventional designs possible. If you are considering an observational study, you would probably want to go to Chapters 6–8, selecting the appropriate one(s) based on the overview material in Chapter 4. We know that many readers may be planning to do record reviews. Although Chapter 9 does discuss this, the chapter – and the design of your record review – will make much more sense to you after reading Chapters 6, 7, or 8, depending on the design used for the record review. Finally, Chapter 10 attempts to synthesize how to select the basic design to be used for your study.

Your protocol also needs details about the participants being studied, the types of data being collected, and how you are intending to control bias. Part III (Chapters 11–18) discusses a number of core concepts that we believe apply across all study designs. These include such basic ideas as generalizability and validity (Chapter 11), practical issues about recruiting and retaining participants (Chapters 12 and 13), the types and uses of data that you will be collecting (Chapters 14–16), and bias and methods to avoid it (Chapters 17 and 18).

Depending on the study design, additional details are needed. Parts IV and V help with these details. Part IV (Chapters 19–24) discusses practical issues relevant to interventional studies, such as how one actually defines the intervention (Chapter 19), how one actually does randomization (Chapters 20 and 21), the hierarchy of blinding and how one does it (Chapters 22 and 23), and how to improve participant adherence (Chapter 24). Part V (Chapters 25–28) discusses the practical issues for observational studies, such as identifying appropriate populations for cohort studies (Chapter 25) or case-control studies including matching (Chapters 26 and 27) and blinding in observational studies (Chapter 28).

The last part (Chapters 29 and 30) discusses the practical issue of data collection methods and data quality.

Two appendixes complete this volume. One discusses the basic ideas behind hypothesis testing, while the second discusses the ideas underlying calculation of an appropriate sample size. A word of warning on this last part of the book: We do not provide formulas, but there are formula in the supplementary material on the book's website (www.cambridge.org/9780521840637) to help you understand sample size calculations and links to appropriate software.

Our examples may reflect real studies we have read, studies planned with colleagues but never done, studies that were completed or may have been completed by the time you read this book, or studies invented solely to make a specific point. We do not include references to any real examples since we have abstracted what we consider the key features illustrating the design point we are trying to make and never present results. Moreover, we often have presented wrong decisions or used hyperbole in the descriptions to help make our point clear.

Of course, just reading a book will not make you an expert in study design or planning. You need to find some mentors – experienced investigators who can help you become a better investigator. We would also recommend that you identify a statistician to work with in developing your study plan.

Given our focus on the ethical aspects of all the topics discussed in the book, although the term “subject” has been used historically for participants in research studies, throughout the book we use terms such as “participant” or “individual” to remind us that the “*subjects*” are *human beings*, with their own rights and needs. You never have the right to use, or treat, or think of participants as objects in your research.

To you, our reader, and all your staff and associates, we wish success as a researcher.

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I thank all the investigators I've worked with, and all the students who have taught me so much. It has been a pleasure working with you.

(R.A.P.)

I would like to thank my husband, Arnold Berman, and our children for their encouragement and support as I worked on this book. I also would like to thank the many investigators who I have worked with both in Washington and at the Harbor-UCLA Medical Center for giving me insight into the investigators' needs in planning clinical studies and providing me with interesting studies to work on.

(N.G.B.)