1

PRELIMINARIES

LEARNING OBJECTIVES

1. Understand audiences and scope for this book
2. Learn a few additional sources for information about clinical trials
3. Understand basic clinical trials terminology and its limitations

1.1 INTRODUCTION

The best time to contemplate the quality of evidence from a clinical trial is before it begins. High-quality evidence about effects of a new treatment is a consequence of good study design and execution, both of which result from careful planning. This book emphasizes that philosophy and presents methods needed in planning, designing, conducting, analyzing, and assessing clinical trials. The goal is always to improve evidence derived from these important studies. Topics discussed here include many that find general agreement among methodologists and others that are contentious. It is unlikely that a reader experienced with clinical trials will agree with everything that follows or how it is emphasized, but my perspective should be mainstream, internally consistent, and useful for learning.

Much of what is written about clinical trials tells us *what* to do. As a result, many investigators, sponsors, and regulators become proficient in standard practice, perhaps to a point that they view it as restrictive. Not as much literature explains *why* we do what is recommended. Knowing only what to do creates patterned thinking, whereas knowing why we do it allows appropriate creative exceptions and coping with atypical circumstances. I try throughout this book to emphasize rationales for what we do in clinical trials and discourage patterned thinking. This challenges dogma and traditions that many young investigators have received from their older colleagues. This book will not stereotype and validate impressions gathered from imperfect cultures of clinical investigation that exist nearly everywhere. This book intends to teach foundational principles and their sometimes complicated implications so that the sublime, ordinary, and absurd in clinical trials become more clear. I will discard cherished perspectives if they lack a strong scientific basis, as some do.

This book is not an introduction to clinical trials and has evolved to become more technical and lengthy as it has been updated over many years. Even so, I am aware from colleagues that portions of it have found their way into

Clinical Trials: A Methodologic Perspective, Fourth Edition. Steven Piantadosi.

Companion website: www.wiley.com/go/Piantadosi/ClinicalTrials4e

didactics for beginning students of clinical trials. This book was first written for a single quarter postgraduate course for an audience with quantitative skills and therapeutic focus. It assumed that students had completed a formal didactic introduction to clinical trials and a basic postgraduate series in biostatistics. That seems like a lot of territory today. The first edition evolved over a dozen years by merging a course in experimental design with one on clinical trials. A second edition was the result of seven additional years of teaching and concomitant changes in the field. A third edition incorporated changes and needs from another 8 to 10 years of evolution. This fourth edition, which will be my final, attempts to take a long view.

An unresolved problem in teaching clinical trials is how to separate introductory versus advanced topics. Few issues in clinical trials are one or the other. Advanced means going into more depth regarding a familiar or basic topic. For example, ethics of human subjects research is taught as a foundation topic to all investigators, for good reason. But ethics also has nearly endless depth. Randomization is another easily approachable foundational subject. Yet it also has technical and logistical advanced aspects. So it goes with nearly every topic in clinical trials. Hence, most subjects in this book will show both basic and advanced perspectives.

1.2 DECONSTRUCTION

Students of clinical trials, in classrooms especially, always want topics deconstructed in a way amenable to short summaries or notes—essentially the antithesis of this book. Condensations are not sufficient for learning about trials. Consider some apparent laws of nature for clinical trials in no particular order:

1. Every constraint on a clinical trial increases cost and complexity.
2. A clinical trial is an experiment with human subjects.
3. An experiment is observation under conditions controlled by an observer.
4. Statistical science is relevant to all sciences.
5. A doctor–patient relationship is not the same as an investigator–subject relationship.
6. Clinical trials cannot draw representative samples from any population.
7. Clinical trials test treatment policy, not treatment.
8. Discarding subjects when a clinical trial ends moves further away from, not closer to, relevant clinical questions.
9. Successful development relies more on therapeutic ideas and less on trial design.
10. No strong treatment effect has ever been missed by traditional trial design.
11. Shared biology is more relevant than empirical representation.
12. Power of a trial cannot be separated from effect size or sample size.
13. Two opposing design quantities are likely to be connected by an inverse square law.
14. Your lifetime false-positive error rate is 100%.
15. Virtuous analyses cannot correct design flaws.
16. Scientists believe weird things as readily as non-scientists do.
17. Confirmation bias is the mother of all biases.
18. Convenient data analysis cannot replace designed data production.
19. Technology improves clinical trials faster than it makes them obsolete.
20. Randomization does not guarantee balance, but does assure a valid test of the null.
21. Randomization controls selection bias and unknown confounders.
22. *P*-values do not represent evidence.
23. Middle development is not at fault for late development failures.
24. Predevelopment clinical trials rely on biological models of disease and treatment.
25. Incremental improvement is slow and reliable; designed data production is fast and reliable.
26. Placebo effects are real and strong, but may be extraneous to intended objectives of a trial.

Many more could be stated, but these are representative. If every one of these points feels solid and true in your soul, you may not need to spend hours with this book. But if some seem unfamiliar, controversial, or do not ring true, read on.

1.3 A CLINICAL TRIAL IS A TEST OF TREATMENT UNDER CONTROLLED CONDITIONS

For many years it did not appear necessary to formally define a clinical trial: everyone seemed to understand implicitly. A formal definition for purposes of design and methods is offered in Section 2.3.2 and detailed characteristics are in Chapter 8. Presently there seems to be confusion or piracy in what is labeled as a clinical trial. I once read a manuscript partly titled *clinical trial* that described a study without any biological subjects. Reviewing history of the twenty-first Century Cures Act that gave impetus to a *real-world evidence* movement, we find clinical trials explicitly excluded from the real world. Section 505F(b) of the Act defines real-world evidence as

> data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional clinical trials [663, 1965].

Amazingly, the government defined *evidence* explicitly as *data*, and pointedly not from clinical trials. This problem is discussed further in Section 30.2. In recent years, NIH has promulgated its own definition *to enhance its stewardship over clinical trials* [1457]. NIH's definition requires extensive footnotes which might indicate another problem. Further discussion is in Section 2.3.2.

It is obvious that some bureaucrats should not be defining scientific terms. So it seems best to state early what a clinical trial is, which is simply the title of this section. *Treatment* is meant broadly, so instincts about it are appropriate. Obvious implications of *controlled conditions* will also suffice for now. At a minimum they imply scientific observation. A controlled condition might also imply an internal comparator.

Missing from this early minimalist definition is the word *human*. For now we can take human to be redundant with *clinical*. But a broader question is if a clinical trial is restricted to human subjects. Perspectives in this book will be strictly on human trials. Some tests of therapy in non-human subjects with spontaneous disease are described as clinical trials: for example, comparative oncology treatments for cancer in dogs. Such studies are not discussed here. An important implication here is that clinical trials are experiments with human subjects. Because this gets directly into Chapter 8, further discussion will be presented there.

1.4 AUDIENCE

Intended audiences for this book include both medical and statistical professionals early in their clinical research careers. Each component audience presents a certain dilemma. This book assumes a working knowledge of basic biostatistics. It is not possible to get beyond superficial ideas of clinical trials without statistics. It is helpful if readers understand some more advanced statistical concepts, including methods of inference, error control, lifetables, survival models, and likelihoods. Clinicians often lack this knowledge. However, modern clinical researchers are often seeking this quantitative background through formal training in clinical investigation methods and experimental therapeutics.

Biostatistics professionals need some minimal clinical knowledge to understand concepts in this book. A non-clinical view of clinical trials is incomplete. Principles of clinical research are necessary, including some basic human biology, application specific biology, research ethics, therapeutic developmental paradigms, clinical terminology, and ideas of clinical pharmacology. Eventually for a clinical trials biostatistician, immersion in a disease-oriented discipline will be vital to make substantive collaborative contributions and to identify and solve relevant methodological problems. While immersion is good for a biostatistician, exposure to more than one clinical discipline is even better.

A mixture of basic and advanced discussion results from this diverse target audience as well as from the nature of clinical trials. Classes that I teach using this book typically contain a mixture of biostatistics graduate students, medical doctors in specialty or subspecialty training (especially working toward a degree in clinical investigation), and other health professionals training to be sophisticated managers or consumers of clinical trials. A composite audience needs breadth and clarity in how the subject is presented. This book should be supplemented with lecture and discussion, and possibly a computer lab. Some exercises and discussion questions are provided with each chapter. Most are intentionally made open ended, with a suggestion that students answer them using a short memorandum, as though providing an expert opinion to less experienced investigators.

In short, this book targets clinical trialists, a difficult phenotype to define. Operationally, a clinical trialist is someone whose career is focused on trials as a science. A trialist uses investigational methods across disciplinary boundaries, as compared to a specialist who might perform some trials in a single domain. Being true interdisciplinary experts, trialists

can emerge from various sources: (i) quantitative or biostatistical, (ii) administrative or managerial, (iii) clinical, or (iv) ethics. Students can effectively approach this subject from any of these perspectives. Eventually however, a mature trialist will be conversant with important details from all foundational fields.

It is common today for rigorous trialists to be strongly statistical. This is because of an ongoing rapid recent pace of methods for clinical trials coming from that field, and because statistics pertains to all disciplines in which trials are conducted (or all of science for that matter). However, this book does not neglect other viewpoints essential to understanding trials. Many examples relate to cancer because that is the primary field in which I work, but concepts generalize to other areas. Studying trials in different clinical disciplines is a good device for understanding principles. Unfortunately many institutional structures and collaborations inhibit this.

Scientists who specialize in clinical trials are frequently dubbed *statisticians* by clinical colleagues. I will sometimes use that term with one warning regarding rigor: statistics is an old and broad profession. There is imperfect correspondence between statisticians or biostatisticians and knowledge of clinical trials. However, trial methodologists, whether statisticians or not, are likely to know a lot about biostatistics and will be accustomed to working with statistical experts. Many trial methodologists are not statisticians at all, but evolve from epidemiologists or clinicians with a strongly quantitative orientation, as indicated above. There are many excellent clinical trialists whom statisticians would label *physicians*. Stereotyping is not important—the subject has many doorways.

In recent years, many biostatistics professionals have gravitated toward bioinformatics, data science, computational biology, or high-dimensional data. I will not take space here to define these terms or distinguish them from research informatics or (bio-)medical informatics but simply point out that many biostatisticians have no experience with clinical trials. Technologies are of high value, but each waxes and wanes with limited impact on methods of therapeutic comparison.

Principles of valid comparisons in medicine have evolved over a millennium, and especially the recent century. Those principles have not been altered by the phenomenal ongoing scientific and technological advances during that period of time. Revolutions such as germ theory, drug development, anesthesia and surgery, immunology, genomic science, biomedical imaging, nutrition, computerization, and many others of history have not diminished foundational needs of medicine to assay treatments fairly. In fact, as new revolutions integrate themselves into scientific medicine, need for fair therapeutic comparison expands while principles for doing so remain constant.

1.5 SCOPE

This work attempts to emphasize principles common to all types of trials: translational, developmental, safety, comparative, and large-scale studies. My belief is that it is more helpful to learn about similarities among trials rather than differences. However, distinctions are unavoidable and some discussion is tailored to specific types of studies. Other distinctions are artificial and will be minimized. Various clinical contexts also treat trials differently, a topic discussed in Chapter 4.

There are many important aspects of clinical trials not covered here in any detail. These include administration, governance, funding, conduct, quality control, and infrastructure necessary to conduct trials. These topics might be described as trial technology, whereas my intent is to focus on trial science. Fortunately there are excellent sources for technology supporting trials. No book or course can substitute for regular interaction with a trial methodologist when conducting a clinical investigation. Passive reliance on such consultations is unwise, but true collaborations between clinicians and trialists will result when both are continually engaged. Although many clinicians think of bringing their final data to a statistician, a collaboration will be most valuable when designing a study at which time an experienced trialist could prevent serious methodologic errors, create efficiencies, and help avoid mistakes of inference.

Modern computing and software systems benefit clinical research, but can also present dangers. Although computers facilitate efficient, accurate, and timely keeping of data, systems also permit or encourage researchers to produce statistical reports without much attention to study design, and without fully understanding assumptions, methods, limitations, and pitfalls of procedures being employed. An illustration of this is in the aforementioned call for real-world data to supplement or supplant clinical trial evidence. Such data come from transactional (cash register) health records. Those records are electronic, not unlike how a photocopy of a document is electronic. They are made convenient by modern computing systems and data warehouses but usually comprise unstructured and noninteroperable data. Data are not fit for purpose merely because they are convenient.

Similarly a person who knows how to run procedure packages on data may be called a statistician even though they might be a novice in basic theory of analyses. It then becomes possible to produce a final report of a study without investigators understanding study execution, limitations of analysis, and without an analyst being conversant with data. What a weak chain that is!

An additional warning about technology limits is necessary: there is no computerized *summary* of clinical data that can assure its correctness. Inspection via a computer-generated printout of data values by a knowledgeable investigator can help reassure that gross errors are at a low frequency. But when data are collapsed, re-coded, tabulated, transformed, summarized, or otherwise aggregated by computer, errors will be hidden. Orderly looking summaries do not assure correctness of underlying data.

Ideas in this book are intended to assist reliability, not by being old fashioned but by being rigorous. Good design inhibits errors by involving an expert statistical collaborator at study inception. Most aspects of trials will improve as a result, including data reliability, resource utilization, quality assurance, precision, and scope of inference. Good design can also simplify analyses by reducing bias and variability and removing influences of irrelevant factors. Number crunching becomes less important than expert statistical data production.

Students of clinical trials should understand that a picture of good methodology today may soon change. Designing trials to use biomarkers and genomics data effectively is one area of evolution. Change is also evident in analytic methods more than in design where fundamentals change slowly. Analysis methods depend on new statistical developments which in turn depend on (i) computing hardware, (ii) reliable and accessible software, (iii) training and re-training of trialists to use new methods, (iv) acceptance by statistical and biological communities, and (v) sufficient time for innovations to diffuse into practice.

It is equally important to understand what changes or new concepts do not improve methodology, but come forward in response to nonscience issues or because of creeping regulation. One example of this is the sacrifice of expertise in favor of objectivity in clinical trial monitoring (discussed in Chapter 18). Well-meaning practices may be promulgated by sponsors without peer review or national consensus.

Good trial design requires that we examine many alternatives that can reliably answer a question. Complex designs especially create alternatives and should be studied via operating characteristics before being implemented. This topic is discussed in Chapter 25. Common errors related to trial design are devoting insufficient resources or time, rigidly using standard types of designs when better or more efficient methods are available, or undoing benefits of good design with poor execution or analysis. I hope that readers of this book will come to understand where there is much flexibility in design and analysis and where there is not.

1.6 OTHER SOURCES OF KNOWLEDGE

Journal literature related to clinical trial methods is extensive but easily accessible via internet searches. A considerable volume of methodology appears in clinical journals. Some useful internet resources are listed in Table 1.1. Internet sources are not static and are therefore not optimal references for a book of this type—links provided herein may not be valid for long. However many documents important for clinical trials can be found online with simple search terms. Most such documents are not reproduced here because they can be easily located. Government-sponsored web pages tend to be stable but many move, as do relevant documents.

A huge number of publications deal with clinical trials methods: this sketch is incomplete. Early discussions of clinical trial methods in journals were given by Hill [931] and Lasagna [1175]. A classic text by Meinert [1349] is recently updated and takes a practical view of the organization, infrastructure, and administrative supports necessary to perform multicenter randomized trials. Additional advice comes in a handbook by the same author [1347]. In fifth edition as of 2015 is a book by Friedman et al. [723] which is a useful introduction. Pocock also discusses conceptual and practical issues without need for extensive statistical background [1595], and has a series of design papers oriented toward clinician investigators [1598, 1599, 1602]. A similar series by du Prel et al. is initiated by their 2009 paper [1620]. The edited work by Piantadosi and Meinert, also a recent living reference on the web, is intended as a comprehensive overview of clinical trials for trialists [1588]. Some design developments were covered by Harrington [883], and controversial topics were discussed by Chow [338]. Many young investigators are exposed to Hulley et al. [971] which discusses research planning and some non-experimental designs. Every trialist should read the extensive work on placebos by Shapiro and Shapiro [1789]. Monographs about clinical trials appear occasionally in disease-specific contexts. This was true in cancer and AIDS in the last decade or two, but many books are now slightly dated.

TABLE 1.1 Some Web Resources for Clinical Trials Information

spirit-statement.org	Standards for protocols [322].
cochrane.org	Evidence summaries from clinical trials.
clinical trials.gov	World's largest registry of clinical trials.
consort-statement.org	Recommendations for reporting randomized trials.
jameslindlibrary.org	History of evolution of fair tests of medical treatments; examples and key passages of text.
icmje.org	Journal editors promoting uniform requirements for manuscripts submitted to biomedical journals.
fda gcp	Laws and regulations intended to ensure integrity of clinical data.
fda.gov	Guidance documents for good clinical practice and clinical trials conduct [651, 656].
ich.org	Harmonized guidelines for global pharmaceutical development.
isrctn.com	WHO and ICMJE registry of clinical research studies; content validation and unique identification number.

The U.S. Food and Drug Administration (FDA) publishes extensive advice on many aspects of clinical trials for investigators, regulators, and sponsors [651, 656, 657]. Topics range from broad principles to specific regulatory issues [651]. FDA guidance is first published in draft form while public comments are invited. Ultimately a guidance document becomes final but with non-binding recommendations. Many FDA guidance documents are endorsed by other regulatory agencies. Some are periodically revised.

A relatively short exposure to practicalities of clinical trials cannot illustrate all important lessons, even in an active program of clinical research. It usually takes years for any single clinical trial to yield all its information that might be instructive about methodology. Even so, students of clinical trials will learn some lessons more quickly by being involved in a study compared with only theory. In this book, many concepts are illustrated with published trials so readers can have some long-term perspective, which would otherwise might be difficult to acquire.

1.7 NOTATION AND TERMINOLOGY

There is no escaping need for mathematical formalism in clinical trials. According to Wigner [2042] it is mysterious why mathematics is so useful in describing nature. Nevertheless it is, and the mathematics of probability and statistics is most helpful for clinical trials. Galileo said:

> The book of the universe is written in mathematical language, without which one wanders in vain through a dark labyrinth.

Statisticians light their dark labyrinth using abstract ideas and symbols (Greek letters among them) as a shorthand for important summaries and concepts. I will use these ideas and symbols when appropriate in this book. Mathematics is a superb shorthand, and many essential ideas cannot be explained well without it. However, because this is not a book primarily about statistics, symbols and abstraction are used as minimally as possible. A review and explanation of common usage of symbols consistent with clinical trials literature is given in Appendix A. Because statistical terms may be unfamiliar to some readers, definitions and examples are also listed there. Abbreviations used in the book are also explained.

This book cannot provide fundamental statistical background needed to understand clinical trial design and analysis thoroughly. As stated above, I assume readers already have much of this knowledge. Help with statistical principles that underlie clinical trial methods is available in many practical and readable references for medical statistics. Some older texts dealing with that topic may be perfectly satisfactory since the fundamentals change quite slowly. Some specialized references will be mentioned later.

1.7.1 Clinical Trial Terminology

Typography of clinical trials is increasingly a problem, as illustrated in Table 1.2 showing some names presently in use. A few of these terms lack good definitions as indicated. Other terms are simply jargon with definitions implicit in how they are used. Some have rigorous important definitions that are occasionally ignored. In any case, the landscape can be bewildering and it is crucial to look for commonalities and principles that cross phenotypes.

TABLE 1.2 Trial Typography in 2023

Translational	Expanded safety	Noninterventional
Treatment mechanism	Large scale, large simple	Supportive care
Dose finding	Biomarker	Patient centered
Dose ranging	Pilot*	Real world*
Futility	Phase I	Screening
Risk and activity	Phase II	Prevention
Safety and efficacy	Phase III	Delayed start
Early development	Phase IV	Platform
Middle development	Phase V	Umbrella
Selection	Phase 0	Basket
Comparative efficacy	Interventional	Adaptive
Effectiveness	SMART[a]	Bayesian adaptive
Factorial	Randomized discontinuation	Equivalence
Partial factorial	MAMS[b]	Noninferiority
Incomplete factorial	Cluster randomized	Diagnostic
Crossover	N of 1	Population based

*Poorly defined terms to avoid.
[a] Sequential multiple assignment randomized trial.
[b] Multi-arm multi-stage trial.

Meinert has made considerable effort to standardize clinical trial terminology in a dictionary devoted to the topic [1346]. Most of my usage is consistent with those definitions (also see Appendix A). At risk of sounding old fashioned, it is important to pay attention to good terminology. Doing so helps communication both inside and outside the field. More importantly, consistent terms help avoid sloppiness in how we think.

As much as possible, this book avoids phase I, II, III, or IV labels for clinical trials because they do not generalize well despite being frequently used. Definitions of those terms are suggested next, and possible replacements following that. Those terms evolved from heavy use of developmental trials for cytotoxic drugs in late decades of the twentieth century. They have become jargon and found their way inappropriately to many other contexts. In clinical care, physicians and nurses would never permit imprecision allowed by such jargon. Imprecise language also inhibits creative design.

Drug development terms can be ambiguous or inappropriate for trials testing other interventions. Even new cancer therapies may not fit well into the old terminology. Although medical disciplines tend to view their own research issues as being unique and encourage local or specialty specific terminology, teaching requires terminology independent of context. Some terms that I specifically avoid are *pilot*, *proof of concept*, *real world*, and *exploratory*. Meanings for these tend to be context dependent. They seem to be used mainly to deflect criticism from obvious design flaws.

1.7.2 Drug Development Traditionally Recognizes Four Trial Design Types

We do need terminology to describe the developmental paradigm. A look at Chapter 10 might be useful now. There a paradigm with consistent descriptive terminology is offered. In therapeutic drug (especially cytotoxic drug) development historically, clinical trials were classified simply as phase I, II, III, and IV. *Phase I studies are pharmacologically oriented* and usually attempt to find an optimal dose of drug to employ. *Phase II trials look for evidence of activity, efficacy*, and *safety* at a fixed dose. Phases I and II are usually not formally hypothesis driven, meaning that comparisons to other treatments are often external to the experiment.

In phase III, new treatments are compared to alternatives, no therapy, or placebo. Comparison groups are internal to the design. Investigators would not undertake great expense and effort of phase III comparative testing unless there was preliminary evidence from phase I and II that a new treatment was safe and active or effective. *Phase IV is postmarketing surveillance* and may occur after regulatory approval of a new treatment or drug to look for uncommon side effects. This type of study design is also used for purposes other than safety and activity, such as marketing, and to uncover potential new indications that might support continued product exclusivity.

Phase II is sometimes divided into IIa and IIb. Phase IIa trials are small-scale feasibility studies using surrogate or intermediate outcomes such as cancer precursor lesions or biomarkers. Surrogate outcomes are defined and discussed

TABLE 1.3 Descriptive Terminology for Clinical Trials

Jargon	Developmental Stage	Descriptive Terminology
Pilot or Phase 0	Translation: Predevelopment	Translational Trial
Phase I	Early	Treatment Mechanism
		Dose finding
		Dose ranging
Phase II	Middle	Safety and Activity
Phase IIa		
Randomized[a]	Late	Under powered
Phase II[a]		Comparative
Phase IIb		Comparative
Phase III		Comparative Efficacy
Phase IV	Post development	Expanded Safety
		Large Scale, Large Simple

[a] Usually discussed as part of phase II but is a comparative (late development) design.

in Chapter 5. Phase IIb trials are randomized comparative studies using intermediate outcomes. Phase III cancer prevention trials are comparative designs (like IIb) using definitive clinical outcomes such as cancer incidence [1081]. Some cancer prevention investigators have used the term phase IV to mean a defined population study [840, 841], and define phase V to be demonstration and implementation trials.

1.7.3 Descriptive Terminology Is Better

The labels discussed above have become strong metaphors and frequently interfere with creativity regarding study purposes and designs. It is common to see protocols with phase I/II titles, and I have even seen one or two titled phase I/II/III, indicating how investigators labor under restrictive labels to accommodate flexible goals—or how confused they are.

A more general and useful description of studies should take into account design purposes and development stage independent of a treatment being studied. A mapping from old to descriptive terminology is provided in Table 1.3. Although mostly obvious, my descriptions are unconventional, so I will use them in parallel with traditional labels when needed for clarity. Phase I, II, III, and IV, if used at all, will refer only to drug trials.

Descriptive terminology also accounts for translational trials, an important class of predevelopmental designs discussed in Chapter 11. Simple description distinguishes several types of early developmental designs, particularly those aimed at establishing a safe dose of a new drug or agent to study. Comparative efficacy is an important class of trial designs that embody many rigorous design fundamentals discussed throughout this book. Details about these design types are given in Chapter 14.

1.8 PROGRAMS, EXAMPLES, AND DATA

It is not possible to learn all important lessons about clinical trials from classroom instruction or reading, nor is it possible for every student to be involved with actual trials inside a structured course. This problem is most correctable for topics related to analysis, where real or simulated trial data can be provided. Data for some examples and problems used in this book are provided in supplemental materials. Examples given are instructive but small, so as to be digestible by students.

Most numerical tables and figures in this book were generated by programs written in *Mathematica* [2065]. The complete program file, organized by chapter but not necessarily by section, is available in supplemental materials. This text does not point to specific program code, but most chapters used some computation. *Mathematica* is not a typical tool for either statisticians or clinicians. It is a computational language more than a computer program, so its syntax may seem dense. As an example, exact binomial confidence limits are used in several places in this text with tables provided in Section 16.4.3. Relevant computational code can be found in supplemental materials for Chapter 16.

Experience with design of clinical trials can be difficult to acquire. Although oriented primarily toward that topic, this book cannot replace an experienced teacher, good mentorship, collaborations with knowledgeable experts, and participation in many trials. I encourage students to work as many examples as feasible and return to this discussion as actual circumstances arise. Other data files and programs to read and analyze them can be found in various places online, as can software helpful for design calculations. More powerful sample size (and other) design software is widely available commercially.

1.9 SUMMARY

Well-designed experimental research is a necessary basis for therapeutic development and clinical care decisions. The purpose of this book is to address issues in clinical trials methods in a format accessible to interested clinical trialists and statistical scientists. Audiences are intended to be practicing clinicians, statisticians, trialists, and others with a need for understanding good clinical research methodology. Readers familiar with clinical trials will notice a few differences from usual discussions, including descriptive terms for types of trials, and an even-handed treatment of different statistical perspectives. Examples from clinical trials literature are used, and data and computer programs for some topics are available. A review of essential notation and terminology is also provided.