Fundamentals of Clinical Trials

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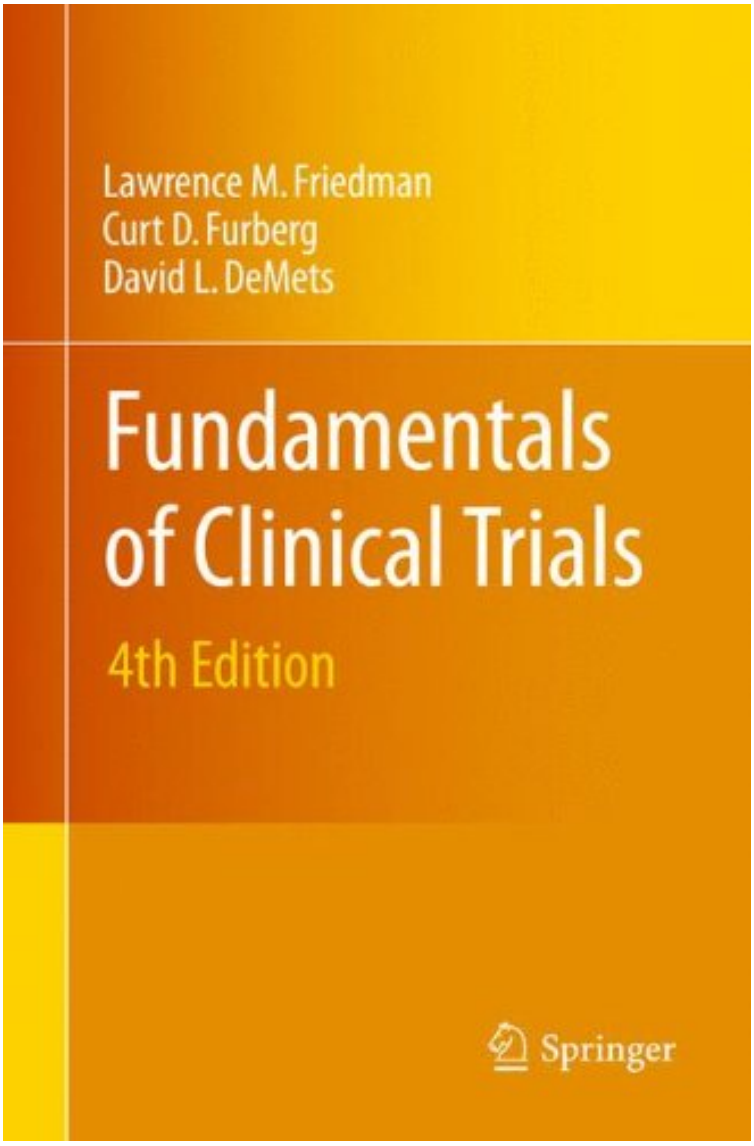

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Lawrence M. Friedman, Curt D. Furberg, David DeMets : Fundamentals of Clinical Trials before purchasing it in order to gage whether or not it would be worth my time, and all praised Fundamentals of Clinical Trials:

9 of 9 people found the following review helpful. Excellent logical, smooth writing. Provides guidance on many subtle things.By Tom BrodyPOST-SCRIPT. I am adding this sentence and the next few sentences, four years after I originally posted my review. My new book, CLINICAL TRIALS," recently published by ELSEVIER/ACADEMIC PRESS. My book is more detailed on "specifics" than is Dr. Friedman's book. My new book provides real-life

examples from about 100 clinical trials, mostly in oncology. My new book provides examples of real consent forms, a real DMC charter, and excerpts from a dozen real Clinical Study Protocols. My book takes an unusual approach in the chapters on CONSENT FORMS and PACKAGE INSERTS in that I provides excerpts from a dozen lawsuits that centered around disputed information in consent forms and package inserts. As is well known, it is a fact that the outcome of lawsuits is a primary driver for many of the activities of companies, including pharmaceutical companies, corporations, manufacturers, and so on. My book is also unusual, in that it includes an entire chapter on PLACEBOS, and an entire chapter on INTENT TO TREAT analysis, and an entire chapter on the STUDY SCHEMA. These three topics are grossly ignored by most or perhaps all other books on clinical trials. Too bad! My book corrects these deficiencies.FUNDAMENTALS OF CLINICAL TRIALS, 3rd ed., by Lawrence M. Friedman, et al, is 360 pages long. The book contains 19 chapters, each concluding with a carefully chosen collection of 30 to 100 references. One of Lawrence Friedman's other books, the informative and lucid, "DATA MONITORING IN CLINICAL TRIALS," is centered around case histories. In contrast, this book is not focused on case histories. FUNDAMENTALS OF CLINCAL TRIALS was a source of inspiration for me, shortly before I started writing my book, CLINICAL TRIALS. My book is a bit longer (over 600 pages). My book digs deeper into practical details than what is found in FUNDAMENTALS OF CLINICAL TRIALS. My book also discloses and solves a handful of perplexing contradictions and loose ends, that are found in the Guidance for Industry documents and in the ICH Guidelines. Also, unlike all other books on clinical trials, my book contains actual examples of standard documents that need to be filled, e.g., Consent Forms, DMC Charter, and Package Inserts and Black Box Warnings.Here is my review of FUNDAMENTALS OF CLINICAL TRIALS -- In chapter 3, we learn that, in capturing response variables, e.g., efficacy or adverse events, the investigator needs to be careful not to count one event more than once, where the same event repeatedly presents in the same subject (page 22). We also learn that the response variable must be capable of being assessed in all subjects, not just in a subgroup of the subjects. We learn that a surrogate may or may not reflect clinical outcome, for example, where tumor response is a surrogate for survival of the subject (page 26). Undesirable aspects of measuring surrogates are disclosed (the surrogate might be hard to measure), and desirable aspects of measuring surrogates (they are needed for accelerated approval) (page 26).Regarding inclusion and exclusion criteria, we learn that these must be defined carefully in the Clinical Study Protocol (CSP). For example, "headache" is not a good criterion, since it is not easily or objectively determined (page 33). For example, where age of the subject is a criterion, the CSP must define if this is the age attained at the time of baseline screening, or at some other time (page 32). We learn the benefits of having an available mechanism of action (MOA). Availability of a MOA enables the investigator to set forth subgroups in the CSP, for example, subgroups with severity of vessel growth, or subgroups with different locations of vessel growth (page 33). (Vessels growing in the eye, in a study of treatment by photocoagulation.) In other words, if the MOA is known, specific subgroups (and not others) can be chosen to include in the study, thereby reducing cost of the study and improving the number of favorably responding subjects."Today's homogeneous group may be considered heterogeneous tomorrow."We learn about the fact-pattern where a subject who initially meets the inclusion exclusion criteria, during the trial develops a condition that removes the subject from meeting all these criteria. The authors suggest that, where this happens, the subject should be taken off the study drug, but kept in the study for the purposes of analysis only (page 36). (Obviously, the P.I. of any trial will need to decide what to do if this fact-pattern presents.)We learn that exclusion criteria need to include conditions that prevent the diagnosis of the events of interest (page 36). For example, we learn that exclusion criteria need to list conditions that would likely cause the subject to die shortly after the study is initiated (page 36). (For example, this would include infection with flesh-eating bacteria or glioblastoma.)Regarding age as an inclusion/exclusion criterion, we learn that for any given disorder, the cause might be different in the young and old, as for the disorder of myocardial infarction (page 38). Also, we learn that exclusion criteria should list persons likely to be harmed by the treatment, or persons unlikely to comply with the study (page 39).In chapter 4, we learn about the problem of changes in names of diseases, and that these might change during the course of the study (page 49). Unfortunately, as this point in the book, the authors do not tell the reader about naming systems for disorders or for adverse events (AEs), for example, MedDra and Common Terminology Criteria for Adverse Events (CTCAE).In chapter 5, we learn about the desired ration of study drug subjects/control subjects. We learn that a common ratio is 2:1, and that this ratio is especially desirable for gaining knowledge on AEs (page 62). Once it is decided what ratio to use, the subjects are randomized. We learn that randomization can be by way of a coin toss, but we also learn why this method must not be used. This is because, "if the blind is broken on one participant, the entire sequence of assignments is known." (page 64). The authors then tell us about a better method of randomization, blocked randomization, where coin toss is used to determine if the next 4 subjects will be in this group AABB, or ABAB, or BAAB, or BABA, or BBAA, or ABBA. Delving further into details, we learn about stratified randomization and that this "in a sense, breaks the trial down into smaller trials" (page 68). We also learn that for huge studies, it won't matter much if you determine strata (for each subject) before or after randomization is done.In chapter 6, we learn various reasons for blinding. For example, if a physician knows that a subject is a control (placebo), he is likely to compensate by prescribing additional treatment to that particular subject (page 84). We also learn that sometimes machines used for diagnostic purposes, e.g., platelet aggregation, might need

to be modified to prevent inadvertent unblinding (page 87). We learn that sometimes pills degrade, so that the resulting discoloration can produce inadvertent unblinding. We also learn that it is better for every vial to have its own code, and worse for all vials (having study drug) or all vials (having placebo) to have the same code.Chapter 7 (sample size) and chapter 14 (survival analysis), are entirely statistics.In chapter 8, we learn once again that stratification can be done before randomization, or later on at the time of analysis (page 131). We learn that subgroups should be defined ahead of time, and that subgrouping should be based on BASELINE DATA (and not be based on data collected after unblinding). We are told that if subgroup is defined, for the first time, after analyzing unblended data, then this subgroup is appropriately used only for subsequent trials (page 132). Regarding baseline data, we are warned that it needs to be decided if baseline data is to be collected with the subject on his currently used drugs (or if it is to be collected with the subject taken off all drugs) (page 133).In chapter 9, we learn of problems with recruitment: lack of funding for screening; failure of physicians to refer subjects, over-estimation of prevalence of the disorder in the general population; too stringent entry criteria. We also learn of a related problem, where the study actually begins, but where the expected outcome does not occur with the expected frequency (pages 259-260). Also, we learn techniques for improving recruiting: relax inclusion criteria, extend time for recruiting, add more recruiting centers, refrain from telling placebo/standard of care subjects that they are in a study, re-testing of potential subjects until they meet inclusion criteria, accept smaller number of subjects.In chapter 10, we learn about problems in data quality. We learn of the problem where definitions for a symptom or an AE can be different from a definition in common use, and the definition set forth in the CSP (page 158). We learn of incompletely filled out forms, badly calibrated equipment, mislabeling, overt errors in making calculations, and inter-observer variability, and the fact that different physicians participating in the study might use different methods to read an EKG or to interpret histology, and various ways of referring to the same chemical (e.g., free propanolol versus propanolol HCl) (page 159-160). We learn various methods to QC a clinical study, e.g., sending drug samples to a lab for analysis.Chapter 11 provides definitions of expected AEs and unexpected AEs. An expected AE is one that, based on previous knowledge of intervention, is known or likely to occur (page 171). We learn that it is good for the CSP to provide definitions of AEs and of primary and secondary responses (page 172). We learn differences in acquiring AEs by check lists and by open-ended questions during interviews. We learn that documenting AEs are especially important for trials that attempt to find that the only difference between the study drug and standard of care is fewer AEs with the study drug (page 175). We learn of the phenomenon where a subject might get tired of reporting a particular AE. We learn that subject who hold a job might have compliance problems, where a drug needs to be taken for a plurality of times during the day (page 177).Chapter 12 discloses quality of life questionnaires, and tells us that the better way to phrase questions is: "Do you feel that your quality of life has changed?" and that the worse way to phrase the question is: "Has your quality of life improved?" The authors tell us that "the critical factor is not actual performance, but the degree to which one's perception of functioning changes." (page 195) We learn that the questionnaire can give wrong information, where the subject has experienced some tragedy (bereavement; work layoff) or some great success (child graduating college). We learn that better quality results might be obtained where a relative fills out the questionnaire. A criticism of this chapter, is that it fails to include an example, e.g., EORTC questionnaire, Karnofsky 11 point scale, or WHO Handbook for Reporting Results for Cancer Treatment (5-point scale).Chapter 13 tells us how to increase subject compliance: shorter trials are easier to maintain compliance, trials conducted in hospitals (vs. at home), simple dosing regimens, seriousness of the disorder being treated, educating subjects in the drugs and disease, birthday cards to subjects, telephone reminders to subjects, lower turnover of study staff, paying subjects taxi fare for getting to clinic, presence of a spouse, using special containers for study drug (pill count), providing subjects with phone # of investigator, give subjects a brochure, tests on blood and urine to monitor adherence, adding an inert chemical to study drug that can be measured in blood or urine.Chapter 15 tells us that the Greenberg Report was the basis for the Data Monitoring Committee (DMC), and that its goals are to protect subjects from harm and to ensure integrity of the trial. We learn that it is the DMC that produces recommendations on continuing, termination, and protocol modification. A criticism here is that this chapter fails to emphasize that the DMC's role is only to provide recommendations, and NOT actually to terminate or modify the study. We learn that the DMC can unblind the data, but that this should only happen when trends begin to emerge in either direction (drug causes harm or drug shows efficacy) (page 249). We learn that the DMC should meet when 10%, 25%, 50%, 75%, and 100%, of the outcomes have been observed. We are warned that "trends may emerge and disappear, especially early in the trial." We learn that the DMC contemplates the impact of missing data, participant adherence, whether results are consistent across all subgroups, whether data is unusual at one particular center (page 253). This chapter provides us with a list of studies that were stopped early. We learn that hasty (and incorrect) judgment was avoided, because of a discovery of a delay in missing data (page 255). We learn that stopping can be applied to only one of the subgroups. We learn about a drug that improved a surrogate (improved exercise tolerance) but that unfortunately led to greater deaths (page 258). This fact-pattern was a good example of an emerging negative trend (trend of deaths). The difficult nature of the DMCs decision here, involves deciding if the negative trend of the study drug is less harmful than negative trend of positive control drug (page 259). We also learn that, where there is an emerging positive trend, it still might be a good idea to continue with the trial, in

order to discover AEs that present only after longer treatment. Finally, we learn that a CSP may have instructions for increasing sample size, e.g., by extending recruitment phase, and that this decision should be linked to # of events (not to # of subjects) (page 260).The book fails to disclose the time-line of the drug-application process, and fails to show how all the different regulatory documents fit into each other. This shortcoming can be remedied by FDA REGULATORY AFFAIRS by Pisano and Mantus. The book does provide some elementary statistics, but not enough to learn from scratch. This shortcoming might be remedied by ESSENTIALS OF MEDICAL STATISTICS by Kirkwood and Sterne. Also, I recommend the Lange series book on statistics, for its excellent discription of Kaplan-Meier curves.I also recommend DATA MONITORING IN CLINICAL TRIALS, by the same three authors as the book currently under review.5 of 5 people found the following review helpful. Fundamentals of Clinical TrialsBy Deepak ParakkalUsed this with my course on clinical research methods. Very exhaustive description of the details of clinical trial design, implementation, analysis and reporting. Recommended for any clinical researcher conducting or wanting to improve their knowledge of clinical trials.3 of 3 people found the following review helpful. Easy to readBy Patrick J. ToppinI found this book very easy to read and it gave many real life examples. I started with basically no experience or knowledge of the subject matter. I think it was an excellent introduction to the topic.

This book addresses the fundamentals of randomized control clinical trials, devoting a chapter to each of the critical areas of a protocol. The new edition is revised and expanded, with the number of examples illustrating the fundamentals considerably increased.

From the reviews of the fourth edition:This book is clearly written for students in the arena of health care. Physicians and health care providers can use it as a reference book. The organization and structure is good and logical. it deepens the understanding of applications of statistical methods and the analysis of clinical trials. Also, it provides a list of references at the end of each chapter. In summary, this is an important contribution, providing up-to-date coverage on clinical trial methodology in a logical and systematic manner. (Technometrics, Vol. 53 (2), May, 2011)From the Back CoverThis is the fourth edition of a very successful textbook on clinical trials methodology, written by three recognized experts who have long and extensive experience in all areas of clinical trials. Most chapters have been revised considerably from the third edition. A chapter on ethics has been added and topics such as noninferiority and adaptive designs now receive considerable discussion. There is much new material on adverse events, adherence, data monitoring, and issues in analysis. This book is intended for the clinical researcher who is interested in designing a clinical trial and developing a protocol. It is also of value to researchers and practitioners who must critically evaluate the literature of published clinical trials and assess the merits of each trial and the implications for the care and treatment of patients. The authors use numerous examples of published clinical trials from a variety of medical disciplines to illustrate the fundamentals. The text is organized sequentially from defining the question to trial closeout. One chapter is devoted to each of the critical areas to aid the clinical trial researcher. These areas include pre-specifying the scientific questions to be tested and appropriate outcome measures, determining the organizational structure, estimating an adequate sample size, specifying the randomization procedure, implementing the intervention and visit schedules for participant evaluation, establishing an interim data and safety monitoring plan, detailing the final analysis plan, and reporting the trial results according to the pre-specified objectives. Although a basic introductory statistics course is helpful in maximizing the benefit of this book, a researcher or practitioner with limited statistical background would still find most if not all the chapters understandable and helpful. While the technical material has been kept to a minimum, the statistician may still find the principles and fundamentals presented in this text useful. This book has been successfully used for teaching courses in clinical trial methodology.About the AuthorLawrence M. Friedman is Marion Rice Kirkwood Professor at Stanford Law School. He is the author, among other works, of A History of American Law; The Legal System: A Social Science Perspective; Crime and Punishment in American History; and The Human Rights Culture.