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"Fundamentals of Clinical Trials, 5th edition"

Lawrence M. Friedman, Curt D. Furberg, David L. DeMets, David M. Reboussin, and Christopher B. Granger, 2015, 550 pages, Springer, $79.99

Review by Norman M. Goldfarb

"Fundamentals of Clinical Trials, 5th edition" is a comprehensive and sophisticated guide to clinical research. This book leads the field for its coverage of the key issues of clinical research with such insight, breadth and depth in a single volume.

The following passages illustrate the thoughtful and clear writing in the book:

Questions Regarding Harm

Important questions that can be answered by clinical trials concern adverse effects of or reactions to therapy. Here, unlike the primary or secondary questions, it is not always possible to specify in advance the questions to he answered. What adverse effects might occur and their severity may be unpredictable. Furthermore, rigorous, convincing demonstration of serious toxicity is usually not achieved because it is generally thought unethical to continue a study to the point at which a drug has been conclusively shown to be more harmful than beneficial. Investigators traditionally monitor a variety of laboratory and clinical measurements, look for possible adverse events, and compare these in the intervention and control groups. Some of the most serious adverse effects, however, are rare and do not occur commonly enough to be detected reliably in clinical trials. Statistical significance and the previously mentioned problem of multiple response variables become secondary to clinical judgment and participant safety. While this will lead to the conclusion that some purely chance findings are labeled as adverse effects, responsibility to the participants requires a conservative attitude toward safety monitoring, particularly if an alternative therapy is available. Trials have been stopped early for less than statistically convincing evidence of adverse effects. In such cases, only other trials of the identical or related interventions noting the same adverse effect…or convincing nonclinical studies will provide irrefutable evidence that the adverse finding is true.

Transfer of Post-Trial Care

Termination of a long-term study can be difficult due to the bonding that often develops between participants and clinic staff. The final visit needs to be carefully planned to deal not only with this issue, but also with the need in many trials to inform the participants of which medication they were on (in a blinded study), their individual study data, and the overall study findings (often at a later time). Referral of the participant to a regular source of medical care is another important issue.

If the closeout is extended over a long period, as it would be if each participant were followed for the same duration, any early recommendation to an individual participant would have to be based on incomplete follow-up data, which may not reflect the final conclusions of the trial. Moreover, any information given could "leak" to participants still actively treated, thus affecting the integrity of the trial. Although it is highly desirable to provide each participant with a recommendation regarding

continued treatment, doing so may not be possible until the study is completely over and the trial results have been published. When unblinding occurs over a span of months or years, the investigator is in the uncomfortable position of ending a participant's involvement in the trial and asking him or her to wait months before being told the study results and being advised about what to do. On the other hand, if the incomplete results are clear cut, it would be easy to arrive at such recommendations. However, in such an instance, the investigator would be confronted with an ethical dilemma: How can the investigator recommend that a participant start, continue or discontinue a new intervention while keeping other participants active in the trial? For this reason, we generally prefer a shortened period of trial closeout.

The book includes the following 22 chapters:

- Introduction to Clinical Trials
- Ethical Issues
- What Is the Question?
- Study Population
- Basic Study Design
- The Randomization Process
- Blinding
- Sample Size
- Baseline Assessment
- Recruitment of Study Participants
- Data Collection and Quality Control
- Assessment and Reporting of Harm
- Assessment of Health-Related Quality of Life
- Participant Adherence
- Survival Analysis
- Monitoring Committee Structure and Function
- Statistical Methods Used in Interim Monitoring
- Issues in Data Analysis
- Closeout
- Reporting and Interpreting of Results
- Multicenter Trials
- Regulatory Issues

The book is available in bookstores.

Reviewer

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