"Clinical Trials: A Methodological Perspective, 3rd Edition"

Steven Piantadosi, 2017, 886 pages, Wiley, $165.00

Review by Norman M. Goldfarb

"Clinical Trials: A Methodological Perspective, 3rd edition" adds 200 pages — and 10 years of expertise — to the second edition. The book includes clearly written, practical presentations of an encyclopedic range of topics, from absolute risk reduction to zidovudine (AZT), an important drug for HIV treatment that demonstrated why a retrospective control group can be misleading (in this case, because the control group was sicker than the earlier untreated population).

The following passage illustrates the clear and thoughtful writing in the book:

**Participation may select subjects with better prognosis**

Subjects who participate in a clinical trial tend to have more favorable outcomes than those who refuse, even if the treatment is not effective. This effect of selection can be quite strong, and could be called the trial participant effect, much like the healthy worker effect, a name for the observation that the general health of individuals who are employed is better than average. It is likely to occur in situations where one treatment requires better baseline health and organ system function than alternative therapies. Studies that require subjects to travel to a referral center or have more intensive follow-up visits to clinic can also create the effect.

Such an effect is common for surgical treatments where, on average, subjects must be healthier to undergo an operative procedure than to receive medical therapy. However, even within surgical treatment, selection effects can be pronounced.

Similar issues surround “ventricular remodeling,” a proposed surgical treatment for end-stage congestive heart failure in which a portion of heart muscle is removed to improve cardiac function.

The trial participant effect is largely unavoidable in noncomparative designs, although as mentioned above, eligibility criteria can partially control it. In randomized comparative trials, it is less of a problem, provided the selection effects do not affect the treatment groups differentially. Treatment differences are unlikely to be affected by selection effects that operate prior to randomization. This is a reason why we perform randomization as late as possible in a trial scheme. However, if selection effects operate differentially in the treatment groups because of either poor design or subject exclusions, the estimated treatment effect can be biased.

Selection could, in principle, yield a study cohort with either a more favorable or less favorable prognosis, although the former seems to be more common. It is usually not possible to find a single cause (risk factor) for what appears to be a strong effect. It is likely that several factors, each with modest effects, combine to produce an overall bias. Consider factors that produce relative risks in the range of 1.2 (20% increase or decrease). This risk ratio is moderate and would probably be below the resolution of all but the largest studies. However, only four such factors together could produce a net relative risk over 2.0 ($1.2^4$), or under 0.5, if operating in the...
opposite direction. This exceeds the size of most treatment effects, and it is perhaps not surprising that we see selection biases frequently.

The book includes 26 chapters:

- Preliminaries
- Clinical Trials as Research
- Why Clinical Trials Are Ethical
- Contexts for Clinical Trials
- Measurement
- Random Error and Bias
- Statistical Perspectives
- Experimental Design in Clinical Trials
- The Trial Cohort
- Development Paradigms
- Translational Clinical Trials
- Early Development and Dose-Finding
- Middle Development
- Comparative Trials
- Adaptive Design Features
- Sample Size and Power
- Treatment Allocation
- Treatment Effects Monitoring
- Counting Subjects and Events
- Estimating Clinical Effects
- Prognostic Factor Analysis
- Factorial Designs
- Crossover Designs
- Meta-Analyses
- Reporting and Authorship
- Misconduct and Fraud in Clinical Research

Even complicated statistical material is understandable, for example:

To balance several clinically important prognostic factors, the randomization can be blocked and stratified. Every relevant prognostic factor combination can define an individual stratum, with blocking in each. Then the treatment assignments will be balanced in each stratum, yielding balanced prognostic factors in each treatment group. To be most advantageous, stratification should be used only for prognostic factors with relatively strong effects, such as risk ratios over about 2.0.

**Reviewer**

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