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"Can You Handle the Truth?"

"Evaluating Clinical Research: All That Glitters Is Not Gold, 2nd Edition"

Bengt D. Furberg and Curt D. Furberg, 2007, 161 pages, Springer, \$32.95

Review by Norman M. Goldfarb

"Evaluating Clinical Research: All That Glitters Is Not Gold, 2nd Edition" is simply the best introductory book on the science of clinical research you can read in two hours. The title grossly understates the appropriate readership; every new investigator and clinical research professional should start with this book.

This book has been selected for
[The First Clinical Research Bookshelf](#)

The book consists of a series of questions and answers, such as the following two examples:

How may selection bias affect trial findings?

Exclusion of high-risk patients in clinical trials has other ramifications. Several post myocardial infarction studies that evaluated prophylactic beta-blocker therapy included patients with a broader spectrum of risk. Contrary to what one would expect, these trials showed that the benefits of beta-blockade were more pronounced in patients with complicated infarcts (and no contraindications to beta-blocker therapy) than in patients with uncomplicated infarcts. By excluding high-risk patients, beneficial effects may be missed.

Selection bias may also increase the chances of finding favorable treatment effects. Study subjects typically have above-average education, as well as a personal interest in the research project. As a consequence, their level of adherence with the study medication is usually high. Additionally, since study subjects are usually free of other conditions and take few if any other medications (healthy volunteer effect), the likelihood of drug-drug interactions is small.

A focus on low-risk patients can lead to an underestimation of harmful drug effects and/or a delay in their detection. The development of the selective COX-2 inhibitors serves as a recent example. By conducting small, short-term trials in mostly low-risk subjects, the safety signals pointing to this class of agents causing serious thrombotic events (especially heart attacks) were missed.

According to a Medline search, there were 1,430 randomized clinical trials of calcium channel blockers published between 1990 and 1995. Most of them focused on surrogate outcomes. There was no single large trial conducted during that period to determine whether and to what extent these agents reduce the risks of strokes, heart attacks, and heart failure in subjects with hypertension, the major indication for these agents.

Was selection of the active-control fair?

In evaluating an antihypertensive drug, the optimal comparator should be a low-dose diuretic, which has proven to be highly beneficial in reducing all vascular complications of hypertension, is fairly safe when properly used, and is very inexpensive. Since showing superiority over, or even equality with, a generic diuretic is difficult, a manufacturer of a novel class of antihypertensive agents or of a new

member of an established class (so-called "me-too" drugs) may tip the balance in favor of its drug. In LIFE and in ASCOT, losartan (Cozaar) and amlodipine (Norvasc) were compared to atenolol given once daily. Atenolol is clearly inferior to thiazide diuretics and appears to be the least effective beta-blocker for the treatment of hypertension and for secondary prevention post-infarction. A once-daily regimen of atenolol may not provide adequate blood pressure control over 24 hours. LIFE and ASCOT, though positive for losartan and amlodipine, were therefore fairly uninformative with regard to how hypertensive patients should best be treated.

Some of the pitfalls of evaluating clinical study reports include the following:

- A survey of 102 Danish trials observed incomplete reporting of outcomes reflecting efficacy and safety in 50% and 65% of the trials. At least one primary outcome was introduced, changed or omitted in 62% of the trials.
- One difficulty arises when the study drug and the treated condition cause the same complication. The most severe adverse reaction induced by the antiarrhythmic agents in the Cardiac Arrhythmia Suppression Trial was sudden cardiac death, the very complication these agents were supposed to treat!
- The ISIS-2 study evaluated streptokinase and aspirin for treating acute myocardial infarction. The investigators demonstrated the potential fallacy of subgroup analysis when they observed that subjects averaged a 30% lower mortality on aspirin compared to placebo patients, except for those born under the Zodiac signs of Gemini and Libra, who exhibited a 5% higher mortality.
- In a review of new drugs in oncology, it was found that trials funded by non-profit organizations were 8 times more likely to reach unfavorable cost-effectiveness conclusions (5% vs. 38%) compared with trials funded by pharmaceutical companies.

The book includes 26 chapters:

- What is the purpose of this book?
- Why is benefit-to-harm balance essential to treatment decisions? What are the strengths of randomized controlled clinical trials? What are the weaknesses of randomized controlled clinical trials? Do meta-analyses provide the ultimate truth?
- What are the strengths of observational studies?
- What are the weaknesses of observational studies? Were the scientific questions stated in advance?
- Were the treatment groups comparable initially?
- Why is blinding/masking so important?
- How is symptomatic improvement measured?
- Is it really possible to assess quality of life?
- What is the value of biologic markers in drug evaluation? How are adverse drug reactions measured?
- How representative are study subjects in clinical trials? What happened to the study subjects who disappeared from the analysis?
- How reliable are active-control trials?
- How informative are composite outcomes?
- Do changes in biologic markers predict clinical benefit? How trustworthy are the authors?
- Does publication in a reputable scientific journal guarantee quality?

- Is it necessary to be a biostatistician to interpret scientific data? Are all drugs of a class interchangeable?
- How much confidence can be placed on economic analysis? How should I handle the massive flow of information? How well is research translated into clinical care?

The book is available in bookstores.

Reviewer

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