“Clinical Trial Biostatistics and Biopharmaceutical Applications”
Walter R. Young and Ding-Geng (Din) Chen, editors, 2015, 544 pages, CRC Press, $119.95

Review by Norman M. Goldfarb

“Clinical Trial Biostatistics and Biopharmaceutical Applications” is a collection of articles on cutting-edge developments in biostatistics by speakers at the Deming Conference on Applied Statistics. In other words, the book focuses on important, topical material and is not intended to provide a comprehensive review.

The following is an excerpt from an article on biomarkers:

In our experience, there are four primary purposes for which biomarkers may be usefully employed in clinical drug development, and three of those are the subject of this chapter. Those four uses roughly correspond to time frames from a subject’s screening and initial therapeutic intervention through to clinical outcome.

The first purpose is patient selection, before a therapeutic intervention occurs. The selection biomarker is used to identify subjects most likely to have a favorable benefit/risk ratio when a specific investigational therapy is administered, relative to a specific control and for a specific therapeutic purpose. Once well established, this marker could be used to guide therapy. It is important to note that the “selection” properties of this biomarker only apply in the context of the specific proposed investigational and control therapies; with a different investigational agent, or control, this biomarker might offer no aid in a treatment decision. Among biomarker uses, this use is currently receiving the most attention for several compelling reasons: it could dramatically reduce the size of phase 3 clinical trials, it embodies personalized medicine, and its use in routine clinical practice is favorable from a public health point of view. (Note: It also addresses a legal requirement, US 21 CFR 201.57 (2010), inappropriate labeling for selected subgroups expected to benefit.) Essentially, it informs the best treatment choice for a specific patient for the relevant therapies. This use is the basis for a companion diagnostic and will be discussed later in this chapter at some length.

The second use occurs very soon after treatment administration, when a biomarker might indicate whether a target pathway is successfully being modulated. The biomarker could potentially be any marker between the point of intervention and a clinical outcome, though it would, ideally, be near the point of pathway intervention. This pathway biomarker may be very useful in early trials to identify whether a molecule is reaching and modulating its intended target, to provide objective evidence of pathway intervention. If this does not occur in essentially all eligible subjects in a trial, then the value of the intervention may be very limited. If the biomarker is directly on the targeted pathway, it may be thought of as necessary, but not sufficient, for a favorable clinical outcome. If the marker is too distal, its modulation may be impacted by signal cross-talk, thus making it potentially less reliable for evidence of pathway intervention; however, this reason might also make such a marker useful as a response biomarker (see next paragraph). An early trial that reliably shows little or no pathway intervention may allow for a drug program to be terminated early due to unlikely chance of success. Further, showing that the desired pathway is modulated in the manner desired in early clinical studies is critically important for the case where subsequent studies in patients reveal no
impact to the disease symptoms. If this is the case, one can distinguish between a drug that has failed to impact its target and a pathway that does not impact the course of the disease in humans.

The third use also occurs early after treatment administration, where a response biomarker is used to identify whether a subject is expected to experience a favorable outcome. In general, the pathway biomarker is near the drug target, while the response biomarker is nearer the clinical response, from a chain of causality point of view. A pathway biomarker might also be a response biomarker. The difference between the two might be very subtle or perhaps nonexistent, with the pathway biomarker being more about evidence that the investigational drug reaches and modulates the target, while the response biomarker is generally considered to suggest desirable activity further along on the causal pathway and nearer to the clinical response. Generally speaking, one would expect a pathway biomarker signal in all suitably chosen subjects in a trial, while the response biomarker signal would be expected to be associated with subjects who respond to the intervention (a subset of the study population). A response biomarker may or may not be a good candidate to be a surrogate. An example of a response biomarker that is not a pathway biomarker and that is also not currently a surrogate marker (though it has often been suggested, and may one day be) is the appearance of rash in oncology patients receiving EGFR therapy. This example is very interesting because the association of rash with clinical effectiveness was found by observation, rather than being suggested as a marker because of known or presumed biology, and there is currently still no general agreement regarding mechanism for rash or for this association. The primary use of a response biomarker would be to determine whether a subject ought to continue therapy or not.

The fourth biomarker use is when a biomarker is used as a substitute for a clinical endpoint, also known as a “surrogate” (e.g., cholesterol, blood pressure). Surrogate biomarkers will not be covered in this chapter as they have been thoroughly covered elsewhere.

The book consists of 19 articles by 37 contributors:

- Emerging Challenges of Clinical Trial Methodologies in Regulatory Applications
- Review of Randomization Methods in Clinical Trials
- First Dose Ranging Clinical Trial Design: More Doses? Or a Wider Range?
- Thorough QT/QTc Clinical Trials
- Controversial (Unresolved) Issues in Noninferiority Trials
- Adaptive Designs in Drug Development
- Optimizing Group-Sequential Designs with Focus on Adaptability: Implications of Nonproportional Hazards in Clinical Trials
- Group Sequential Design in R
- Issues in the Design and Analysis of Oncology Clinical Trials
- Competing Risks and Their Applications in Cancer Clinical Trials
- Dose Finding with Escalation with Overdose Control in Cancer Clinical Trials
- Interval-Censored Time-to-Event Data and Their Applications in Clinical Trials
- Introduction to Multiple Test Problems, with Applications to Adaptive Designs
- Graphical Approaches to Multiple Testing
- Pairwise Comparisons with Binary Responses: Multiplicity-Adjusted P-Values and Simultaneous Confidence Intervals
• Comparative Study of Five Weighted Parametric Multiple Testing Methods for Correlated Multiple Endpoints in Clinical Trials
• Statistical Analysis of Biomarkers from -Omic Technologies
• Understanding Therapeutic Pathways via Biomarkers and Other Uses of Biomarkers in Clinical Studies
• Statistical Evaluation of Surrogate Endpoints in Clinical Studies

The book is available in bookstores.

Reviewer
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