

"Adaptive Clinical Trials: Innovations in Trial Design, Management, and Analysis"

Hermann A.M. Mucke, 2007, 120 pages, Insight Pharma Reports, \$2,995

Review by Norman M. Goldfarb

"Adaptive Clinical Trials: Innovations in Trial Design, Management, and Analysis" fills the gap between "adaptive trials sound like a good idea" and "the statistical properties of Friedman's urn are fascinating." Any organization thinking of embarking on a program of adaptive trials (i.e., those using Bayesian statistical methods) needs to know what it is getting itself into, and would be well-advised to read this report.

The report includes eight chapters:

- Introduction
- The Traditional Clinical Trial: An Experiment in Medical Statistics
- Adaptive Trial Designs
- Hybrid and Seamless Designs
- The Adaptive Approach, Industry and Regulatory Authorities
- Adaptive Trials in Current Practice Survey – May 2007
- Adaptive Trials to 2015: Scenarios for Acceptance
- Interviews with Adaptive Trial Experts

In theory, adaptive trials can substantially reduce the time, cost and subject drug-exposure of clinical development. The report provides a useful analogy:

A classical (or, to use the statistical term, frequentist) clinical trial is equivalent to a military campaign that has been planned with dutiful detail but, once launched, fails to acknowledge the fact that direct contact with enemy forces immediately makes new information available about the opponents' strength and deployment patterns (and, by inference, their likely intention). While it is common knowledge among soldiers that a battle plan is needed, it is equally well-known that hardly any battle plan survives the exchange of the first shots unchanged. A military commander who refuses to adapt his battle design in the face of this new tactical information would be reprimanded, or even court-martialed. With clinical trials, however, the unwavering adherence to a preconceived and preapproved design still counts as a virtue.

Adaptive trials provide the missing flexibility, but they are not a license to plunge off into any promising direction. Clear time points, alternatives and decision rules must be established in advance for practical reasons and also to minimize the chance of false positive (type I) errors. Adaptive designs are most commonly used in Phase I trials to expedite pharmacokinetic data and in Phase II dose-ranging studies, but they offer other options. For example, rules can be established to further investigate the study drug in a sub-group such as women, Asians or the severely-ill. However, if the interesting sub-group turns out to be people who are taking a statin drug, that option may not be available without detailed advance planning.

In practice, numerous practical issues must be addressed. Timely decisions require timely therapeutic effects and data reporting. In dose-ranging studies, clinical supplies must be available to cover every scenario. Stopping a dosage arm is much simpler than replacing it

on the fly with the ideal new dosage. The project team must be able to handle the complexities of an adaptive design. The software must prevent disclosure of certain information to study personnel not involved in the adaptation decisions.

Although FDA and EMEA are generally supportive of adaptive designs, there is no guarantee that their position on a given trial may not change when the NDA truck arrives at the loading dock. Regulators like to compare new results with the results from previous studies, reducing design flexibility. Study sponsors and readers of scientific articles face similar comparability challenges.

Adaptive designs can eliminate delays between phases with so-called "hybrid" or "seamless" designs. For example, a Phase II dose-ranging study can establish the optimal dose, and then roll into Phase III, with all of the subjects at that dose contributing to the final sample. However, because hybrid trials take longer to complete, issues may arise. For example, a competitor may publish results that beg adjustments not anticipated in the adaptation parameters.

The report concludes with the findings of an industry survey. Despite the practical challenges discussed above, 30% of respondents agreed that "certain adaptive trial designs might become mandatory at some point."

The report is available at <http://www.InsightPharmaReports.com>.

Reviewer

Norman M. Goldfarb is Managing Director of First Clinical Research LLC, a provider of clinical research best practices information, consulting and training services. Contact him at 1.650.465.0119 or ngoldfarb@firstclinical.com.