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Opinion on Adaptive Designs in Clinical Trials

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Introduction

Starting from a couple of research papers in this type published in Europe's peer-reviewed statistical journals, adaptive designs have made much progress in the development and implementation in the past 20 years, which are anticipated to increase the information value of clinical trial data in order to enable better decisions during the course and speed up the development process in the context of fierce competition and limited trial budgets. So far for now, main types of adaptive deigns are: 1) adaptive randomization which allows changing randomization probabilities using information from past treatment assignment (such as the biased coin design), or covariate-adaptive, or response-adaptive or covariate-adjusted-adaptive; 2) adaptive dose-response designs; 3) sample size re-estimation; 4) Treatment selection designs; 5) group sequential designs. All areas in this topic are undergone active development because analytic derivations are not well investigated for many methods. Meanwhile, new methods or old methods but applying to new problems is mushrooming in the literature. In my opinion, topics having noticeably importance in coming years are dose-response designs and treatment selection designs.

In the past, phase II dose finding studies were often designed using a small number of doses and a narrow dose-range, focusing on the upper end of the dose–response relationship. Only in recent years has there been a noticeable shift towards investigating the full dose–response range and estimating the minimum effective dose. This shift was partially driven by the PhRMA "Adaptive Dose-Ranging Studies" (ADRS) working group. The objectives of this group were to develop and evaluate novel adaptive and non-adaptive dose-ranging methods and to provide methodological recommendations for industry and regulatory agencies alike. Extensive simulation work conducted by the ADRS working group showed that no single type of clinical trial design or analysis is universally best, though novel approaches outperform conventional designs in many plausible scenarios. Simulations also showed that with current phase II trial sizes, even novel dose ranging approaches have non-negligible chance of making erroneous dose selection. There are imperative needs for research work from this aspect.

After identifying correct dose ranging, choosing right dose s and confirming their efficacies are then the goals of the confirmatory phase III trials, development of novel methods accompanying with rigorous investigations on analytic properties are what both industrial and academic statisticians are aiming at in the near future. A particularly appealing application occurs in phase III studies with treatment selection at interim. Consider, for example, a phase III study that starts with several treatments and a control. At a pre-specified interim analysis, one (or more) treatment(s) would be selected based on the available information, external information, and expert knowledge. Recruitment would continue, but now patients will only be randomized to the selected treatment(s) with a possibly reassessed sample size. The final analysis of the selected treatment(s) consists of patients in both stages and is performed in such a way that the overall type I error rate is controlled at a pre-specified level, thus providing confirmatory evidence of efficacy that is of the registration quality and of statutory requirement.

Another important trend is to expand application of adaptive design on the trial level to the program or portfolio level. Choosing which development candidate to back when there is a large portfolio of products competing for a fixed level of investment can be a difficult and complex process. The adoption of an adaptive design strategy at the portfolio level can provide significant value to the critical decision making required to deliver an optimized pipeline of products.

As one of the researcher in this area, I have implemented many adaptive design methods using R or SAS, compared them via simulations, have a manuscript under journal review process on a new combination test for designing a two-stage adaptive design; one accepted for publication on sample size increase for survival data when interim results are in the promising zone and a couple of accepted (or being reviewed) articles on group sequential methods and optimal group sequential designs.