Issues in Regulatory Acceptability of Bayesian Historical Data Borrowing Methods

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We present a case study of the process of Bayesian adaptive trial design incorporating meta-analysis and issues with its reception in the regulatory environment. In our setting, a sponsor's previous, failed Phase III clinical trial left them with a large historical dataset showing a near-significant treatment effect. To increase power while reducing new trial costs, we proposed an adaptive design featuring partial borrowing from the first study's efficacy data. After FDA regulators expressed willingness to consider a "development program-wide" assessment of the candidate drug's efficacy, we cast our partial borrowing adaptive trial design in the context of Bayesian meta-analysis. To control program-wide (unconditional) Type I error, we first determined early and final stopping boundaries using an overall one-sided alpha of 0.025 by simulating 1000 null datasets from both the historic and prospective trials, the latter featuring an interim look. We then simulated the prospective trial's interim and final data for various efficacy assumptions, given the selected stopping times. Then, to assess (conditional) trial power, we computed interim and final efficacies using meta-analysis of the posterior distributions of the effect sizes from the historical data and the simulated prospective data. Unfortunately, our proposal to downweight the historical data to just 10-20% of that of the prospective trial in the meta-analysis was met with significant pushback from regulators. Despite their earlier position, ultimately they insisted on limiting the inflation of the *conditional* Type I error to just 10% (i.e., from 0.025 to 0.0275). While we eventually came to agreement by drastic downweighting of the historical data, the approach retained little Bayes advantage. Our experience suggests that effective use of Bayesian methods in regulatory science awaits better regulatory understanding of the impact of historical data borrowing on conditional Type I error, and a willingness to consider the benefit-risk tradeoffs arising from such borrowing.