Supplement to “Efficient adaptive designs with mid-course sample size adjustment in clinical trials”

Jay Bartroff[1*†] and Tze Leung Lai[2‡]

[1] Department of Mathematics, University of Southern California, Los Angeles, CA 90089, U.S.A.
[2] Department of Statistics, Sequoia Hall, Stanford University, Stanford, CA 94305, U.S.A.

SUMMARY

We provide a proof and discussion of the asymptotic optimality results in our paper “Efficient adaptive designs with mid-course sample size adjustment in clinical trials.” All equation numbers below refer to that paper.

1. PROOF AND DISCUSSION OF (10)-(11)

As shown in Theorem 2(i) of [1], the sample size M of the Neyman-Pearson test with type I error probability α at θ_0 and type II error probability $\widetilde{\alpha}$ at θ_1 satisfies $M \sim |\log\alpha|/I(\theta^*, \theta_0)$ as $\alpha + \widetilde{\alpha} \to 0$ with $\log\alpha \sim \log\widetilde{\alpha}$, where $\theta^* \in (\theta_0, \theta_1)$ is the unique solution of $I(\theta^*, \theta_0) = I(\theta^*, \theta_1)$. Our three-stage test chooses $n_3 = M$ and inflates somewhat the type II error probability while maintaining the type I error probability at α via (7)-(9). In fact, by an argument similar to Theorem 3 (ii) of [1], it can be shown that the type II error probability of our three-stage test is of the order $(1 + \kappa_{\tilde{\varepsilon}})\widetilde{\alpha}$ as $\alpha + \widetilde{\alpha} \to 0$ with $\log\alpha \sim \log\widetilde{\alpha}$, where $\kappa_{\tilde{\varepsilon}}$ is a positive constant depending on $\tilde{\varepsilon}$, θ_0 and θ_1 such that $\kappa_{\tilde{\varepsilon}} = O(\tilde{\varepsilon})$ as $\tilde{\varepsilon} \to 0$.

Lorden [2] has introduced a similar three-stage test of $H_0 : \theta \le \theta_0$ versus $H_1 : \theta \ge \theta_1$ under the additional assumption that θ is known to belong to a bounded interval $[\underline{\theta}, \overline{\theta}]$, and has shown that his test satisfies (10) for $\underline{\theta} < \theta < \overline{\theta}$ as $\alpha + \widetilde{\alpha} \to 0$ such that $\log\alpha \sim \log\widetilde{\alpha}$. Since the right hand side of (10) is asymptotically equivalent to Hoeffding's [3] lower bound in this case, (11) also follows. The n_3 he chooses is larger than M but is kept within the order $(1 + o(1))M$. With this inflation of the maximum sample size, he can use crude bounds of the form $n_3 \exp\{(\log\alpha)(1 + o(1))\}$ for the type I error probability, with $\log\alpha$ replaced by $\log\widetilde{\alpha}$ for the type II error probability, so that these upper bounds do not exceed α and $\widetilde{\alpha}$ respectively (by manipulating the $o(\log\alpha)$ and $o(\log\widetilde{\alpha})$ terms in the exponent); note that

*Correspondence to: Jay Bartroff, University of Southern California, Department of Mathematics, 3620 South Vermont Ave., KAP 108, Los Angeles, CA 90089-2532, U.S.A.
†E-mail: bartroff@usc.edu
‡E-mail: lait@stat.stanford.edu

Contract/grant sponsor: NIH, NSF; contract/grant number: RO1-CA08890, DMS-0403105, DMS-0305709

$\log n_3 = o(|\log \alpha|) = o(|\log \widetilde{\alpha}|)$. His choice of the first-stage sample size depends on $\underline{\theta}$ and $\overline{\theta}$. Without requiring prespecified lower and upper bounds on θ, we require the first-stage sample size to satisfy

$$m/|\log \alpha| \to a, \quad \rho_m \to 0, \quad \sqrt{m}\rho_m/(\log m)^{1/2} \to \infty.$$

Then the same arguments as those in Lorden [2] can be used to show that (10) holds for $\theta_{(a)} < \theta < \theta^{(a)}$, where $\theta_{(a)}$ and $\theta^{(a)}$ are defined by

$$\theta_{(a)} < \theta^* \quad \text{and} \quad I(\theta_{(a)}, \theta_1) = a^{-1}, \quad \theta^{(a)} > \theta^* \quad \text{and} \quad I(\theta^{(a)}, \theta_0) = a^{-1},$$

and take the roles of $\underline{\theta}$ and $\overline{\theta}$ in Lorden's arguments.

Since $\log \alpha \sim \log(\varepsilon\alpha)$ as $\alpha \to 0$ for any fixed $0 < \varepsilon < 1$, the asymptotic formula for $E_\theta(N)$ in (10) is unchanged if one replaces the type I error probability α by a fraction of it, and this is why Lorden [2] can use crude bounds of the type above for the type I error probability. For values of the type I error probability α (e.g., .05 or .01) commonly used in practice, replacing α by $\alpha/10$, say, can substantially increase $E_\theta(N)$. Note that our adaptive test keeps the error probability at θ_0 to be α (instead of less than α) by using recursive numerical integration or Monte Carlo simulation to evaluate it , and that the ε and $\widetilde{\varepsilon}$ in (7)-(9) are related to the first two stages of a 3-stage group sequential test with the modified Haybittle-Peto stopping boundary introduced by Lai and Shih [1].

REFERENCES

1. T. L. Lai and M. C. Shih. Power, sample size and adaptation considerations in the design of group sequential clinical trials. *Biometrika*, 91:507–528, 2004.
2. G. Lorden. Asymptotic efficiency of three-stage hypothesis tests. *Annals of Statistics*, 11:129–140, 1983.
3. W. Hoeffding. Lower bounds for the expected sample size and the average risk of a sequential procedure. *Annals of Mathematical Statistics*, 31:352–368, 1960.