A Comparison of Eight Methods for the Dual-Endpoint Evaluation of Efficacy in a Proof-of-Concept HIV Vaccine Trial

Devan V. Mehrotra,¹,* Xiaoming Li,¹ and Peter B. Gilbert²

¹Merck Research Laboratories, UN-A102, 785 Jolly Road, Blue Bell, PA 19422, U.S.A.
²Fred Hutchinson Cancer Research Center and Department of Biostatistics, University of Washington, Seattle, WA 98109, U.S.A.

*email: devan_mehrotra@merck.com

APPENDIX

Details on how data were generated in the simulation study

Based on data from the Multicenter AIDS Cohorts Study (Lyles et al., 2000), for infected subjects in the placebo group, the viral load set-points were assumed to follow a normal distribution with mean \( \mu_p = \log_{10}(30,000) \) and standard deviation \( \sigma_p = 0.75 \log_{10} \) copies/ml. Under \( H_0^{vl} \), the same distribution was assumed for the vaccine group, so that \( \delta_{vl} = 0 \). Under \( H_1^{vl} \), as noted earlier, a mixture of three normal distributions was assumed for the vaccine group: 20% normal with \( \mu_{vl,1} = \log_{10}(27,200) + b \), 24.3% normal with \( \mu_{vl,2} = \log_{10}(27,200) + b - 0.5 \), and 55.7% normal with \( \mu_{vl,3} = \log_{10}(27,200) + b - 1.5 \), all with \( \sigma_{vl,all} = 0.65 \), where \( b \) is a fixed constant. The resulting overall standard deviation for the viral load set-point distribution for the vaccine group was \( \sigma_v = 0.91 \), and the overall mean difference (infected placebo - infected vaccine) in viral load set-points was \( \delta_{vl} = 1 - b \).

For given \( n_v + n_p = n \) and \( VE_s \), the number of HIV infections in the vaccine arm \( n_v \) was drawn randomly from a Binomial\((n, \theta)\) distribution with \( \theta = (1 - VE_s)/(1 + r - VE_s) \). For the \( n_v \) and \( n_p = (n - n_v) \) infected subjects, viral load set-points were drawn from the aforementioned vaccine and placebo distributions, respectively. Type I error rates and
powers were estimated by empirical rejection rates (using 1-tailed $\alpha = 5\%$) based on 5,000 simulated trials.

**Derivation of $w_{2,\text{optimal}}$ in expression (4)**

For given $\delta_{vl} = \mu_p - \mu_v$, $VE_s$ and $n \left(= n_v + n_p \right)$, it can be deduced from Follmann (1995) that the power of the weighted 2-part Z test is maximized if $w_2 = E_2/(E_1 + E_2)$, where $E_1 = E(Z_1 | VE_s, n)$ and $E_2 = E(Z_2 | VE_s, \delta_{vl}, \sigma_v^2, \sigma_p^2, n)$. Since $n_v$ given $VE_s$ and $n$ is distributed as $\text{Binomial}(n, \theta)$, where $\theta = (1 - VE_s)/(1 - VE_s + r)$, it follows that

$$E_1 = \frac{VE_s \sqrt{n r}}{(VE_s - (1 + r))}.$$ 

To determine $E_2$, define $U_{ij} = 1$ if $y_j < x_i$ and 0 otherwise, for $1 \leq i \leq n_v$ and $1 \leq j \leq n - n_v$. Using the well-known equivalence of the Wilcoxon (1945) and Mann-Whitney (1947) tests, note that $Z_2$ can be written as $Z_2 = (U - 0.5)/\sqrt{(n+1)/12 n_v (n-n_v)}$, where $U = \sum_{i=1}^{n_v} \sum_{j=1}^{n-n_v} U_{ij} / n_v (n-n_v)$. Since $E(U_{ij}) = P(Y_j < X_i) = \Phi \left(-\delta_{vl} / \sqrt{\sigma_v^2 + \sigma_p^2} \right)$, where $\Phi(.)$ is the N(0,1) c.d.f., we have

$$E_2 = \frac{\Phi \left(-\delta_{vl} / \sqrt{\sigma_v^2 + \sigma_p^2} \right) - 0.5}{\sqrt{(n+1)/12}} \sum_{k=0}^{n} \binom{n}{k} \theta^k (1-\theta)^{n-k} \sqrt{k(n-k)}.$$ 

The result in (4) follows after using a first order Taylor series approximation for the sum in $E_2$, and taking the limit as $n \to \infty$ in the resulting ratio $E_2/(E_1 + E_2)$.

**REFERENCES**


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