Biostatistics (2015), **0**, 0, *pp.* 1–5
doi:10.1093/biostatistics/2nd˙Revision˙Composite˙U˙Supplementary

Large Sample Inference for a Win Ratio Analysis of a Composite Outcome Based on Prioritized Components Supplementary Material

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APPENDIX

A. DETAILS: TWO GROUPS

Let

$$S_{ij}^{v} = \phi_v(X_i, Y_j)\,, \quad S_{i\cdot}^{v} = \sum_j S_{ij}^{v}\,, \quad S_{\cdot j}^{v} = \sum_i S_{ij}^{v}\,,$$

where $i = 1, \ldots, m$, $j = 1, \ldots, n$, and $v = 1, 2$. The probability terms in (2.4) can be estimated as follows:

$$\hat{P}(X_1 \succ Y_1) = \frac{1}{m \cdot n} \sum_{i,j} S_{ij}^{1}$$
$$\hat{P}(X_1 \prec Y_1) = \frac{1}{m \cdot n} \sum_{i,j} S_{ij}^{2}$$

$$\hat{P}(X_1 \succ Y_1 \,\&\, X_1 \succ Y_1') = \frac{\sum_i S^1_{i\cdot}(S^1_{i\cdot}-1)}{m\cdot n\cdot(n-1)}$$
$$\hat{P}(X_1 \succ Y_1 \,\&\, X_1' \succ Y_1) = \frac{\sum_j S^1_{\cdot j}(S^1_{\cdot j}-1)}{n\cdot m\cdot(m-1)}$$
$$\hat{P}(X_1 \prec Y_1 \,\&\, X_1 \prec Y_1') = \frac{\sum_i S^2_{i\cdot}(S^2_{i\cdot}-1)}{m\cdot n\cdot(n-1)}$$
$$\hat{P}(X_1 \prec Y_1 \,\&\, X_1' \prec Y_1) = \frac{\sum_j S^2_{\cdot j}(S^2_{\cdot j}-1)}{n\cdot m\cdot(m-1)}$$
$$\hat{P}(X_1 \succ Y_1 \,\&\, X_1 \prec Y_1') = \frac{\sum_i S^1_{i\cdot}S^2_{i\cdot}}{m\cdot n\cdot(n-1)}$$
$$\hat{P}(X_1 \succ Y_1 \,\&\, X_1' \prec Y_1) = \frac{\sum_j S^1_{\cdot j}S^2_{\cdot j}}{n\cdot m\cdot(m-1)}\,.$$

B. STRATIFIED ANALYSES

The proposed approach can be easily extended to a stratified analysis with a fixed number of strata. Within each strata s ($s = 1, \ldots, S$), one obtains, asymptotically,

$$U_s \sim \mathcal{N}(\tau_s, \Sigma_s)\ ,$$

where $U_s = (U_{s1}, U_{s2})'$, $\tau_s = (\tau_{s1}, \tau_{s2})'$. Notice that, for simplicity, the $\sqrt{N_s}$ factor (see (2.2)) has been incorporated in Σ_s. Then

$$\hat{\Delta}_s \sim \mathcal{N}\left(\Delta, \sigma^2_{s\Delta}\right)\ ,$$

where $\hat{\Delta}_s = U_{s1} - U_{s2}$, and $\sigma^2_{s\Delta} = \sigma_{s11} + \sigma_{s22} - 2\sigma_{s12}$.

The overall estimate for Δ is given by

$$\hat{\Delta} = \frac{\sum_s 1/\sigma^2_{s\Delta}\cdot\hat{\Delta}_s}{\sum_s 1/\sigma^2_{s\Delta}}\ .$$

Tests and confidence intervals for the proportion in favor of treatment Δ can be obtained based on the following normal approximation

$$\hat{\Delta} \sim \mathcal{N}\left(\Delta, \left(\sum_s 1/\sigma^2_{s\Delta}\right)^{-1}\right)\ .$$

A similar approach together with the Delta method can be used for inference about the win ratio parameter Ψ. Alternatively, one can employ Fieller's theorem. One has

$$U_{s1} - \Psi \cdot U_{s2} \sim \mathcal{N}\left(0, \sigma_{s11} + \Psi^2 \cdot \sigma_{s22} - 2 \cdot \Psi \cdot \sigma_{s12}\right) ,$$

and Fieller's confidence interval for Ψ is obtained by inverting the following inequality

$$\left| \frac{\sum_s 1/\sigma_{sF}^2 \cdot V_{sF}}{\left(\sum_s 1/\sigma_{sF}^2\right)^{1/2}} \right| \leqslant z_{\alpha/2} ,$$

where $V_{sF} = U_{s1} - \Psi \cdot U_{s2}$, and $\sigma_{sF}^2 = \sigma_{s11} + \Psi^2 \cdot \sigma_{s22} - 2 \cdot \Psi \cdot \sigma_{s12}$. Notice that this is no longer a quadratic equation for $s > 1$, and some approximations can be employed. Alternatively, a simple line search was used herein.

Example The analysis of the PEACE study data is repeated stratified by gender. A total of 1494 (18%) females were included in the study, 17% in the placebo group and 19% in the trandolapril group.

In a time-to-first-event analysis, the treatment effect was not significant (p-value=0.325) using a Cox model stratified by gender.

Although higher in females than in males, $\hat{\Delta}\left(SE_{\hat{\Delta}}\right)$ of 0.0182 (0.0133) versus 0.0015 (0.0064), the proportion in favor of treatment was not statistically different between males and females. The stratified estimate (standard deviation) for Δ was 0.0046 (0.0057), with a 95% CI (-0.0066,0.0158).

The win ratio parameter was also larger in females than in males, 1.2761 (0.2255) versus 1.0188 (0.0811), and the difference was again not statistically significant. The estimate using the delta method was 1.0483 (0.0763), 95% CI (0.8988,1.1978), while the 95% confidence interval using Fieller's approach was (0.9189,1.2251).

All methods provided consistent results with the unstratified analysis.

C. DETAILS: THREE GROUPS

The covariance matrix Σ has elements

$$\sigma_{uv} = \frac{N}{n_1} \cdot \xi_{100}^{uv} + \frac{N}{n_2} \cdot \xi_{010}^{uv} + \frac{N}{n_3} \cdot \xi_{001}^{uv}\,,\;\; u, v = 1, \ldots, 4\,,$$

with

$$\begin{aligned}
\xi_{100}^{uv} &= Cov\left(\phi_u(X,Y,Z), \phi_v(X,Y',Z')\right) \\
\xi_{010}^{uv} &= Cov\left(\phi_u(X,Y,Z), \phi_v(X',Y,Z')\right) \\
\xi_{001}^{uv} &= Cov\left(\phi_u(X,Y,Z), \phi_v(X',Y',Z)\right)\;,
\end{aligned}$$

where X, $X' \sim F$, Y, $Y' \sim G$, and Z, $Z' \sim H$ all independent. The submatrices $\Sigma_{11} = (\sigma_{uv})_{u,v=1,2}$ and $\Sigma_{22} = (\sigma_{uv})_{u,v=3,4}$ have the same expression as the variance-covariance matrix for the two-sample problem in Section 2. One needs to estimate σ_{uv} with $u = 1, 2$, and $v = 3, 4$. First notice that in this case $\phi_u(X,Y,Z)$ only involves X and Y, while $\phi_v(X',Y,Z')$ is a function of X' and Z'. Since the four random variables X, Y, X', and Z' are independent, it follows that $\xi_{010}^{uv} = 0$, and similarly, $\xi_{001}^{uv} = 0$.

The remaining terms are given by

$$\begin{aligned}
\xi_{100}^{13} &= Cov\left(I(X \succ Y), I(X \succ Z')\right) \\
&= P(X \succ Y \,\&\, X \succ Z) - P(X \succ Y) \cdot P(X \succ Z) \\
\xi_{100}^{14} &= P(X \succ Y \,\&\, X \prec Z) - P(X \succ Y) \cdot P(X \prec Z) \\
\xi_{100}^{23} &= P(X \prec Y \,\&\, X \succ Z) - P(X \prec Y) \cdot P(X \succ Z) \\
\xi_{100}^{24} &= P(X \succ Y \,\&\, X \succ Z) - P(X \succ Y) \cdot P(X \succ Z)\,.
\end{aligned}$$

One can estimate $P(X \succ Y \,\&\, X \succ Z)$ using

$$\hat{P}(X \succ Y \,\&\, X \succ Z) = \frac{1}{n_1 \cdot n_2 \cdot n_3} \sum_{i,j,k} \phi_1(X_i, Y_j, Z_k) \cdot \phi_3(X_i, Y_j, Z_k)\,,$$

or

$$\hat{P}(X \succ Y \,\&\, X \succ Z) = \frac{1}{n_1 \cdot n_2 \cdot n_3} \sum_i T^1_{i\cdot} \cdot T^3_{i\cdot}\,,$$

where $T^1_{ij} = I_{\{X_i \succ Y_j\}}$, $T^3_{ik} = I_{\{X_i \succ Z_k\}}$, and $T^1_{i\cdot} = \sum_j T^1_{ij}$, $T^3_{i\cdot} = \sum_k T^3_{ik}$.

From (4.13), it follows that

$$\sigma_{uv} = \frac{N}{n_1} \left(\frac{1}{n_1 \cdot n_2 \cdot n_3} \sum_i T^u_{i\cdot} \cdot T^v_{i\cdot} - \frac{1}{n_1 \cdot n_2} T^u_{\cdot\cdot} \cdot \frac{1}{n_1 \cdot n_3} T^v_{\cdot\cdot} \right),$$

where $T^u_{ij} = \phi_u(X_i, Y_j, Z_k)$, $T^v_{ik} = \phi_u(X_i, Y_j, Z_k)$, and $u = 1, 2$ and $v = 3, 4$.

The elements σ_{11}, σ_{12}, σ_{22}, and σ_{33}, σ_{34}, σ_{44} are obtained as in the two-group case using (2.3) and (2.4).

Under the null hypothesis of equality of the three groups ($F = G = H$), one has $(\tau_1 - \tau_2, \tau_3 - \tau_4) = (0, 0)$, which can be tested using a chi-squared test with 2 d.f. associated with the asymptotic bivariate normality of $(U_1 - U_2, U_3 - U_4)$, easily obtained by a linear transformation using (4.12). Alternatively, one can use the asymptotic normality of $(U_1/U_2, U_3/U_4)$.