1 Relationship between the increase of favorable outcomes proportion and the win ratio

Let X and Y be Bernoulli random variables representing outcomes in the treatment and control groups, respectively. Here,

$$X = 1 \quad \text{(favorable outcome)} \quad \text{and} \quad X = 0 \quad \text{(unfavorable outcome)},$$

and likewise for Y.

Suppose there is a difference δ in the probability of a favorable outcome for the treatment group compared to the control group, formally defined by

$$\delta = \Pr(X = 1) - \Pr(Y = 1).$$

We wish to understand how this difference δ relates to the following measures:

- The *proportion in favor of the treatment*, defined as

$$\Delta = \Pr(X > Y) - \Pr(Y > X).$$

- The *win ratio*, given by

$$\Psi = \frac{\Pr(X > Y)}{\Pr(Y > X)},$$

  where, for Bernoulli variables, $X > Y$ means $X = 1$ and $Y = 0$.

We now seek to establish the relationship between δ and the metrics Δ and Ψ.

For two Bernoulli variables $X, Y \in \{0, 1\}$, the event $X > Y$ happens exactly when $X = 1$ and $Y = 0$. Similarly, $Y > X$ happens if $Y = 1$ and $X = 0$. Thus,

$$\Pr(X > Y) = \Pr(X = 1,\, Y = 0) = p_X(1 - p_Y),$$

and

$$\Pr(Y > X) = \Pr(Y = 1,\, X = 0) = p_Y(1 - p_X),$$

where

$$p_X = \Pr(X = 1) \quad \text{and} \quad p_Y = \Pr(Y = 1).$$

Therefore, the proportion in favor of treatment is given by

$$\Delta = p_X(1 - p_Y) - p_Y(1 - p_X) = p_X - p_Y = \delta$$

Thus, Δ and δ are actually the same metric.

The win ratio is given by

$$\Psi = \frac{\Pr(X > Y)}{\Pr(Y > X)} = \frac{p_X\,(1 - p_Y)}{p_Y\,(1 - p_X)}.$$

From

$$\delta = \Pr(X = 1) - \Pr(Y = 1)$$

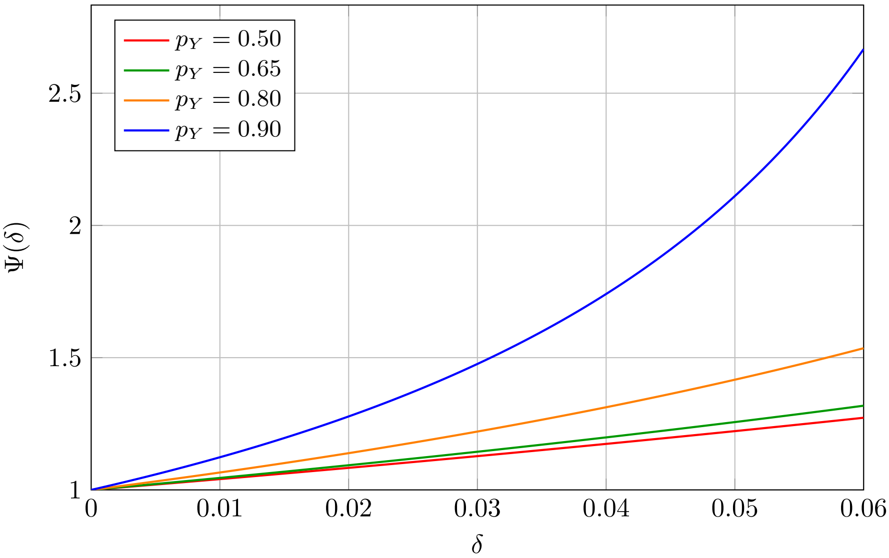

Figure 1: Relationship between the win ratio and the proportion in favor of treatment for different values of p_Y (baseline probability of a favorable outcome).

we deduce that

$$p_X = p_Y + \delta.$$

Substituting p_X in the expression for Ψ, we obtain

$$\Psi = \frac{(p_Y + \delta)(1 - p_Y)}{p_Y(1 - p_Y - \delta)} = 1 + \frac{\delta}{p_Y(1 - p_Y - \delta)}.$$

An illustration of the relationship between δ and Ψ is given in Figure 1.

Using the probability of a tie

Since $\Pr(X > Y) + \Pr(Y > X) + \Pr(Y = X) = 1$, we have

$$\Psi = \frac{\Pr(X > Y)}{\Pr(Y > X)} = \frac{2\Pr(X > Y)}{2\Pr(Y > X)} = \frac{1 - \Pr(X = Y) + \Delta}{1 - \Pr(X = Y) - \Delta}$$

and thus

$$\Psi = \frac{1 - p_{\text{tie}} + \Delta}{1 - p_{\text{tie}} - \Delta} \quad \text{and} \quad \Delta = \frac{\Psi - 1}{\Psi + 1}(1 - p_{\text{tie}}),$$

where

$$p_{\text{tie}} = \Pr(X = Y).$$

2 Variance of the win ratio estimator

In this section, we first follow the developement presented in [BL16].

2.1 Asymtotic distribution of the win ratio

Let X and Y be the outcomes of two patients, one in the treatment, and one in the control group, respectively.

We define the following kernel functions:

$$\phi_1(X,Y) = 1_{\{X \succ Y\}} \quad \text{and} \quad \phi_2(X,Y) = 1_{\{Y \succ X\}}$$

where $A \succ B$ means that A wins over B.

The probabilities of the events $X \succ Y$ and $Y \succ X$ are given by:

$$\tau_k = E[\phi_k(X,Y)], \quad k = 1, 2.$$

We want to test the null hypothesis of no difference between the two treatments:

$$H_0 : \tau_1 = \tau_2.$$

There are two statistics that can be used to test this hypothesis:

- The *proportion in favor of treatment* $\hat{\Delta}$ with expected value $\Delta = \tau_1 - \tau_2$.
- The *win ratio* $\hat{\Psi}$ with expected value $\Psi = \tau_1/\tau_2$.

Consider two samples $X_1, \dots X_m$ and $Y_1, \dots Y_n$ and $N = m + n$ denotes the total sample size.

An unbiased estimator for τ_k can be obtained using the U-statistic:

$$\hat{\tau}_k = \frac{1}{n\,m} \sum_{i=1}^{m} \sum_{j=1}^{n} \phi_k(X_i, Y_j), \quad k = 1, 2.$$

Inference regarding Δ and Ψ will be based on the joint distribution of $\hat{\tau}_1$ and $\hat{\tau}_2$.

The joint distribution of $\hat{\tau} = (\hat{\tau}_1, \hat{\tau}_2)$ is asymptotically normal:

$$\sqrt{N}\,(\hat{\tau} - \tau) \sim \mathcal{N}(0, \Sigma),$$

where $\tau = (\tau_1, \tau_2)$ and $\Sigma = \begin{pmatrix} \sigma_{11} & \sigma_{12} \\ \sigma_{21} & \sigma_{22} \end{pmatrix}$

2.2 Distribution of the proportion in favor of treatment and of win ratio

We have:

$$(\hat{\tau}_1 - \hat{\tau}_2) \sim \mathcal{N}(\Delta, (\sigma_{11} + \sigma_{22} - 2\,\sigma_{12})/N),$$

and (using the delta method):

$$\log(\hat{\tau}_1/\hat{\tau}_2) \sim \mathcal{N}(\log(\Psi), (\tau_1^{-2}\sigma_{11} + \tau_2^{-2}\sigma_{22} - 2\,(\tau_1\tau_2)^{-1}\sigma_{12})/N).$$

2.3 Variance-covariance matrix

The covariance of two U-statistics is given by:

$$\mathrm{Cov}(\hat{\tau}_k, \hat{\tau}_l) = \mathrm{Cov}\left(\frac{1}{mn}\sum_{i=1}^{m}\sum_{j=1}^{n}\phi_k(X_i, Y_j), \frac{1}{mn}\sum_{i'=1}^{m}\sum_{j'=1}^{n}\phi_l(X_{i'}, Y_{j'})\right).$$

Expanding the covariance:

$$\mathrm{Cov}(\hat{\tau}_k, \hat{\tau}_l) = \frac{1}{m^2n^2}\sum_{i=1}^{m}\sum_{j=1}^{n}\sum_{i'=1}^{m}\sum_{j'=1}^{n}\mathrm{Cov}(\phi_k(X_i, Y_j), \phi_l(X_{i'}, Y_{j'})).$$

We consider four different cases for the indices (i, j) and (i', j'):

- **Case 1:** Same X, Same Y (i.e., $i = i'$ and $j = j'$)

  We define the covariance between the two kernel functions as:

  $$\xi_{11}^{kl} := \mathrm{Cov}(\phi_k(X_1, Y_1), \phi_l(X_1, Y_1)).$$

  Since we have mn total pairs, this case contributes:

  $$m\,n\,\xi_{11}^{kl}.$$

- **Case 2:** Same X, Different Y (i.e., $i = i'$, but $j \neq j'$)

  This means we are comparing the same subject from Group 1 with two different subjects from Group 2:

  $$\xi_{10}^{kl} := \mathrm{Cov}(\phi_k(X_1, Y_1), \phi_l(X_1, Y_1')).$$

  Since there are m choices for i and $n(n-1)$ choices for $j \neq j'$, this case contributes:

  $$m\,n\,(n-1)\,\xi_{10}^{kl}.$$

- **Case 3:** Same Y, Different X (i.e., $j = j'$, but $i \neq i'$)

  Here, we compare two different subjects from Group 1 with the same subject from Group 2:

  $$\xi_{01}^{kl} := \mathrm{Cov}(\phi_k(X_1, Y_1), \phi_l(X_1', Y_1)).$$

  Since there are n choices for j and $m(m-1)$ choices for $i \neq i'$, this case contributes:

  $$n\,m\,(m-1)\,\xi_{01}^{kl}.$$

- **Case 4:** Different X, Different Y (i.e., $i \neq i'$ and $j \neq j'$) Since X_1, X_1' and Y_1, Y_1' are independent, the covariance in this case is zero:

  $$\mathrm{Cov}(\phi_k(X_1, Y_1), \phi_l(X_1', Y_1')) = 0.$$

  Thus, this case does not contribute to the total covariance.

Summing all contributions, we get:

$$\mathrm{Cov}(\hat{\tau}_k, \hat{\tau}_l) = \frac{1}{m^2 n^2} \left[m\, n\, \xi_{11}^{kl} + m\, n\, (n-1) \xi_{10}^{kl} + m\, n\, (m-1) \xi_{01}^{kl} \right].$$

Approximating $m - 1 \approx m$ and $n - 1 \approx n$ for large samples:

$$\mathrm{Cov}(\hat{\tau}_k, \hat{\tau}_l) \approx \frac{1}{mn} \xi_{11}^{kl} + \frac{1}{m} \xi_{10}^{kl} + \frac{1}{n} \xi_{01}^{kl}.$$

For large sample, the $\frac{1}{mn}\xi_{11}^{kl}$ term is negligeable compared to the two others, and can be ignored.

Finally, we get:

$$\sigma_{kl} = \frac{N}{m} \xi_{10}^{kl} + \frac{N}{n} \xi_{01}^{kl}.$$

The terms ξ_{10}^{kl} and ξ_{01}^{kl} can be simplified to:

$$\begin{aligned}
\xi_{10}^{11} &= \Pr(X_1 \succ Y_1, X_1 \succ Y_1') - \tau_1^2 \\
\xi_{10}^{22} &= \Pr(X_1 \prec Y_1, X_1 \prec Y_1') - \tau_2^2 \\
\xi_{10}^{12} &= \Pr(X_1 \succ Y_1, X_1 \prec Y_1') - \tau_1 \tau_2 \\
\xi_{01}^{11} &= \Pr(X_1 \succ Y_1, X_1' \succ Y_1) - \tau_1^2 \\
\xi_{01}^{22} &= \Pr(X_1 \prec Y_1, X_1' \prec Y_1) - \tau_2^2 \\
\xi_{01}^{12} &= \Pr(X_1 \succ Y_1, X_1' \prec Y_1) - \tau_1 \tau_2
\end{aligned}$$

2.4 Estimation of the Variance-covariance matrix

The preceding probabilities can be estimated from the data:

$$s_i^{(k)} = \sum_{j=1}^{n} \phi_k(X_i, Y_j), \quad t_j^{(k)} = \sum_{i=1}^{m} \phi_k(X_i, Y_j)$$

$$\begin{aligned}
\hat{\xi}_{10}^{11} &= \frac{\sum_i^m s_i^{(1)} (s_i^{(1)} - 1)}{mn(n-1)} - \hat{\tau}_1^2 \\
\hat{\xi}_{10}^{22} &= \frac{\sum_i^m s_i^{(2)} (s_i^{(2)} - 1)}{mn(n-1)} - \hat{\tau}_2^2 \\
\hat{\xi}_{10}^{12} &= \frac{\sum_i^m s_i^{(1)} s_i^{(2)}}{mn(n-1)} - \hat{\tau}_1 \hat{\tau}_2 \\
\hat{\xi}_{01}^{11} &= \frac{\sum_j^n t_j^{(1)} (t_j^{(1)} - 1)}{mn(m-1)} - \hat{\tau}_1^2 \\
\hat{\xi}_{01}^{22} &= \frac{\sum_j^n t_j^{(2)} (t_j^{(2)} - 1)}{mn(m-1)} - \hat{\tau}_2^2 \\
\hat{\xi}_{01}^{12} &= \frac{\sum_j^n t_j^{(1)} t_j^{(2)}}{mn(m-1)} - \hat{\tau}_1 \hat{\tau}_2
\end{aligned}$$

2.5 Estimation of the variance under the null hypothesis

The same developement is made in [Don+16]. The formulas (5c)-(5e) correspond to the calculation of σ_{11}. However, the estimation of the variance components (formulas (8a)-(8c)) use the estimate of the *win* probability τ under the null hypothesis (constrained estimator). Their estimator $\hat{\theta}_{K0}$ of the *win* probability is equal to $(\hat{\tau}_1 + \hat{\tau}_2)/2$. When the estimated win ratio is far from the null hypothesis, the confidence interval calculated with this estimator of the variance do not have the correct coverage.

The R package WINS implements the estimator of the variance described in [Don+16]

See [LR22] section 14.4.2 for more details on the use of the **unconstrained** estimator.

2.6 Estimation of the variance according to Yu and Ganju

A straightforward estimation of the variance is given in [YG22] for power calculation:

$$\mathrm{Var}(\log(\hat{\Psi})) \approx \frac{1}{N} \frac{4\,(1 + p_{\mathrm{tie}})}{3\,k\,(1-k)(1-p_{\mathrm{tie}})}$$

where $p_{\mathrm{tie}} = 1 - \tau_1 - \tau_2$ is the probability of ties and k is the proprtion of patient allocated to one of the two groups.

This is equivalent to:

$$\mathrm{Var}(\log(\hat{\Psi})) \approx \frac{4\,(m+n)(2 - \tau_1 - \tau_2)}{3\,m\,n\,(\tau_1 + \tau_2)}$$

This method has the advantage of being very simple. However, the variance estimation seems to be larger[1]from those presented in [BL16] and [Don+16].

The PASS Sample Size Software from NCSS[2]and the R package WRestimates implement both this method to estimate the variance.

3 Sample size

The variance estimators presented in [BL16] and [Don+16] are based on sample data and are not useable for sample size calculation.

We use [YG22] to estimate the sample size:

$$N \approx \frac{\sigma^2 (z_{1-\alpha} + z_{1-\beta})^2}{\log^2(\Psi_{\mathrm{true}})},$$

where

[1]TO DO: simulations

[2]See PASS documentation, Chapter 352, *Tests for Two Groups using the Win-Ratio Composite Endpoint.*

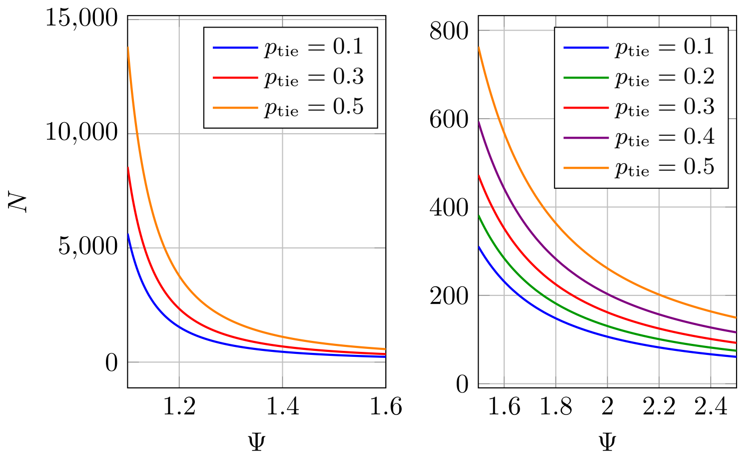

Figure 2: Total sample size for different values of Ψ (win ratio) and p_{tie} (probability of tie). Calcutaion based on formula (2) in [YG22].

- Ψ_{true} refers to the assumed or true value of the win ratio.
- The term σ^2 is given by

$$\sigma^2 = \frac{4\,(1 + p_{\text{tie}})}{3\,k\,(1-k)(1-p_{\text{tie}})}$$

- k is the proportion of patients allocated to one of the two groups (it does not matter which one, as we use $k\,(1-k)$ in the above formula).
- The probability of tie is given by $p_{\text{tie}} = 1 - \tau_1 - \tau_2$

The PASS Sample Size Software from NCSS and the R package WRestimates implement both this method for power calculation.

Sample size calculation is given Figure 2.

After discussion with the team about the parameters used for the sample size calculation, the power will be estimated based on simulations.

Another sample size formula is presented in [MKM22]. The latter requires more hypotheses on the parmaters and is less straightforward to use.

A sample size formula for the win odds (which closely related to the win ratio) has been presented in [Gas+21] and compared to the one of [YG22] in [GKK22].

4 Simulate a population with a given win ratio

Let π_W, π_L, and π_T be given probabilities satisfying $\pi_W + \pi_L + \pi_T = 1$. We wish to define two probability distributions F and G for random variables $X \sim F$ and $Y \sim G$, respectively, so that the following conditions hold:

$$\Pr(X > Y) = \pi_W, \quad \Pr(X < Y) = \pi_L, \quad \Pr(X = Y) = \pi_T.$$

A simple way is to make both X and Y take only two values (0 and 1) with appropriate probabilities.

We put all of the probability mass on exactly three outcomes for the pair (X, Y):

$$\Pr(X = 0, Y = 0) = \pi_T$$
$$\Pr(X = 1, Y = 0) = \pi_W$$
$$\Pr(X = 0, Y = 1) = \pi_L$$

The marginal distributions of X and Y are

$$\Pr(X = 0) = \pi_T + \pi_L, \quad \Pr(X = 1) = \pi_W$$
$$\Pr(Y = 0) = \pi_T + \pi_W, \quad \Pr(Y = 1) = \pi_L$$

or, in other words,

$$F \sim \text{Ber}(\pi_W), \quad G \sim \text{Ber}(\pi_L).$$

Does the variance of the estimator depend on the underlying distributions F and G? *Can be tested with data simulated from two normal distributions (no ties).*

5 Stratified win ratio

We use the definition given in [Don+18] and [Don+23].

We consider S strata, and define

- $X^{(s)}$ and $Y^{(s)}$ as the random outcomes of two patients in stratum s, with $s = 1, \dots, S$.
- $\tau_k^{(s)} = E[\phi_k(X^{(s)}, Y^{(s)})]$, $k = 1, 2$, as the probabilities of the events $X^{(s)} \succ Y^{(s)}$ and $Y^{(s)} \succ X^{(s)}$, respectively.

Consider two stratified samples $X_1^{(1)}, \dots, X_{m^{(1)}}^{(1)}, \dots, X_1^{(S)}, \dots, X_{m^{(S)}}^{(S)}$ and $Y_1^{(1)}, \dots, Y_{n^{(1)}}^{(1)}, \dots, Y_1^{(S)}, \dots, Y_{n^{(S)}}^{(S)}$ with $N^{(s)} = m^{(s)} + n^{(s)}$ denoting the sample size of stratum s.

Inside each stratum, an unbiased estimator of $\tau_k^{(s)}$ is given by:

$$\hat{\tau}_k^{(s)} = \frac{1}{m^{(s)}\, n^{(s)}} \sum_{i=1}^{m^{(s)}} \sum_{j=1}^{n^{(s)}} \phi_k(X_i^{(s)}, Y_j^{(s)}), \quad k = 1, 2,$$

The stratified estimator for τ_k is defined as

$$\hat{\tau}_k^{\text{strat}} = \frac{1}{W} \sum_{s=1}^{S} w^{(s)} \hat{\tau_k}^{(s)}$$

where

$$w^{(s)} = \frac{m^{(s)}\, n^{(s)}}{N^{(s)}} \quad \text{and} \quad W = \sum_{s=1}^{S} w^{(s)}.$$

We define the startified estimators of Δ and Ψ as follows:

$$\hat{\Delta}^{\text{strat}} = \hat{\tau}_1^{\text{strat}} - \hat{\tau}_2^{\text{strat}} \quad \text{and} \quad \hat{\Psi}^{\text{strat}} = \frac{\hat{\tau}_1^{\text{strat}}}{\hat{\tau}_2^{\text{strat}}}.$$

5.1 Variance

The strata are independent, so the variances and covariance of the stratified estimators $\hat{\tau}_k^{\text{strat}}$ and $\hat{\Psi}^{\text{strat}}$ are

$$\sigma_{kk}^{\text{strat}} = \text{Var}\left(\hat{\tau}_k^{\text{strat}}\right) = \frac{1}{W^2} \sum_{s=1}^{S} \left(w^{(s)}\right)^2 \text{Var}\left(\hat{\tau}_k{}^{(s)}\right)$$

and

$$\sigma_{12}^{\text{strat}} = \text{Cov}\left(\hat{\tau}_1^{\text{strat}}, \hat{\tau}_2^{\text{strat}}\right) = \frac{1}{W^2} \sum_{s=1}^{S} \left(w^{(s)}\right)^2 \text{Cov}\left(\hat{\tau}_1{}^{(s)}, \hat{\tau}_2{}^{(s)}\right)$$

where the components $\sigma_{kl}^{\text{strat}}$ are estimated as in the unstratified case.

6 Clustered win ratio

In this section, we refer to both [LD05] and [ZJ21]. However, since [ZJ21] contains errors, we adhere to [LD05] while following the general development outlined in [ZJ21].

Suppose we have p clusters in the treatment group, and q clusters in the control group. The clustered observations are vectors

$$\boldsymbol{X}^{(r)} = (X_1^{(r)}, \ldots, X_{m_r}^{(r)}), \quad r = 1, \ldots, p$$
$$\boldsymbol{Y}^{(s)} = (Y_1^{(s)}, \ldots, Y_{n_s}^{(s)}), \quad s = 1, \ldots, q$$

where $X_i^{(r)}$ denote the endpoint of the i-th subject in the r-th treatment cluster, and $Y_j^{(s)}$ be the endpoint of the j-th subject in the s-th control cluster.

We make the following assumptions concerning the distribution:

- The vectors $\boldsymbol{X}^{(1)}, \ldots, \boldsymbol{X}^{(p)}, \boldsymbol{Y}^{(1)}, \ldots, \boldsymbol{Y}^{(q)}$ are independent.
- The components of a same vector are exchangeable.
- The one-dimensional marginal distributions of all components of the $\boldsymbol{X}$-vectors are identical and denoted by F and similarly for the $\boldsymbol{Y}$-vectors where the one-dimensional marginal distributions are denoted by G.

We define the following clustered estimators

$$\hat{\tau}_k^{\text{clust}} = \frac{1}{p\,q\,\bar{m}_p\,\bar{n}_q} \sum_{r=1}^{p} \sum_{s=1}^{q} \sum_{i=1}^{m_r} \sum_{j=1}^{n_s} \phi_k(X_i^{(r)}, Y_j^{(s)}), \quad k = 1, 2$$

where

$$\bar{m}_p = \frac{1}{p} \sum_{r=1}^{p} m_r, \quad \text{and} \quad \bar{n}_q = \frac{1}{q} \sum_{s=1}^{q} n_s.$$

According to [LD05], each of $\hat{\tau}_k^{\text{clust}}$, $k = 1, 2$ are asymptotically normal with mean τ_k and variance $\sigma_{kk}^{\text{clust}}$ given by

$$\begin{aligned}\sigma_{kk}^{\text{clust}} =& \frac{1}{p\,\bar{m}_p^2} \Big(\bar{m}_p \operatorname{Var}(\phi_{k1}(X_1^{(1)})) + \bar{m}_p^{(2)} \operatorname{Cov}(\phi_{k1}(X_1^{(1)}), \phi_{k1}(X_2^{(1)})) \Big) \\ &+ \frac{1}{q\,\bar{n}_q^2} \Big(\bar{n}_q \operatorname{Var}(\phi_{k2}(Y_1^{(1)})) + \bar{n}_q^{(2)} \operatorname{Cov}(\phi_{k2}(Y_1^{(1)}), \phi_{k2}(Y_2^{(1)})) \Big)\end{aligned}$$

where

$$\bar{m}_p^{(2)} = \frac{1}{p} \sum_{r=1}^{p} (m_r^2 - m_r) \quad \text{and} \quad \bar{n}_q^{(2)} = \frac{1}{q} \sum_{s=1}^{q} (n_s^2 - n_s),$$

and

$$\begin{aligned}\phi_{11}(X) &= E(\phi_1(X,Y) \mid X) - \tau_1 = \Pr(X \succ Y \mid X) - \tau_1, \\ \phi_{12}(Y) &= E(\phi_1(X,Y) \mid Y) - \tau_1 = \Pr(X \succ Y \mid Y) - \tau_1, \\ \phi_{21}(X) &= E(\phi_2(X,Y) \mid X) - \tau_2 = \Pr(X \prec Y \mid X) - \tau_2, \\ \phi_{22}(Y) &= E(\phi_2(X,Y) \mid Y) - \tau_2 = \Pr(X \prec Y \mid Y) - \tau_2.\end{aligned}$$

Covariance

We use the following kernel decomposition

$$\phi_k(x,y) = \tau + \phi_{k1}(x) + \phi_{k2}(y) + \chi_k(x,y)$$

where the terms on the right hand side are defined by

$$\begin{aligned}\phi_{11}(X) &= E(\phi_1(X,Y) \mid X) - \tau_1 = \Pr(X \succ Y \mid X) - \tau_1, \\ \phi_{12}(Y) &= E(\phi_1(X,Y) \mid Y) - \tau_1 = \Pr(X \succ Y \mid Y) - \tau_1, \\ \phi_{21}(X) &= E(\phi_2(X,Y) \mid X) - \tau_2 = \Pr(X \prec Y \mid X) - \tau_2, \\ \phi_{22}(Y) &= E(\phi_2(X,Y) \mid Y) - \tau_2 = \Pr(X \prec Y \mid Y) - \tau_2, \\ \chi_k(x,y) &= \phi_k(x,y) - \phi_{k1}(x) - \phi_{k2}(y) - \tau_k.\end{aligned}$$

The esimator $\hat{\tau}_k^{\text{clust}}$ can be rewritten as[3]

$$\begin{aligned}\hat{\tau}_k^{\text{clust}} = \tau_k &+ \frac{1}{p\,\bar{m}_p}\sum_{r=1}^{p}\sum_{i=1}^{\bar{m}_p}\phi_{k1}(X_i^{(r)}) + \frac{1}{q\,\bar{n}_q}\sum_{s=1}^{q}\sum_{j=1}^{\bar{n}_q}\phi_{k2}(Y_j^{(s)})\\ &+ \frac{1}{p\,q\,\bar{m}_p\,\bar{n}_q}\sum_{r=1}^{p}\sum_{s=1}^{q}\boldsymbol{\chi}_k^{(r,s)}\end{aligned}$$

where

$$\boldsymbol{\chi}_k^{(r,s)} = \sum_{i=1}^{m_r}\sum_{j=1}^{n_s}\chi_k(X_i^{(r)}, Y_j^{(s)})$$

Let define the following quantities

$$A_k := \sum_{r=1}^{p}\sum_{i=1}^{m_r}\phi_{k1}(X_i^{(r)}), \quad B_k := \sum_{s=1}^{q}\sum_{j=1}^{n_s}\phi_{k2}(Y_j^{(s)}), \quad \Gamma_k := \sum_{r=1}^{p}\sum_{s=1}^{q}\boldsymbol{\chi}_k^{(r,s)}$$

and

$$\begin{aligned}
\zeta_{11}^{kl} &:= \text{Cov}(\phi_{k1}(X_1^{(1)}), \phi_{l1}(X_1^{(1)}))\\
\zeta_{12}^{kl} &:= \text{Cov}(\phi_{k1}(X_1^{(1)}), \phi_{l1}(X_2^{(1)}))\\
\zeta_{21}^{kl} &:= \text{Cov}(\phi_{k2}(Y_1^{(1)}), \phi_{l2}(Y_1^{(1)}))\\
\zeta_{22}^{kl} &:= \text{Cov}(\phi_{k2}(Y_1^{(1)}), \phi_{l2}(Y_2^{(1)}))\\
\eta_{11}^{kl} &:= \text{Cov}(\chi_k(X_1^{(1)}, Y_1^{(1)}), \chi_l(X_1^{(1)}, Y_1^{(1)}))\\
\eta_{12}^{kl} &:= \text{Cov}(\chi_k(X_1^{(1)}, Y_1^{(1)}), \chi_l(X_1^{(1)}, Y_2^{(1)}))\\
\eta_{21}^{kl} &:= \text{Cov}(\chi_k(X_1^{(1)}, Y_1^{(1)}), \chi_l(X_2^{(1)}, Y_1^{(1)}))\\
\eta_{22}^{kl} &:= \text{Cov}(\chi_k(X_1^{(1)}, Y_1^{(1)}), \chi_l(X_2^{(1)}, Y_2^{(1)}))
\end{aligned}$$

Using the same arguments as those used in the proof of Proposition 1 in [LD05], we have

$$\text{Cov}(A_k, B_l) = 0,\ \text{Cov}(A_k, \Gamma_l) = 0,\ \text{Cov}(B_k, \Gamma_l) = 0,$$

for $k = 1, 2$ and $l = 1, 2$.

Thus, the covariance of the estimators $\hat{\tau}_k^{\text{clust}}$ expands as

$$\begin{aligned}\text{Cov}(\hat{\tau}_k^{\text{clust}}, \hat{\tau}_l^{\text{clust}}) = &\frac{1}{(p\,\bar{m}_p)^2}\text{Cov}(A_k, A_l) + \frac{1}{(q\,\bar{n}_q)^2}\text{Cov}(B_k, B_l)\\ &+ \frac{1}{(p\,q\,\bar{m}_p\,\bar{n}_q)^2}\text{Cov}(\Gamma_k, \Gamma_l)\end{aligned}$$

---

[3] Details of the development:

$$\begin{aligned}
&\sum_{r=1}^{p}\sum_{s=1}^{q}\sum_{i=1}^{m_p}\sum_{j=1}^{n_q}\phi_k(X_i^{(r)}, Y_j^{(s)})\\
&= \sum_{r=1}^{p}\sum_{s=1}^{q}\sum_{i=1}^{m_r}\sum_{j=1}^{n_q}\Big(\tau_k + \phi_{k1}(X_i^{(r)}) + \phi_{k2}(Y_j^{(s)}) + \chi_k(X_i^{(r)}, Y_j^{(s)})\Big)\\
&= p\,q\,\bar{m}_p\,\bar{n}_q\tau_k + q\,\bar{n}_q\sum_{r=1}^{p}\sum_{i=1}^{m_p}\phi_{k1}(X_i^{(r)}) + p\,\bar{m}_p\sum_{s=1}^{q}\sum_{j=1}^{n_q}\phi_{k2}(Y_j^{(s)}) + \sum_{r=1}^{p}\sum_{s=1}^{q}\boldsymbol{\chi}_k^{(r,s)}
\end{aligned}$$

Since the vectors $\boldsymbol{X}^{(r)}, r = 1, \dots, p$ are independent, we have

$$\begin{aligned}
\operatorname{Cov}(A_k, A_l) &= \sum_{r=1}^{p} \operatorname{Cov}\big(\sum_{i=1}^{m_r} \phi_{k1}(X_i^{(r)}), \sum_{i'=1}^{m_r} \phi_{l1}(X_{i'}^{(r)})\big) \\
&= \sum_{r=1}^{p} \sum_{i=1}^{m_r} \operatorname{Cov}(\phi_{k1}(X_i^{(r)}), \phi_{l1}(X_i^{(r)})) \\
&\quad + \sum_{r=1}^{p} \sum_{i=1}^{m_r} \sum_{\substack{i'=1 \\ i' \neq i}}^{m_r} \operatorname{Cov}(\phi_{k1}(X_i^{(r)}), \phi_{l1}(X_{i'}^{(r)})) \\
&= p \left(\bar{m}_p \zeta_{11}^{kl} + \bar{m}_p^{(2)} \zeta_{12}^{kl} \right)
\end{aligned}$$

where

$$\bar{m}_p^{(2)} := \frac{1}{p} \sum_{r=1}^{p} (m_r^2 - m_r).$$

Similarly, we obtain

$$\operatorname{Cov}(B_k, B_l) = q \left(\bar{n}_q \zeta_{21}^{kl} + \bar{n}_q^{(2)} \zeta_{22}^{kl} \right)$$

where

$$\bar{n}_q^{(2)} := \frac{1}{q} \sum_{s=1}^{q} (n_s^2 - n_s).$$

The quantities $\boldsymbol{\chi}_k^{(r,s)}$ are all independent, and thus

$$\operatorname{Cov}(\Gamma_k, \Gamma_l) = \sum_{r=1}^{p} \sum_{s=1}^{q} \operatorname{Cov}(\boldsymbol{\chi}_k^{(r,s)}, \boldsymbol{\chi}_l^{(r,s)})$$

where

$$\operatorname{Cov}(\boldsymbol{\chi}_k^{(r,s)}, \boldsymbol{\chi}_l^{(r,s)}) = \sum_{i=1}^{m_r} \sum_{j=1}^{n_s} \sum_{i'=1}^{m_r} \sum_{j'=1}^{n_s} \operatorname{Cov}\big(\chi_k(X_i^{(r)}, Y_j^{(s)}), \chi_l(X_{i'}^{(r)}, Y_{j'}^{(s)})\big)$$

The terms in the sum in the right hand side of the previous equation can be treated in 4 different cases:

- There are $m_r \, n_s$ indices such that

$$\operatorname{Cov}(\chi_k(X_i^{(r)}, Y_j^{(s)}), \chi_l(X_i^{(r)}, Y_j^{(s)})) = \eta_{11}^{kl}.$$

- There are $m_r \, n_s \, (n_s - 1)$ indices such that

$$\operatorname{Cov}(\chi_k(X_i^{(r)}, Y_j^{(s)}), \chi_l(X_i^{(r)}, Y_{j'}^{(s)})) = \eta_{12}^{kl}.$$

- There are $m_r \, n_s \, (m_r - 1)$ indices such that

$$\operatorname{Cov}(\chi_k(X_i^{(r)}, Y_j^{(s)}), \chi_l(X_{i'}^{(r)}, Y_j^{(s)})) = \eta_{21}^{kl}.$$

- There are $m_r\, n_s\, (m_r - 1)\, (n_s - 1)$ indices such that

$$\mathrm{Cov}(\chi_k(X_i^{(r)}, Y_j^{(s)}), \chi_l(X_{i'}^{(r)}, Y_{j'}^{(s)})) = \eta_{22}^{kl}.$$

Thus, the covariance $\mathrm{Cov}(\Gamma_k, \Gamma_l)$ can be expressed as

$$\mathrm{Cov}(\Gamma_k, \Gamma_l) = p\, q \left(\bar{m}_p\, \bar{n}_q\, \eta_{11}^{kl} + \bar{m}_p\, \bar{n}_q^{(2)}\, \eta_{12}^{kl} + \bar{m}_p^{(2)}\, \bar{n}_q\, \eta_{21}^{kl} + \bar{m}_p^{(2)}\, \bar{n}_q^{(2)}\, \eta_{22}^{kl} \right)$$

Finally, putting everything together, the covariance of the estimators $\hat{\tau}_k^{\mathrm{clust}}$ is

$$\begin{aligned} \mathrm{Cov}(\hat{\tau}_k^{\mathrm{clust}}, \hat{\tau}_l^{\mathrm{clust}}) = \frac{1}{p\, \bar{m}_p^2} \left(\bar{m}_p \zeta_{11}^{kl} + \bar{m}_p^{(2)} \zeta_{12}^{kl} \right) + \frac{1}{q\, \bar{n}_q^2} \left(\bar{n}_q \zeta_{21}^{kl} + \bar{n}_q^{(2)} \zeta_{22}^{kl} \right) \\ + \frac{1}{p\, q} \left(\frac{\eta_{11}^{kl}}{\bar{m}_p\, \bar{n}_q} + \frac{\bar{n}_q^{(2)}\, \eta_{12}^{kl}}{\bar{m}_p\, \bar{n}_q^2} + \frac{\bar{m}_p^{(2)}\, \eta_{21}^{kl}}{\bar{m}_p^2\, \bar{n}_q} + \frac{\bar{m}_p^{(2)}\, \bar{n}_q^{(2)}\, \eta_{22}^{kl}}{(\bar{m}_p\, \bar{n}_q)^2} \right) \end{aligned}$$

References

[BL16] Ionut Bebu and John M. Lachin. "Large Sample Inference for a Win Ratio Analysis of a Composite Outcome Based on Prioritized Components". In: *Biostatistics* 17.1 (Jan. 2016), pp. 178–187. DOI: 10.1093/biostatistics/kxv032.

[Don+16] Gaohong Dong et al. "A Generalized Analytic Solution to the Win Ratio to Analyze a Composite Endpoint Considering the Clinical Importance Order among Components". In: *Pharmaceutical Statistics* 15.5 (2016), pp. 430–437. DOI: 10.1002/pst.1763.

[Don+18] Gaohong Dong et al. "The Stratified Win Ratio". In: *Journal of Biopharmaceutical Statistics* 28.4 (July 2018), pp. 778–796. DOI: 10.1080/10543406.2017.1397007.

[Don+23] Gaohong Dong et al. "The Stratified Win Statistics (Win Ratio, Win Odds, and Net Benefit)". In: *Pharmaceutical Statistics* 22.4 (2023), pp. 748–756. DOI: 10.1002/pst.2293.

[Gas+21] Samvel B. Gasparyan et al. "Power and Sample Size Calculation for the Win Odds Test: Application to an Ordinal Endpoint in COVID-19 Trials". In: *Journal of Biopharmaceutical Statistics* 31.6 (Nov. 2021), pp. 765–787. DOI: 10.1080/10543406.2021.1968893.

[GKK22] Samvel B. Gasparyan, Elaine K. Kowalewski, and Gary G. Koch. "Comments on "Sample Size Formula for a Win Ratio Endpoint" by R. X. Yu and J. Ganju". In: *Statistics in Medicine* 41.14 (2022), pp. 2688–2690. DOI: 10.1002/sim.9379.

[LD05] Mei-Ling Ting Lee and Herold G. Dehling. "Generalized Two-Sample U-statistics for Clustered Data". In: *Statistica Neerlandica* 59.3 (2005), pp. 313–323. DOI: 10.1111/j.1467-9574.2005.00298.x.

[LR22] Erich L. Lehmann and Joseph P. Romano. *Testing Statistical Hypotheses*. Forth edition. Springer Texts in Statistics. Cham: Springer, 2022. DOI: 10.1007/978-3-030-70578-7.

[MKM22] Lu Mao, KyungMann Kim, and Xinran Miao. "Sample Size Formula for General Win Ratio Analysis". In: *Biometrics* 78.3 (Sept. 2022), pp. 1257–1268. DOI: 10.1111/biom.13501.

[YG22] Ron Xiaolong Yu and Jitendra Ganju. "Sample Size Formula for a Win Ratio Endpoint". In: *Statistics in Medicine* 41.6 (2022), pp. 950–963. DOI: 10.1002/sim.9297.

[ZJ21] Di Zhang and Jong-Hyeon Jeong. "Inference on Win Ratio for Cluster-Randomized Semi-Competing Risk Data". In: *Japanese Journal of Statistics and Data Science* 4.2 (Dec. 2021), pp. 1263–1292. DOI: 10.1007/s42081-021-00131-1.

A Estimation of $\xi_{\cdot\cdot}^{kl}$

To estimate the value ξ_{11}^{10}, we estimate $\Pr(X \succ Y, X \succ Y')$ with

$$\widehat{\Pr}(X \succ Y, X \succ Y') = \frac{1}{m\,n\,(n-1)} \sum_{i=1}^{m} \sum_{j=1}^{n} \sum_{\substack{j'=1 \\ j' \neq j}}^{n} 1_{\{X_i \succ Y_j, X_i \succ Y_{j'}\}}$$

Using that

$$1_{\{X \succ Y, X \succ Y'\}} = 1_{\{X \succ Y\}} 1_{\{X \succ Y'\}} \quad \text{and} \quad 1_{\{X \succ Y\}}^2 = 1_{\{X \succ Y\}},$$

the multiple sum can be rewritten as

$$\begin{aligned}
&\sum_{i=1}^{m} \sum_{j=1}^{n} \sum_{\substack{j'=1 \\ j' \neq j}}^{n} 1_{\{X_i \succ Y_j, X_i \succ Y_{j'}\}} \\
&\quad = \sum_{i=1}^{m} \sum_{j=1}^{n} 1_{\{X_i \succ Y_j\}} \sum_{\substack{j'=1 \\ j' \neq j}}^{n} 1_{\{X_i \succ Y_{j'}\}} \\
&\quad = \sum_{i=1}^{m} \sum_{j=1}^{n} 1_{\{X_i \succ Y_j\}} \Big(\sum_{j'=1}^{n} 1_{\{X_i \succ Y_{j'}\}} - 1_{\{X_i \succ Y_j\}} \Big) \\
&\quad = \sum_{i=1}^{m} \Big(\sum_{j=1}^{n} 1_{\{X_i \succ Y_j\}} \sum_{j'=1}^{n} 1_{\{X_i \succ Y_{j'}\}} - \sum_{j=1}^{n} 1_{\{X_i \succ Y_j\}} \Big) \\
&\quad = \sum_{i=1}^{m} \Big(\big(s_i^{(1)}\big)^2 - s_i^{(1)} \Big) \\
&\quad = \sum_{i=1}^{m} s_i^{(1)} \big(s_i^{(1)} - 1\big)
\end{aligned}$$