Chapter 353

Tests for Two Groups using the Win-Ratio Composite Endpoint in a Stratified Design

Introduction

This procedure calculates power and sample size for tests that compare two groups in a stratified design using the weighted stratified win ratio composite endpoint. The win ratio is a method of combining several endpoints in survival-type studies. The original paper on this method, Pocock, Ariti, Collier, and Wang (2012), appeared in the European Heart Journal and cardiology has continued to show interest in this technique. The sample size formulas used by this procedure were published in Yu and Ganju (2022).

Technical Details

The Win Ratio

The weighted stratified win ratio (*WR*) is the ratio of wins to losses. It is calculated as

$$WR = \frac{\sum_{h=1}^{H} w_h N_h P_{W_h}}{\sum_{h=1}^{H} w_h N_h P_{L_h}}$$

where H is the number of strata which are indexed by h, w_h is a fixed weight of stratum h, N_h is the sample size of stratum h, P_{W_h} is the probability of a win in group 1 (the treatment group) of stratum h, and P_{L_h} is the probability of a loss in group 1, which is the same as a win in group 2 (the reference group) of stratum h. These wins or losses are the result of comparisons between each member of the treatment group with each member of the reference group within stratum h.

The composite endpoints Win and Loss are calculated in a particular way so that more serious outcomes receive more weight than outcomes of lesser importance. This is done as follows. During the planning phase, the endpoints are sorted in order of priority (importance or seriousness) from high to low. Each subject in group 1 of stratum h is compared with each subject in group 2 of stratum h. Hence there are $N_{1h} \times N_{2h}$ comparisons.

These comparisons are made as follows. First, the endpoint of highest seriousness (e.g., cardiovascular death) is evaluated. If this comparison points to a win or a loss, the comparison process stops and the comparison is recorded as a win or loss. Otherwise, the comparison focuses on the next highest priority endpoint (e.g., hospitalization for heart failure). If there is a clear winner or loser, that outcome is recorded and the process stops. If the comparison does not produce a winner or a loser, focus continues on down the line until the last endpoint is evaluated. If the comparison based on the last endpoint does not determine a winner or loser, the comparison is declared a tie. P_{T_h} is the probability of a tie within stratum h. In this procedure, it is assumed that $P_{T_h} = P_T = P_{TIE}$ for all strata.

Using this method of comparison, the procedure allows several types of outcomes to be assessed together, while making sure that the most serious outcome is considered first.

Each comparison results in one of three possibilities:

Win

Group 1 is determined to be better than group 2. The probability that a win is observed in stratum h is P_{W_h}.

Loss

Group 2 is determined to be better than group 1. The probability that a loss is observed in stratum h is P_{L_h}.

Tie

The winner could not be determined because no endpoint was observed for either subject. The probability of this event occurring in stratum h is P_{T_h}. In this procedure, we assume that $P_{T_h} = P_T = P_{TIE}$ for all strata.

Since there are only three possibilities, $P_{W_h} + P_{L_h} + P_{TIE} = 1$ for all h.

Group Sample Size Allocation

Within each stratum, subjects are allocated to either the treatment group (group 1) or the reference group (group 2). Let N_{1h} be the number of subjects allocated to group 1 and N_{2h} be the number of subjects allocated to group 2 in stratum h. Furthermore, with $N_h = N_{1h} + N_{2h}$ total subjects in stratum h, the proportion of subjects allocated to group 1 in stratum h is

$$k_h = \frac{N_{1h}}{N_h}$$

In this procedure, the proportion of subjects allocated to group 1 (k_h) is assumed to be constant for all strata, i.e.,

$$k_h = k$$

for all strata. In most studies, the percentage of subjects allocated to group 1 is 50%. However, this value may vary from study to study.

Hypotheses

Three statistical hypotheses that are commonly used are

$$H_0: WR \leq 1 \quad \text{vs.} \quad H_1: WR > 1$$

$$H_0: WR \geq 1 \quad \text{vs.} \quad H_1: WR < 1$$

$$H_0: WR = 1 \quad \text{vs.} \quad H_1: WR \neq 1$$

Power Calculation

The power formula shown below is given in Yu and Ganju (2022). It uses the following terminology:

$\#W_h$ the number of wins in stratum h. Note that $\#W_h = N_h P_{W_h}$.

$\#L_h$ the number of losses in stratum h. Note that $\#L_h = N_h P_{L_h}$.

$\#T_h$ the number of ties in stratum h. Note that $\#T_h = N_h P_T$.

N_h the sample size of stratum h, consisting of N_{1h} in group 1 and N_{2h} in group 2.

$k = N_{1h}/N_h$ the proportion of subjects allocated to group 1 for all strata.

w_h a fixed weight for stratum h.

N_{ph} the total number of comparisons between subjects in group 1 and group 2. Note that $N_{ph} = N_{1h} \times N_{2h} = \#W_h + \#L_h + \#T_h = k(1-k)N_h^2$.

P_T the probability of a tie for all strata, i.e., $P_{T_h} = P_T = P_{TIE}$ for all strata.

WR the win ratio where $WR = \frac{\sum_{h=1}^{H} w_h N_h P_{W_h}}{\sum_{h=1}^{H} w_h N_h P_{L_h}}$. This is assumed by the alternative hypothesis.

WR_0 the win ratio assumed by the null hypothesis. Note that here, $WR_0 = 1$.

$V(\ln(WR))$ the variance of $\ln(WR)$. This variance is given by $V(\ln(WR)) \approx \sigma^2 \frac{\sum_{h=1}^{H} w_h^2 N_h^3}{\left(\sum_{h=1}^{H} w_h N_h^2\right)^2}$ where $\sigma^2 = \frac{4(1+P_T)}{3k(1-k)(1-P_T)}$. Because P_T and k are assumed to be constant across strata, σ^2 is also constant across strata.

Using the information above, the power of a one-sided hypothesis is approximated by

$$\text{Power} = 1 - \Phi\left(z_\alpha - \frac{\ln(WR)}{\sqrt{V(\ln(WR))}}\right)$$

This formula can be used in a search algorithm to determine the necessary sample size.

Example 1 – Calculating Sample Size

Researchers wish to determine the sample size of a stratified two-group equal-allocation trial with three strata. They will use a two-sided significance level of 0.05 and require a sample size large enough to achieve a power of 0.9. They set the probability of a tie at 0.3. They want to detect win ratios of 1.5, 1.6, and 1.5 in the three strata. To understand the sensitivity of the sample size to the values of the win ratios, they will use the following win ratio multipliers: 1.00 1.04 1.08.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 1** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab

Solve For	**Sample Size**
Alternative Hypothesis	**Two-Sided (H1: WR ≠ 1)**
Power	**0.90**
Alpha	**0.05**
Sample Size Allocation	**Equal Strata Sample Size Allocation**
Percent in Group 1	**50**
PTIE (Probability of a Tie)	**0.3**
Strata Weights	**All Strata Weights are Equal**
Win Ratio Input Type	**Win Ratio**
Set A Number of Strata	**1**
Set A Win Ratio	**1.5**
Set B Number of Strata	**1**
Set B Win Ratio	**1.6**
Set C Number of Strata	**1**
Set C Win Ratio	**1.5**
Set D Number of Strata	**0**
Set E Number of Strata	**0**
More	**Unchecked**
Add sets of strata win ratios with different magnitudes but identical ratio patterns	**Checked**
Kw (WR Multiplier)	**1 1.04 1.08**

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Reports

Numeric Results

Solve For:	Sample Size
Sample Size Allocation:	Equal Strata Sample Size Allocation
Test Type:	Stratified Weighted Win Ratio
Hypotheses:	H0: WR = 1 vs. H0: WR ≠ 1
Number of Strata:	3

Stratum			Sample Size				Win Ratio	Endpoint Probabilities			Win Ratio Multiplier	
ID	Weight	Power	N1	N2	N	Percent in Group 1	WR	PWIN	PLOSS	PTIE	Kw	Alpha
A	1		96	95	191	50	1.50000	0.42000	0.28000	0.3	1.00	0.05
B	1		96	95	191	50	1.60000	0.43077	0.26923	0.3	1.00	0.05
C	1		96	95	191	50	1.50000	0.42000	0.28000	0.3	1.00	0.05
Total		0.90092	288	285	573		1.53247					
A	1		80	80	160	50	1.56000	0.42656	0.27344	0.3	1.04	0.05
B	1		80	80	160	50	1.66400	0.43724	0.26276	0.3	1.04	0.05
C	1		80	80	160	50	1.56000	0.42656	0.27344	0.3	1.04	0.05
Total		0.90055	240	240	480		1.59375					
A	1		69	68	137	50	1.62000	0.43282	0.26718	0.3	1.08	0.05
B	1		69	68	137	50	1.72800	0.44340	0.25660	0.3	1.08	0.05
C	1		69	68	137	50	1.62000	0.43282	0.26718	0.3	1.08	0.05
Total		0.90068	207	204	411		1.65504					

Stratum ID	The label of the stratum defined on this report line.
Stratum Weight	The weight assigned to this stratum.
Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true. Note that the power is only calculated for the combination of all strata.
N1 and N2	The number of subjects in groups 1 and 2, respectively.
N	The stratum sample size. N = N1 + N2. The last line gives the total sample size for the whole study, summed across all strata.
Percent in Group 1	The percent of the stratum sample size, N, to be allocated to Group 1.
WR	The weighted stratified win ratio, which is total number of wins divided by the total number of losses. This is the effect-size measure.
PWIN, PLOSS, PTIE	The respective probabilities that a comparison between two subjects in this stratum results in a win, a loss, or a tie (neither a win nor a loss) for the subject in group 1 (the treatment group).
Kw	The WR multiplier that is used to transform each stratum win ratio. The transformation is made by multiplying this value times the original value of WR.
Alpha	The probability of rejecting a true null hypothesis.

Summary Statements

A two-group stratified design with 3 strata (with a composite end-point) will be used to test whether the win ratio is different from 1 (H0: WR = 1 versus H1: WR ≠ 1, where WR is the win ratio: PWIN / PLOSS). The comparison will be made using a two-sided, natural-log-based, weighted stratified win ratio Z-test, with a Type I error rate (α) of 0.05. In each stratum, 50% of the subjects will be assigned to the treatment group (Group 1) and the remaining subjects will be assigned to the reference group (Group 2). The probability of a tie is assumed to be 0.3 for all strata. To detect a weighted stratified win ratio of 1.53247 with 90% power, the total number of subjects needed will be 573 (288 in Group 1 and 285 in Group 2, allocated across the 3 strata).

References

Dong, G., Hoaglin, D.C., et al. 2020. 'The Win Ratio: On Interpretation and Handling Ties.' Statistics in Biopharmaceutical Research. 12(1):99-106.

Dong, G., Qiu, J., Wang, D., and Vandemeulebroecke, M. 2018. 'The stratified win ratio.' Journal of Biopharmaceutical Statistics. 28(4):778-796.

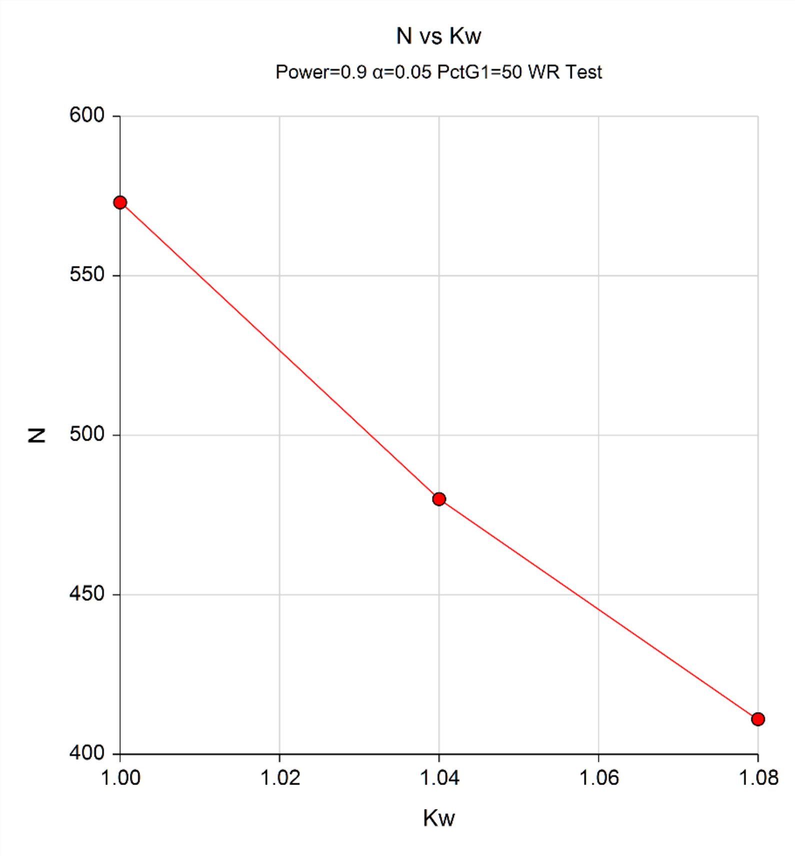
Pocock, S.J., Ariti, C.A., Collier T.J., Wang D. 2012. 'The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities.' European Heart Journal. 33. 176-182.

Yu, R.X., Ganju, J. 2022. 'Sample size formula for a win ratio endpoint.' Statistics in Medicine. 41(6):950-963. doi:10.1002/sim.9297.

This report shows the sample sizes for the indicated scenarios.

Plots Section

Plots



This plot represents the required sample sizes for various win ratio values determined by the win ratio multiplier Kw.

Example 2 – Validation by Hand Calculations

We could not find a validation example in the literature, so we made an example that we could program in Excel. In this example, we will solve for power for a one-sided test with two strata. The total sample size is 200 with equal allocation across strata and groups. This amounts to 50 subjects within each group within each stratum. The probability of obtaining a tie is set to 0.5. The probability of a win in stratum A is 0.31 and in stratum B is 0.32. The corresponding strata weights are 1.5 and 2.2.

Using an Excel spreadsheet, we obtained individual stratum win ratios of 1.631579 and 1.777778. The combined experiment win ratio was 1.716593. The variance of the log win ratio was 0.082863. The power was 0.591826.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 2** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab

Solve For .... **Power**
Alternative Hypothesis .... **One-Sided (H1: WR > 1)**
Alpha.. **0.05**
Sample Size Allocation .... **Enter Total Sample Size and use Equal Strata Allocations**
Total Sample Size... **200**
Percent in Group 1....................................... **50**
PTIE (Probability of a Tie).............................. **0.5**
Strata Weights .... **Enter Strata Weights Individually**
Win Ratio Input Type .... **Probability of a Win**
Set A Number of Strata................................. **1**
Set A Probability of a Win **0.31**
Set A Weight... **1.5**
Set B Number of Strata................................. **1**
Set B Probability of a Win **0.32**
Set B Weight... **2.2**
Set C Number of Strata................................. **0**
Set D Number of Strata................................. **0**
Set E Number of Strata................................. **0**
More.. **Unchecked**
Add sets of strata probabilities of a win with different magnitudes but identical ratio patterns .... **Unchecked**

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Results

Solve For: Power
Sample Size Allocation: Equal Strata Sample Size Allocation
Test Type: Stratified Weighted Win Ratio
Hypotheses: H0: WR ≤ 1 vs. H1: WR > 1
Number of Strata: 2

Stratum			Sample Size					Win Ratio	Endpoint Probabilities			
ID	Weight	Power	N1	N2	N	Percent in Group 1	Stratum Allocation	WR	PWIN	PLOSS	PTIE	Alpha
A	1.5		50	50	100	50	1	1.63158	0.31	0.19	0.5	0.05
B	2.2		50	50	100	50	1	1.77778	0.32	0.18	0.5	0.05
Total		0.59183	100	100	200			1.71659				

PASS also calculates a power of 0.59183 which validates the procedure.