Chapter 537

Tests for Two Correlated Proportions with Incomplete Observations

Introduction

This procedure provides power analysis and sample size calculation for studies that use a paired design that yield two binary outcomes that may be incomplete. That is, in some pairs, either the first or the second observation is missing, but not both.

Without incomplete data, the standard analysis is McNemar's Test (see McNemar (1947)), and **PASS** includes several procedures that analyze this test. This test requires that observations with at least one missing observation must be discarded. Zhang, Cao, and Ahn (2017) present sample size formulas for two extensions of McNemar's Test that use the information provided by pairs that are only partially observed. The first method uses a test that is the result of Thompson (1995), Ekbohm (1982), and Choi and Stablein (1982) the requires the estimation of the two marginal probabilities from the complete and the partial data. The difference of these two estimates is then used for the test.

The second method, proposed by Zhang, Cao, and Ahn (2017), uses the differences between observational pairs directly. This allows this method to be more efficient in most (but not all) situations.

Another method, also available for sample size calculation in **PASS**, deals with the important case in which all missing values occur in the second observation. We refer to this as *dropout*. We refer to that procedure for further details.

Technical Details

Consider the following table that summarizes the results of a paired design in which one observation of the pair is designated as a treatment and the other is designated as a standard.

	Standard		
Treatment	**Yes**	**No**	**Total**
Yes	P11	P10	Pt
No	P01	P11	1 - Pt
Total	Ps	1 - Ps	1

McNemar's test statistic is the estimated odds ratio

$$Mc = \frac{P10}{P01}$$

Our formulation comes from Zhang, Cao, and Ahn (2017). Denote a binary observation by Y_{ij} where *j* = t, s gives the group and *i* = 1, 2, ..., *N* gives the subject. A "success" is represented by $Y_{ij} = 1$ and a "failure" by $Y_{ij} = 0$. Separate the *N* subjects into three sections so that $N = m_1 + m_2 + m_3$ where m_1 are the subjects

that only observed the standard outcome, m_3 are the subjects that only observed the treatment outcome, and m_2 are the subjects that observed both the treatment and standard outcomes.

Let

$$\boldsymbol{Y}_1 = \{Y_{is}, i = 1, \dots, m_1\};$$

$$\boldsymbol{Y}_2 = \{(Y_{is}, Y_{it}), i = m_1 + 1, \dots, m_1 + m_2\};$$

$$\boldsymbol{Y}_3 = \{Y_{it}, i = m_1 + m_2 + 1, \dots, N\};$$

$$Pms = m_1/N;$$

$$Pmt = m_3/N$$

Method P

This method is described as follows

1. Construct the estimators of the marginal proportions $\hat{P}_s^{(P)}$ and $\hat{P}_t^{(P)}$ from $\boldsymbol{Y}_2$, the paired data. Use $\hat{P}_s^{(P)} = \sum_{i=m_1+1}^{m_1+m_2} Y_{is}/m_2$ and $\hat{P}_t^{(P)} = \sum_{i=m_1+1}^{m_1+m_2} Y_{it}/m_2$.
2. Construct the estimator of the marginal standard proportion $\hat{P}_s^{(U)}$ from $\boldsymbol{Y}_1$, the unpaired standard data. Use $\hat{P}_s^{(U)} = \sum_{i=1}^{m_1} Y_{is}/m_1$.
3. Construct the estimator of the marginal treatment proportion $\hat{P}_t^{(U)}$ from $\boldsymbol{Y}_3$, the unpaired treatment data. Use $\hat{P}_t^{(U)} = \sum_{i=m_1+m_2+1}^{N} Y_{it}/m_3$.
4. Construct the hybrid estimator using $\hat{P}_s^{(H)} = w_s\hat{P}_s^{(P)} + (1 - w_s)\hat{P}_s^{(U)}$ where $w_s = m_2/(m_1 + m_2)$. This simplifies to $\hat{P}_s^{(H)} = \sum_{i=1}^{m_1+m_2} Y_{is}/(m_1 + m_2)$.
5. Construct the hybrid estimator using $\hat{P}_t^{(H)} = w_t\hat{P}_t^{(P)} + (1 - w_t)\hat{P}_t^{(U)}$ where $w_t = m_2/(m_2 + m_3)$. This simplifies to $\hat{P}_t^{(H)} = \sum_{i=m_1+m_2+1}^{N} Y_{it}/(m_2 + m_3)$.
6. Construct the difference $\hat{\Delta}_P = \hat{P}_t^{(H)} - \hat{P}_s^{(H)}$. Note that $\sqrt{N}(\hat{\Delta}_P - \Delta)$ is approximately normal with mean 0 and variance $\sigma_P^2 = \frac{P_s(1-P_s)}{1-P_{mt}} + \frac{P_t(1-P_t)}{1-P_{ms}} - \frac{2(1-P_{ms}-P_{mt})(P11-P_sP_t)}{(1-P_{ms})(1-P_{mt})}$. It can be estimated using the hybrid estimators found in steps 4 and 5.

Zhang, Cao, and Ahn (2017) provide a formula for the overall sample size for a two-sided test as follows

$$N_P = \frac{\sigma_P^2\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2}{\Delta^2}$$

where and α is the probability of a type-I error and β is the probability of a type-II error.

Estimating P11

Obtaining an estimate of $P11$ is often problematic. This problem is solved by using the within-subject correlation coefficient which may be easier to estimate. As outlined in Zhang, Cao, and Ahn (2017), the relationship between $P11$ and the correlation is

$$\rho = \frac{P11 - P_s P_t}{\sqrt{P_s P_t (1 - P_s)(1 - P_t)}}$$

Using this relationship, values of ρ can be entered and transformed to the corresponding value of $P11$. The only concern is that values of ρ be used that limit $P11$ to be between 0 and 1.

The lower and upper limits of the correlation are

$$\rho_L = \max\left\{-\sqrt{\frac{P_s P_t}{(1 - P_s)(1 - P_t)}}, -\sqrt{\frac{(1 - P_s)(1 - P_t)}{P_s P_t}}\right\}$$

$$\rho_U = \min\left\{\sqrt{\frac{P_s(1 - P_t)}{P_t(1 - P_s)}}, \sqrt{\frac{P_t(1 - P_s)}{P_s(1 - P_t)}}\right\}$$

Method D

This method is described as follows

1. Construct the paired estimator of the difference $\widehat{\Delta}^{(\mathrm{P})}$ directly from $\boldsymbol{Y}_2$, the paired data. Use $\widehat{\Delta}^{(\mathrm{P})} = \sum_{i=m_1+1}^{m_1+m_2}(Y_{it} - Y_{is})/m_2$.
2. Construct the estimator of the marginal standard proportion $\hat{P}_s^{(U)}$ from $\boldsymbol{Y}_1$, the unpaired standard data. Use $\hat{P}_s^{(U)} = \sum_{i=1}^{m_1} Y_{is}/m_1$.
3. Construct the estimator of the marginal treatment proportion $\hat{P}_t^{(U)}$ from $\boldsymbol{Y}_3$, the unpaired treatment data. Use$\hat{P}_t^{(U)} = \sum_{i=m_1+m_2+1}^{N} Y_{it}/m_3$.
4. Construct the unpaired estimator of the difference $\widehat{\Delta}^{(\mathrm{U})}$ from the results of steps 2 and 3. Use $\widehat{\Delta}^{(\mathrm{U})} = \hat{P}_t^{(U)} - \hat{P}_s^{(U)}$.
5. Construct the hybrid estimator using $\widehat{\Delta}_D = w\,\widehat{\Delta}^{(\mathrm{U})} + (1 - w)\widehat{\Delta}^{(\mathrm{P})}$ where $w = V_U/(V_U + V_P)$, $V_U = \frac{P_s(1-P_s)}{P_{ms}} + \frac{P_t(1-P_t)}{P_{mt}}$, and $V_P = \frac{P01+P10-(P01-P10)^2}{1-P_{ms}-P_{mt}}$.
6. Note that $\sqrt{N}(\widehat{\Delta}_D - \Delta)$ is approximately normal with mean 0 and variance $\sigma_D^2 = V_U V_P/(V_U + V_P)$.

Zhang, Cao, and Ahn (2017) provide a formula for the overall sample size for a two-sided test as follows

$$N_D = \frac{\sigma_D^2\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2}{\Delta^2}$$

where α is the probability of a type-I error and β is the probability of a type-II error.

Estimating P01 and P10

Obtaining estimates of *P*01 and *P*10 is often problematic. This problem is solved by using the within-subject correlation coefficient which may be easier to estimate. As outlined in Zhang, Cao, and Ahn (2017), the relationship between *P*11 and the correlation is

$$\rho = \frac{P11 - P_s P_t}{\sqrt{P_s P_t (1 - P_s)(1 - P_t)}}$$

Using this relationship, values of ρ can be entered and transformed to the corresponding value of *P*11. Once P11 is known, Ps and Pt can be used to solve for *P*10 and *P*01. The only concern is that values of ρ be used that limit *P*11 to be between 0 and 1. These limits are presented above.

Example 1 – Calculating Sample Size

Suppose a dental clinical trial is being planned in which two sites are selected in each subject's mouth. One site is randomly assigned to receive the treatment intervention and the other is assigned the standard intervention. The trial is being conducted to compare two treatments for gingivitis. In the study, suppose *Ps* = 0.5; *Pt* = 0.6, 0.65, 0.7; ρ = 0, 0.2, 0.4, 0.6, 0.8; *alpha* = 0.05; and *power* = 0.9. Similar studies have had *Pmt* = *Pms* = 0.1. Sample size is to be calculated for a two-sided test. Since both missing value rates are non-zero, it is decided to base sample size estimates on the more efficient test method D.

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**
Test Type ..... **Test D (Based on Estimates of Difference)**
Alternative Hypothesis ..... **Two-Sided (Pt ≠ Ps)**
Power **0.9**
Alpha **0.05**
Pt Input Type ..... **Pt**
Pt (Probability (Yt = 1)) **0.6 0.65 0.7**
Ps (Probability (Ys = 1)) **0.5**
P11 Input Type ..... **ρ (Within-Subject Correlation)**
ρ (Within-Subject Correlation) **0 0.2 0.4 0.6 0.8**
Pmt and Pms Input Type ..... **Pmt = Pms (Enter One Value for Both)**
Pm = Pmt = Pms (Prob (Yt = Missing)) **0.1**

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Test Statistic: Test D (Based on Estimates of Difference)
Alternative Hypothesis: Two-Sided (Pt ≠ Ps)

Power	Total Sample Size N	Marginal Probabilities Pt	Marginal Probabilities Ps	Difference Pt - Ps	Within-Subject Correlation ρ	Joint Probability that Yt = 1 and Ys = 1 P11	Missing Probabilities Pmt	Missing Probabilities Pms	Alpha
0.9005	573	0.60	0.5	0.10	0.0	0.3000	0.1	0.1	0.05
0.9006	469	0.60	0.5	0.10	0.2	0.3490	0.1	0.1	0.05
0.9006	360	0.60	0.5	0.10	0.4	0.3980	0.1	0.1	0.05
0.9009	246	0.60	0.5	0.10	0.6	0.4470	0.1	0.1	0.05
0.9007	126	0.60	0.5	0.10	0.8	0.4960	0.1	0.1	0.05
0.9003	248	0.65	0.5	0.15	0.0	0.3250	0.1	0.1	0.05
0.9003	203	0.65	0.5	0.15	0.2	0.3727	0.1	0.1	0.05
0.9006	156	0.65	0.5	0.15	0.4	0.4204	0.1	0.1	0.05
0.9017	107	0.65	0.5	0.15	0.6	0.4681	0.1	0.1	0.05
		0.65	0.5	0.15	0.8		0.1	0.1	0.05
0.9016	135	0.70	0.5	0.20	0.0	0.3500	0.1	0.1	0.05
0.9001	110	0.70	0.5	0.20	0.2	0.3958	0.1	0.1	0.05
0.9017	85	0.70	0.5	0.20	0.4	0.4417	0.1	0.1	0.05
0.9007	58	0.70	0.5	0.20	0.6	0.4875	0.1	0.1	0.05
		0.70	0.5	0.20	0.8		0.1	0.1	0.05

Warning: One or more input parameter combinations resulted in a table (possibly undefined) for which no calculations are possible.

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N The total number of subjects in the study.
Pt The marginal probability of a "true" response in the treatment observation.
Ps The marginal probability of a "true" response in the standard observation.
Pt - Ps The difference between the two marginal probabilities.
ρ The correlation between the two observations within a subject.
P11 The joint probability that both observations in a pair are true (equal to 1).
Pmt The probability that the treatment observation is missing and the standard observation is observed.
Pms The probability that the standard observation is missing and the treatment observation is observed.
Alpha The probability of rejecting a true null hypothesis.

Summary Statements

A paired design will be used to test whether the treatment proportion (Pt) is different from the standard proportion (Ps) (H0: Pt = Ps versus H1: Pt ≠ Ps). The comparison will be made using a two-sided, incomplete data, paired-sample hybrid test (weighted average of the information contained in the complete pairs and the information contained in the partially observed pairs) using estimation method D, based on the paired differences, as proposed by Zhang, Cao, and Ahn (2017). The Type I error rate (α) will be 0.05. The joint probabilities are calculated from Pt, Ps, and a within-subject correlation of 0. The proportion of missing treatment observations is anticipated to be 0.1, and the proportion of missing standard observations is anticipated to be 0.1. To detect a difference of 0.1 (treatment response probability = 0.6, standard response probability = 0.5), with 90% power, 573 subject pairs will be needed.

Dropout-Inflated Sample Size

Dropout Rate	Sample Size N	Dropout-Inflated Enrollment Sample Size N'	Expected Number of Dropouts D
20%	573	717	144
20%	469	587	118
20%	360	450	90
20%	246	308	62
20%	126	158	32
20%	248	310	62
20%	203	254	51
20%	156	195	39
20%	107	134	27
20%			
20%	135	169	34
20%	110	138	28
20%	85	107	22
20%	58	73	15
20%			

Dropout Rate The percentage of subjects (or items) that are expected to be lost at random during the course of the study and for whom no response data will be collected (i.e., will be treated as "missing"). Abbreviated as DR.
N The evaluable sample size at which power is computed. If N subjects are evaluated out of the N' subjects that are enrolled in the study, the design will achieve the stated power.
N' The total number of subjects that should be enrolled in the study in order to obtain N evaluable subjects, based on the assumed dropout rate. After solving for N, N' is calculated by inflating N using the formula N' = N / (1 - DR), with N' always rounded up. (See Julious, S.A. (2010) pages 52-53, or Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. (2018) pages 32-33.)
D The expected number of dropouts. D = N' - N.

Dropout Summary Statements

Anticipating a 20% dropout rate, 717 subjects should be enrolled to obtain a final sample size of 573 subjects.

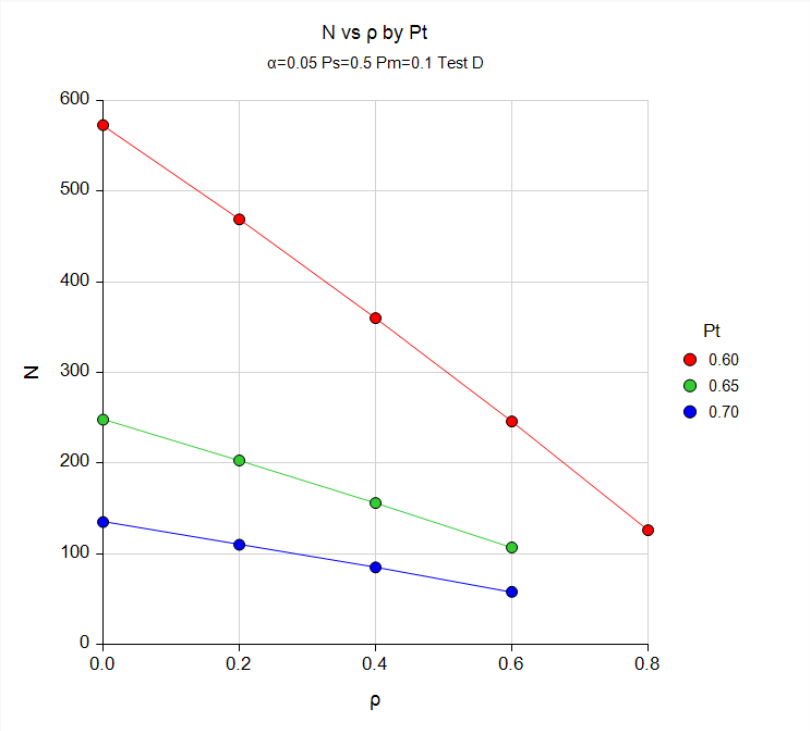
References

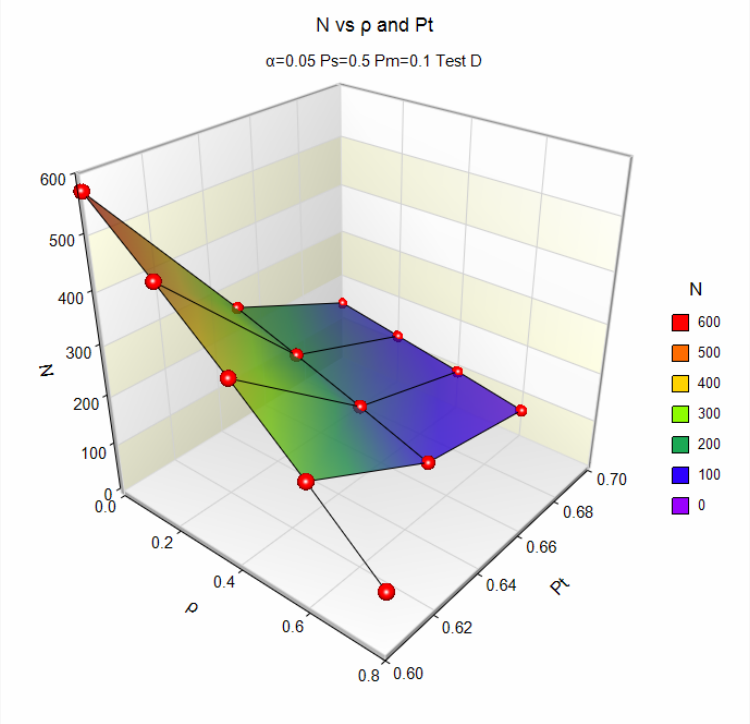
Zhang, S., Cao, J., Ahn, C. 2017. 'Inference and sample size calculation for clinical trials with incomplete observations of paired binary outcomes'. Statistics in Medicine. Volume 36. Pages 581-591.

This report gives the sample size for each of the requested scenarios.

Plots Section

Plots





These plots show the sample size for the various combination of the other parameters.

Example 2 – Finding Sample Size and Validation using Zhang, Cao, and Ahn (2017)

Zhang, Cao, and Ahn (2017) page 587 present Table II which provides examples that we can use to validate this procedure. The set of four rows has the following settings: *Ps* = 0.1; *Pt* = 0.15; ρ = 0, 0.1, 0.25, 0.5; *alpha* = 0.05; *power* = 0.8; and Pmt = Pms = 0.1. Sample size is calculated for a two-sided test. The test method is D. The resulting sample sizes are 759, 692, 588, and 408.

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 ..... **Sample Size**
Test Type ..... **Test D (Based on Estimates of Difference)**
Alternative Hypothesis ..... **Two-Sided (Pt ≠ Ps)**
Power **0.8**
Alpha **0.05**
Pt Input Type ..... **Pt**
Pt (Probability (Yt = 1)) **0.15**
Ps (Probability (Ys = 1)) **0.1**
P11 Input Type ..... **ρ (Within-Subject Correlation)**
ρ (Within-Subject Correlation) **0 0.1 0.25 0.5**
Pmt and Pms Input Type ..... **Pmt = Pms (Enter One Value for Both)**
Pm = Pmt = Pms (Prob (Yt = Missing)) **0.1**

Output

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

Numeric Results

Solve For: Sample Size
Test Statistic: Test D (Based on Estimates of Difference)
Alternative Hypothesis: Two-Sided (Pt ≠ Ps)

Power	Total Sample Size N	Marginal Probabilities Pt	Marginal Probabilities Ps	Difference Pt - Ps	Within-Subject Correlation ρ	Joint Probability that Yt = 1 and Ys = 1 P11	Missing Probabilities Pmt	Missing Probabilities Pms	Alpha
0.8001	759	0.15	0.1	0.05	0.00	0.0150	0.1	0.1	0.05
0.8003	692	0.15	0.1	0.05	0.10	0.0257	0.1	0.1	0.05
0.8000	588	0.15	0.1	0.05	0.25	0.0418	0.1	0.1	0.05
0.8006	408	0.15	0.1	0.05	0.50	0.0686	0.1	0.1	0.05

PASS matches the sample sizes of 759, 692, 588, and 408. The procedure is validated.