Chapter 538

GEE Tests for Two Correlated Proportions with Dropout

Introduction

This procedure provides power analysis and sample size calculation for studies that use a paired design that yield two binary outcomes, one of which may be incomplete. That is, in some pairs, the second observation is missing. The data analysis will use a mixed logistic regression model that is solved with GEE.

With complete data, the standard analysis is McNemar's Test (see McNemar (1947)), and PASS includes several procedures that analyze that test statistic. McNemar's Test requires that observations with one or two missing observations must be discarded. Zhang, Cao, and Ahn (2014) present a closed-form sample size formula for the case when some data pairs include missing values in the second observation. This is often referred to as *dropout*.

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

Our formulation comes from Zhang, Cao, and Ahn (2014). Denote a binary observation by Y_{ij}, where $j = 0$ (for s) and 1 (for t) t, s gives the group and $i = 1, 2, \ldots, N$ gives the subject. A "success" is represented by $Y_{ij} = 1$ and a "failure" by $Y_{ij} = 0$.

GEE Approach

Let $P(Y_{ij} = 1) = p_{ij}$. The GEE method models p_{ij} by the mixed logistic regression

$$\log\left(\frac{p_{ij}}{1 - p_{ij}}\right) = \beta_1 + \beta_2 j$$

The regression coefficient β_2 is equal to the log odds ratio of the two response rates. It is given by

$$\beta_2 = \log\left(\frac{p_{it}}{1 - p_{it}}\right) - \log\left(\frac{p_{is}}{1 - p_{is}}\right)$$

The null hypothesis $H_0\colon \beta_2 = 0$ corresponds to $H_0\colon p_{is} = p_{it}$. The alternative hypothesis is $H_1\colon \beta_2 \neq 0$ or $H_1\colon p_{is} \neq p_{it}$.

Zhang, Cao, and Ahn (2014) provide the following formula for the overall sample size for a two-sided test

$$N = \frac{\sigma^2 \left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2}{\beta_2^2}$$

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

The variance is given by

$$\sigma^2 = \frac{Vs + (Pmt)Vt - 2(Pmt)\rho\sqrt{VsVt}}{(Pmt)VsVt}$$

where Pmt is the proportion of the second observation missing, $Vs = Ps(1 - Ps)$, $Vt = Pt(1 - Pt)$, and ρ is the within-subject correlation coefficient.

Estimating ρ

The relationship between $P11$ and ρ is

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

where $P11$ is the joint probability that both observations are equal to one.

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

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

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

Procedure Options

This section describes the options that are specific to this procedure. These are located on the Design tab. For more information about the options of other tabs, go to the Procedure Window chapter.

Design Tab

The Design tab contains most of the parameters and options that you will be concerned with.

Solve For

Solve For

This option specifies the parameter to be solved for from the other parameters. The parameters that may be selected are *Power*, *Sample Size*, or *Effect Size*.

Note that the value selected here always appears as the vertical axis on the charts.

The program is set up to calculate power directly. To find appropriate values of the other parameters, a binary search is made using an iterative procedure until an appropriate value is found.

Test

Alternative Hypothesis

Specify the direction of the alternative hypothesis. The choices are:

- **Two-Sided (Pt ≠ Ps)**
  Refers to a two-sided test in which the alternative hypothesis is of the type H1: Pt - Ps ≠ 0.

- **One-Sided (Pt < Ps)**
  Refers to a lower-tailed, one-sided test in which the alternative hypothesis is of the type H1: Pt - Ps < 0.

- **One-Sided (Pt > Ps)**
  Refers to an upper-tailed, one-sided test in which the alternative hypothesis is of the type H1: Pt - Ps > 0.

Warning

For one-sided tests, the direction you select must match the values of Pt and Ps you enter. For example, if you select H1: Pt - Ps < 0, then the value of Pt should be less than the value of Ps.

Power and Alpha

Power

This option specifies one or more values for power. Power is the probability of rejecting a false null hypothesis and is equal to one minus Beta. Beta is the probability of a type-II error, which occurs when a false null hypothesis is not rejected.

Values must be between zero and one. Historically, the value of 0.80 (Beta = 0.20) was used for power. Now, 0.90 (Beta = 0.10) is also commonly used.

A single value may be entered or a range of values such as *0.8 to 0.95 by 0.05* may be entered.

If your only interest is in determining the appropriate sample size for a confidence interval, set power to 0.5.

Alpha

This option specifies one or more values for the probability of a type-I error. A type-I error occurs when a true null hypothesis is rejected.

Values must be between zero and one. Usually, the value of 0.05 is used for two-sided tests and 0.025 for one-sided tests.

You may enter a range of values such as *0.01 0.05 0.10* or *0.01 to 0.10 by 0.01*.

Sample Size

N (Number of Pairs)

Enter one or more values for N, the number of pairs in the study. If you enter a list of values, a separate analysis is done for each value.

Range

N > 1

Examples: *10 20 30 40* or *20 to 200 by 20.*

Effect Size – Marginal Probabilities (Pt, Ps)

Pt Input Type

Indicate what type of values to enter to specify Pt, the group 1 event probability. Regardless of the entry type chosen, the same test statistic is used in the power and sample size calculations. This option is simply given for convenience in specifying the Pt.

The choices are

- **Pt**
  Enter values for Pt directly.

- **Difference (Pt - Ps)**
  Enter values for the difference (Pt - Ps) and values for Ps. The corresponding value of Pt will be computed from these two values.

- **Ratio (Pt / Ps)**
  Enter values for the ratio (Pt / Ps) and values for Ps. The corresponding value of Pt will be computed from these two values.

- **Odds Ratio (Ot / Os)**
  Enter values for the odds ratio (Ot / Os) and values for Ps. The corresponding value of Pt will be computed from these two values.

  Note that Ot = Pt / (1 - Pt) and Os = Ps / (1 - Ps)

Pt (Prob (Yit = 1))

Enter a value for the probability that Yit = 1 under the alternative hypothesis, H1. Yit is the binary response of observation t (i = 1, ..., N). In a Pre-Post design, observation t would represent the Posttest.

Values must be between 0 and 1.

You can enter a single value such as *0.1* or a series of values such as *0.1 0.2 0.3* or *0.1 to 0.5 by 0.1*.

Note

This value must be different from Ps.

Difference (Pt - Ps)

Enter the difference between Pt and Ps. This difference is used with Ps to calculate the value of Pt using the formula: Pt = Diff + Ps.

You can enter a single value such as *0.05* or a series of values such as *0.03 0.05 0.10* or *0.01 to 0.09 by 0.02*.

Range

Differences must be between -1 and 1. They cannot take on the values -1, 0, or 1. The resulting value of Pt must be between 0 and 1. If it is not, the scenario is skipped.

Ratio (Pt / Ps)

Enter the ratio of the two probabilities Pt and Ps. This ratio is used with Ps to calculate the value of Pt using the formula: Pt = Ratio x Ps.

You can enter a single value such as *0.5* or a series of values such as *0.5 0.6 0.7 0.8* or *0.25 to 2.0 by 0.25*.

Range

Ratios must be greater than zero. They cannot take on the value of one. The resulting value of Pt must be between 0 and 1. If it is not, it is changed so that it is between 0 and 1.

Odds Ratio (Ot / Os)

This option specifies the odds ratio between the two probabilities Pt and Ps. This value is used with Ps to calculate the value of Pt.

You can enter a single value such as *0.5* or a series of values such as *0.5 0.6 0.7 0.8* or *1.25 to 2.0 by 0.25*.

Range

Odds ratios must be greater than zero. They cannot take on the value of one.

Ps (Prob (Yis = 1))

Enter a value for the probability that Yis = 1 under the both hypotheses, H0 and H1. Yis is the binary response of observation s, i = 1, ..., N. In a Pre-Post design, observation s would represent the Pretest.

Values must be between 0 and 1.

You can enter a single value such as *0.1* or a series of values such as *0.1 0.2 0.3* or *0.1 to 0.5 by 0.1*.

Note

Ps must be different from Pt. That is, you cannot have a zero effect size.

Effect Size – Joint Probability (P11)

P11 Input Type

Indicate how to specify P11, the joint probability that Yis = 1 and Yit = 1. Since this value is seldom known at the time a study is planned, it is usually easier to specify the within-subject correlation, ρ, and let the program compute P11 from it.

Regardless of the entry type chosen, the same test statistic is used in the power and sample size calculations. This option is simply given for convenience in specifying P11.

The choices are

- **ρ (Within-Subject Correlation)**
  Enter values for ρ, the within-subject correlation.

- **P11 (Prob (Yit = Yis = 1))**
  Enter values for P11 directly. This option will usually be used when power is being calculated after an experiment has been run or a reliable estimate of P11 is available from a previous, or pilot, study.

ρ (Within-Subject Correlation)

Enter one or more values for ρ, the correlation of observations within the same subject (pair).

At least one value must be entered. If multiple values are entered, a separate analysis is performed for each value.

Range

$-\rho L < \rho < \rho U$. A value near 0 indicates low correlation. A value near 1 indicates high correlation. The boundaries ρL and ρU are based on the marginal probabilities Pt and Ps. They guarantee that P11 will be within a suitable range.

Examples are a single value such as *0.5* or a list of values such as *0.5 0.6 0.7* or *0 to 0.9 by 0.1*

P11 (Prob (Yit = Yis = 1))

Enter one or more values for P11, the joint probability that Yis = 1 and Yit = 1. This option will usually be used when power is being calculated after an experiment has been run or a reliable estimate of P11 is available from a previous, or pilot, study.

At least one value must be entered. If multiple values are entered, a separate analysis is performed for each value.

Range

$0 < P11 < 1$.

Examples are a single value such as *0.2* or a list of values such as *0.1 0.2 0.3* or *0.1 to 0.9 by 0.1*

Dropout (Missing)

Pmt (Prob (Yit = Missing))

Enter one or more values for the probability of obtaining a missing value for Yit when Yis is non-missing.

At least one value must be entered. If multiple values are entered, a separate analysis is performed for each value.

Range

$0 \le Pmt < 1$.

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* = 0.1. Sample size is to be calculated for a two-sided test.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the procedure window. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
Design Tab	
Solve For	**Sample Size**
Alternative Hypothesis	**Two-Sided (Pt ≠ Ps)**
Power	**0.90**
Alpha	**0.05**
Pt Input Type	**Pt**
Pt (Prob (Yit = 1))	**0.6 0.65 0.7**
Ps (Prob (Yis = 1))	**0.5**
P11 Input Type	**ρ (Within-Subject Correlation)**
ρ (Within-Subject Correlation)	**0 0.2 0.4 0.6 0.8**
Pmt (Prob (Yit = Missing))	**0.1**

Annotated Output

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

Numeric Results

Numeric Results

Test: Mixed Logistic Regression using GEE
Alternative Hypothesis: Two-Sided (Pt ≠ Ps)

Power	Total Sample Size N	Pt	Ps	Pt-Ps Diff	Within Subj Corr ρ	Joint Prob Both Obs=1 P11	Prob Discord P01+P10	Prob Trt Miss Pmt	Alpha
0.9002	552	0.6000	0.5000	0.1000	0.0000	0.3000	0.5000	0.1000	0.050
0.9005	448	0.6000	0.5000	0.1000	0.2000	0.3490	0.4020	0.1000	0.050
0.9002	343	0.6000	0.5000	0.1000	0.4000	0.3980	0.3040	0.1000	0.050
0.9007	239	0.6000	0.5000	0.1000	0.6000	0.4470	0.2061	0.1000	0.050
0.9020	135	0.6000	0.5000	0.1000	0.8000	0.4960	0.1081	0.1000	0.050
0.9005	244	0.6500	0.5000	0.1500	0.0000	0.3250	0.5000	0.1000	0.050
0.9006	198	0.6500	0.5000	0.1500	0.2000	0.3727	0.4046	0.1000	0.050
0.9007	152	0.6500	0.5000	0.1500	0.4000	0.4204	0.3092	0.1000	0.050
0.9010	106	0.6500	0.5000	0.1500	0.6000	0.4681	0.2138	0.1000	0.050
0.9017	60	0.6500	0.5000	0.1500	0.8000	0.5158	0.1184	0.1000	0.050
0.9000	136	0.7000	0.5000	0.2000	0.0000	0.3500	0.5000	0.1000	0.050
0.9015	111	0.7000	0.5000	0.2000	0.2000	0.3958	0.4083	0.1000	0.050
0.9004	85	0.7000	0.5000	0.2000	0.4000	0.4417	0.3167	0.1000	0.050
0.9032	60	0.7000	0.5000	0.2000	0.6000	0.4875	0.2250	0.1000	0.050
0.9018	34	0.7000	0.5000	0.2000	0.8000	0.5333	0.1334	0.1000	0.050

References

Zhang, S., Cao, J., Ahn, C. 2014. 'A GEE approach to determine sample size for pre- and post-intervention experiments with dropout'. Computational Statistics and Data Analysis. Volume 69. Pages 114-121.

Report Definitions

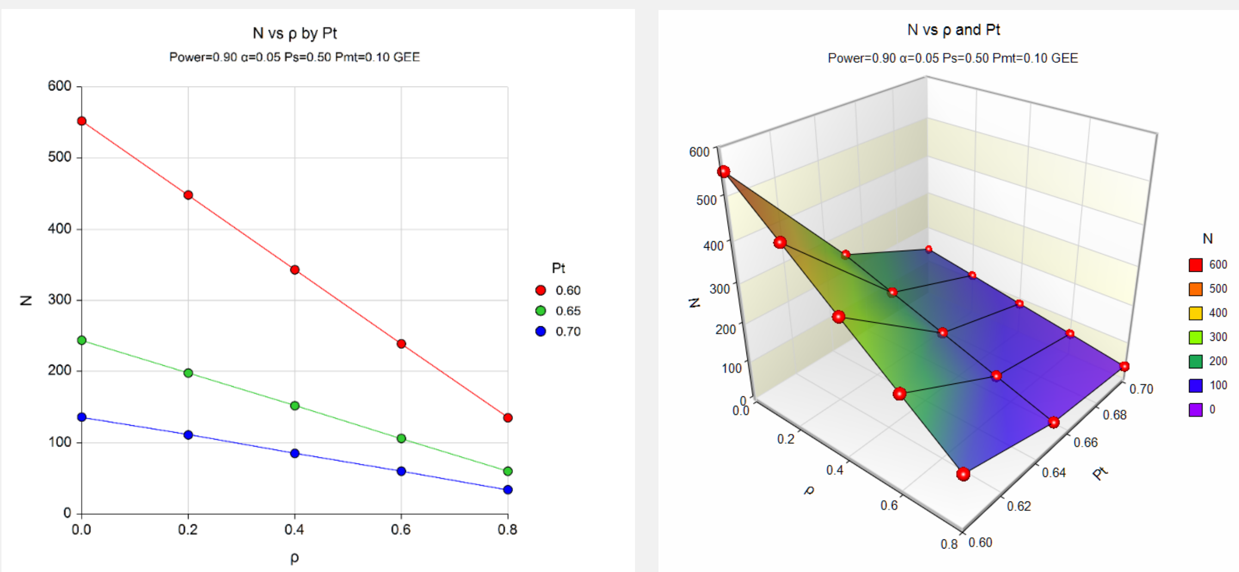
Power is the probability of rejecting a false null hypothesis.
Total Sample Size N is the total number of subjects in the study.
Pt is the probability of a "true" response in the treatment observation.
Ps is the probability of a "true" response in the standard observation.
Diff (Pt-Ps) is the difference between the two probabilities.
ρ (Within Subj Corr) is the correlation between the two observations within a subject.
P11 (Joint Prob Both Obs=1) is the joint probability that both observations in a pair are true (equal to '1').
P01+P10 (Prob Discord) is the probability that of obtaining a discordant event. It is provided to allow easy comparison of these results with those of McNemar's test.
Pmt (Prob Trt Miss) is the probability that the treatment observation is missing and the standard observation is observed.
Alpha is the significance level of the test: the probability of rejecting the null hypothesis of equal probabilities when it is true.

Summary Statements

When all observation pairs are complete, McNemar's test is usually used. When some of the treatment observations are missing, a GEE test statistic is used to test the difference between two response proportions. If the GEE test is used, a sample of 552 subjects achieves 90% power at a significance level of 0.050 to detect a difference of 0.1000. The response proportion of the treatment observation is 0.6000 and of the standard observation is 0.5000. The joint probabilites are calculated from Pt, Ps, and a within-subject correlation of 0.0000. The proportion of missing observations is 0.1000 in the treatment observations.

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

Plots Section



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

Example 2 – Validation using Zhang, Cao, and Ahn (2014)

Zhang, Cao, and Ahn (2014) page 119 present Table 3 which provides examples that we can use to validate this procedure. The second set of three rows, last column, has the following settings: *Ps* = 0.1; *Pt* = 0.2; *ρ* = 0.0, 0.15, 0.3; *alpha* = 0.05; *power* = 0.8; and *Pmt* = 0.4. Sample size is calculated for a two-sided test. The resulting sample sizes are 257, 228, and 198.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the procedure window. You may then make the appropriate entries as listed below, or open **Example 2** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
Design Tab	
Solve For	**Sample Size**
Alternative Hypothesis	**Two-Sided (Pt ≠ Ps)**
Power	**0.8**
Alpha	**0.05**
Pt Input Type	**Pt**
Pt (Prob (Yit = 1))	**0.2**
Ps (Prob (Yis = 1))	**0.1**
P11 Input Type	**ρ (Within-Subject Correlation)**
ρ (Within-Subject Correlation)	**0 0.15 0.3**
Pmt (Prob (Yit = Missing))	**0.4**

Output

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

Numeric Results

Test: Mixed Logistic Regression using GEE
Alternative Hypothesis: Two-Sided (Pt ≠ Ps)

Power	Total Sample Size N	Pt	Ps	Pt-Ps Diff	Within Subj Corr ρ	Joint Prob Both Obs=1 P11	Prob Discord P01+P10	Prob Trt Miss Pmt	Alpha
0.8001	257	0.2000	0.1000	0.1000	0.0000	0.0200	0.2600	0.4000	0.050
0.8015	228	0.2000	0.1000	0.1000	0.1500	0.0380	0.2240	0.4000	0.050
0.8015	198	0.2000	0.1000	0.1000	0.3000	0.0560	0.1880	0.4000	0.050

PASS matches the sample sizes of 257, 228, and 198. The procedure is validated.