

Chapter 542

GEE Tests for Two Proportions in a Split-Mouth Design

Introduction

This procedure assumes that binary data will be obtained from a study that uses a *split-mouth* design. The GEE method is used to analyze the repeated measures model that is assumed. The sample size formula is derived in Zhu, Zhang, and Ahn (2017).

A *split-mouth* design is used in dental trials in which treatments are randomized over segments of the mouth within each subject. In this design, the mouth is divided into two or more *segments* or regions. For example, the segments might be top and bottom, left and right, or a combination of both. Within each segment, specific *sites* (e.g., teeth) are identified. The same treatment is applied to all sites within a segment.

The split-mouth design, also called the *split-cluster* design, is occasionally used in other areas such as dermatology and animal studies. Although the design may be used in other experiments, the terminology of the split-mouth design will be used in this procedure.

Technical Details

Our formulation comes from Zhu, Zhang, and Ahn (2017). The goal of this analysis will be to provide a test comparing the response proportions of two groups. We assume that the two groups are labelled "1" for treatment and "2" for control.

Denote an observation by Y_{ijk} where $i = 1, 2$ gives the group, $j = 1, 2, \dots, N$ gives the subject, and $k = 1, 2, \dots, M$ gives the site. A "success" is represented by $Y_{ijk} = 1$ and a "failure" by $Y_{ijk} = 0$. Note that the segments themselves are not specified directly in the model. Also note that the total number of sites per subject is $2M$.

The following logistic regression model will be analyzed using GEE:

$$\text{logit}\{\Pr(Y_{ijk} = 1)\} = \log\left(\frac{p_{ijk}}{1 - p_{ijk}}\right) = \beta_0 + \beta_1 x_{ij} + \epsilon_{ijk}$$

where Y_{ijk} follows a Bernoulli distribution with parameter p_{ijk} , β_0 is the log-transformed odds for group 2 (control group), β_1 is the log-transformed odds ratio between the treatment and control groups, $x_{ij} = 1$ if the site is in group 1 and $x_{ij} = 0$ if the site is in group 2, and ϵ_{ijk} is random error.

Two alternative models are available to model the correlation between Y_{ijk} and $Y_{i'jk'}$ (responses within the same subject). The simpler model assumes that a common, within-subject, correlation ρ is at work. A more general model assumes that there are two, within-subject, correlations. These are ρ_W , which is the correlation between responses of sites within the same segment, and ρ_B , which is the correlation between responses of sites that are not in the same segment.

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

$$N = \frac{\sigma^2 \left(z_{1-\frac{\alpha}{2}} + z_{1-\beta} \right)^2}{\beta_1^2}$$

where

$$\sigma^2 = \frac{\{1 + (M - 1)\rho_W\}(P_1Q_1 + P_2Q_2) - 2M\rho_B\sqrt{P_1Q_1P_2Q_2}}{MP_1Q_1P_2Q_2}$$

$$P_1 = \frac{\exp(\beta_0 + \beta_1)}{1 + \exp(\beta_0 + \beta_1)}$$

$$P_2 = \frac{\exp(\beta_0)}{1 + \exp(\beta_0)}$$

$$Q_1 = 1 - P_1$$

$$Q_2 = 1 - P_2$$

$$\beta_1 = \log\left(\frac{P_1/Q_1}{P_2/Q_2}\right)$$

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

P_1 and P_2 are the true success rates of groups 1 (treatment) and 2 (control). These are the values assumed by the alternative hypothesis at which the power is calculated

These results are for the general two, within-subject correlations. The sample size for the one correlation method is obtained by setting $\rho = \rho_W = \rho_B$.

Example 1 – Calculating Sample Size

Suppose a dental clinical trial is being planned in which the mouth is divided into four segments with three sites in each. The trial is being conducted to compare a new treatment for gingivitis with a common existing treatment. In the study, suppose $P1 = 0.6, 0.65, 0.7$; $P2 = 0.5$; $\rho_B = 0.2, 0.4, 0.6, 0.8$; $\rho_W = 0.8$; $M = 5$; $\alpha = 0.05$; and $\text{power} = 0.9$. Sample size is to be calculated for a two-sided test.

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
Power.....	0.90
Alpha (Two-Sided Test)	0.05
M (Sites Per Group Per Subject)	5
P1 Input Type	P1
P1 (Group 1 Proportion).....	0.6 0.65 0.7
P2 (Group 2 Proportion).....	0.5
Correlation Matrix Structure	Two Within-Subject Correlations (ρ_B, ρ_W)
ρ_B (Between-Segment Correlation).....	0.2 0.4 0.6 0.8
ρ_W (Within-Segment Correlation).....	0.8

Output

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

Numeric Reports

Numeric Results

Solve For: [Sample Size](#)
 Groups: 1 = Treatment, 2 = Control
 Difference: P1 - P2

Power	Total Sample Size N	Sites per Group per Subject M	Proportion of True Responses			Correlation		Alpha
			P1	P2	Difference	Between- Segment ρ_B	Within- Segment ρ_W	
0.9008	335	5	0.60	0.5	0.10	0.2	0.8	0.05
0.9004	230	5	0.60	0.5	0.10	0.4	0.8	0.05
0.9015	126	5	0.60	0.5	0.10	0.6	0.8	0.05
0.9005	21	5	0.60	0.5	0.10	0.8	0.8	0.05
0.9012	148	5	0.65	0.5	0.15	0.2	0.8	0.05
0.9017	102	5	0.65	0.5	0.15	0.4	0.8	0.05
0.9030	56	5	0.65	0.5	0.15	0.6	0.8	0.05
0.9164	10	5	0.65	0.5	0.15	0.8	0.8	0.05
0.9028	83	5	0.70	0.5	0.20	0.2	0.8	0.05
0.9019	57	5	0.70	0.5	0.20	0.4	0.8	0.05
0.9082	32	5	0.70	0.5	0.20	0.6	0.8	0.05
0.9222	6	5	0.70	0.5	0.20	0.8	0.8	0.05

- Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
- N The total number of subjects in the study.
- M The number of sites per subject per group (used for both groups).
- P1 The proportion of "true" responses in group 1 (treatment group).
- P2 The proportion of "true" responses in group 2 (control group).
- Difference The difference between the two group response proportions. Difference = P1 - P2.
- ρ_B The correlation between sites in different segments within a subject.
- ρ_W The correlation between sites within a segment within a subject.
- Alpha The probability of rejecting a true null hypothesis.

Summary Statements

A split-mouth (split-cluster) design will be used to test whether the Group 1 (treatment) proportion (P1) is different from the Group 2 (control) proportion (P2). The comparison will be made using a two-sided generalized estimating equation (GEE) logistic regression coefficient test, with a Type I error rate (α) of 0.05. The correlation matrix is formed using a correlation of 0.8 for sites within the same segment and a correlation of 0.2 for sites from different segments. To detect a difference of 0.1 (P1 - P2 = 0.6 - 0.5) with 90% power, with 5 sites per group per subject, the total number of needed subjects is 335.

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Dropout-Inflated Sample Size

Dropout Rate	Sample Size N	Dropout- Inflated Enrollment Sample Size N'	Expected Number of Dropouts D
20%	335	419	84
20%	230	288	58
20%	126	158	32
20%	21	27	6
20%	148	185	37
20%	102	128	26
20%	56	70	14
20%	10	13	3
20%	83	104	21
20%	57	72	15
20%	32	40	8
20%	6	8	2

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, 419 subjects should be enrolled to obtain a final sample size of 335 subjects.

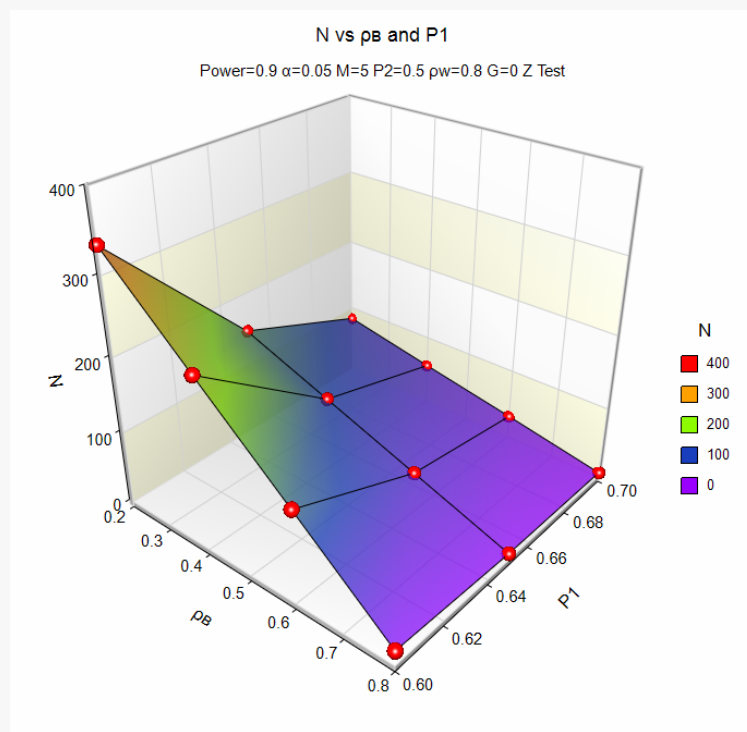
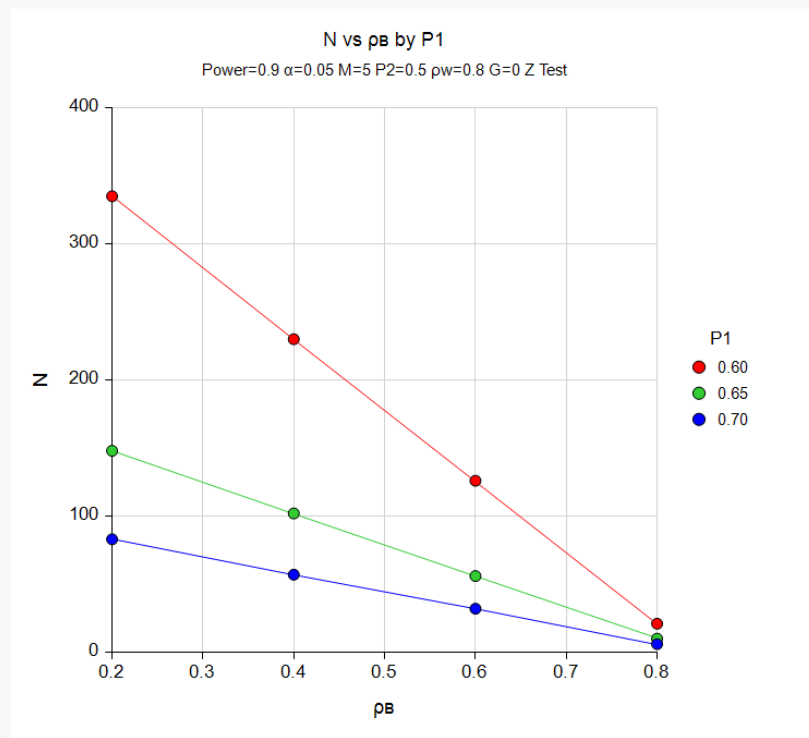
References

Zhu, H., Zhang, S., Ahn, C. 2017. 'Sample size considerations for split-mouth design'. Statistical Methods in Medical Research. Volume 26(6). Pages 2543-2551.

This report gives the sample size for each of the 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 Zhu, Zhang, and Ahn (2017)

Zhu, Zhang, and Ahn (2017) page 2549 provide a table (Table 2) in which several sample size values are presented. We will use the first entry from this table to validate this procedure.

In the first row of Table 2, $P_1 = 0.15$; $P_2 = 0.1$; $\rho_B = 0.05$; $\rho_W = 0.1$; $M = 3$; $\alpha = 0.05$; and power = 0.8. The resulting N is 244.

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
Power.....	0.8
Alpha (Two-Sided Test)	0.05
M (Sites Per Group Per Subject)	3
P1 Input Type	P1
P1 (Group 1 Proportion).....	0.15
P2 (Group 2 Proportion).....	0.1
Correlation Matrix Structure	Two Within-Subject Correlations (ρ_B, ρ_W)
ρ_B (Between-Segment Correlation).....	0.05
ρ_W (Within-Segment Correlation).....	0.1

Output

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

Numeric Results								
Solve For: Sample Size								
Groups: 1 = Treatment, 2 = Control								
Difference: P1 - P2								
Power	Total Sample Size N	Sites per Group per Subject M	Proportion of True Responses			Correlation		Alpha
			P1	P2	Difference	Between-Segment ρ_B	Within-Segment ρ_W	
0.8003	244	3	0.15	0.1	0.05	0.05	0.1	0.05

PASS matches the sample size of 244.