

Chapter 174

Tests for the Difference of Two Proportions in a 2x2 Cross-Over Design

Introduction

Senn (2002) defines a *cross-over* design as one in which each subject receives all treatments, and the objective is to study differences among the treatments. The name *cross-over* comes from the most common case in which there are only two treatments. In this case, each subject *crosses over* from one treatment to the other. It is assumed that there is a *washout* period between treatments during which the response returns back to its baseline value. If this does not occur, there is said to be a *carry-over* effect.

A 2x2 cross-over design contains two *sequences* (treatment orderings) and two time periods (occasions). One sequence receives treatment A followed by treatment B. The other sequence receives B and then A. The design includes a washout period between responses to make certain that the effects of the first drug do not carry over to the second. Thus, the groups in this design are defined by the sequence in which the drugs are administered, not by the treatments they receive. Indeed, higher-order cross-over designs have been used in which the same treatment is used on both occasions.

Cross-over designs are employed because, if the no-carryover assumption is met, treatment differences are measured within a subject rather than between subjects—making a more precise measurement. Examples of the situations that might use a cross-over design are the comparison of anti-inflammatory drugs in arthritis and the comparison of hypotensive agents in essential hypertension. In both cases, symptoms are expected to return to their usual baseline level shortly after the treatment is stopped.

The sample size calculations in the procedure are based on the formulas presented in Chow, Shao, Wang, & Lohknygina (2018).

Advantages of Cross-Over Designs

A comparison of treatments on the same subject is expected to be more precise. The increased precision often translates into a smaller sample size. Also, patient enrollment into the study may be easier because each patient will receive both treatments. Finally, it is often more difficult to obtain a subject than to obtain a measurement.

Disadvantages of Cross-Over Designs

The statistical analysis of a cross-over experiment is more complex than a parallel-group experiment and requires additional assumptions. It may be difficult to separate the treatment effect from the period effect, the carry-over effect of the previous treatment, and the interaction between period and treatment.

The design cannot be used when the treatment (or the measurement of the response) alters the subject permanently. Hence, it should not be used to compare treatments that are intended to provide a cure.

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Because subjects must be measured at least twice, it is often more difficult to keep patients enrolled in the study. It is arguably simpler to measure a subject once than to obtain their measurement twice. This is particularly true when the measurement process is painful, uncomfortable, embarrassing, or time consuming.

Technical Details

The 2x2 crossover design may be described as follows. Randomly assign the subjects to one of two sequence groups so that there are n_1 subjects in sequence one and n_2 subjects in sequence two. In order to achieve design balance, the sample sizes n_1 and n_2 are assumed to be equal so that $n_1 = n_2 = N/2$.

Sequence one is given treatment A followed by treatment B. Sequence two is given treatment B followed by treatment A.

The design can be analyzed using a simple z-test if we ignore period and sequence effects or using a more complex random effects logistic regression model that adjusts for period and sequence effects. The sample size calculations herein ignore period and sequence effects. Julious (2010) suggests on page 175 that the bias due to ignoring period effects if a period-adjusted analysis is planned is not great and that sample size calculations that ignore period effects are adequate.

Cross-Over Design

The discussions that follow summarize the results in Chow, Shao, Wang, & Lohknygina (2018). Consider a 2x2 cross-over design and let x_{ijk} represent the binary response (0 or 1) from the j^{th} subject ($j = 1, \dots, n_i$) in the i^{th} sequence ($i = 1, 2$) given the k^{th} treatment ($k = 1, 2$). Here we assume that the sample sizes are equal in both sequences such that $n_1 = n_2 = n$. If replicates are taken from each subject (as in a 2x2m replicated cross-over design) then $x_{ijk} = \bar{x}_{ijk} = \frac{1}{m} (\sum_{l=1}^m x_{ijkl})$, where x_{ijkl} represents the l^{th} binary response replicate ($l = 1, \dots, m$) from the j^{th} subject ($j = 1, \dots, n_i$) in the i^{th} sequence ($i = 1, 2$) given the k^{th} treatment ($k = 1, 2$). The observations taken from the same subject may be correlated with one another. If we assume no sequence and period effects, then we can state that $P(x_{ijk} = 1) = P_k$. Further define the paired differences of treatment - control for each subject within each sequence as

$$\begin{aligned} d_{ij} &= x_{ijT} - x_{ijC} \\ &= x_{ij1} - x_{ij2} \end{aligned}$$

and the overall treatment - control difference as

$$\begin{aligned} \delta &= P_T - P_C \\ &= P_1 - P_2. \end{aligned}$$

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The overall difference can be estimated as

$$\hat{\delta} = \frac{1}{2n} \sum_{i=1}^2 \sum_{j=1}^n d_{ij}.$$

The estimated difference is asymptotically normally distributed with variance σ_d^2 , which can be estimated as

$$\hat{\sigma}_d^2 = \frac{1}{2(n-1)} \sum_{i=1}^2 \sum_{j=1}^n (d_{ij} - \bar{d}_{i.})^2,$$

where

$$\bar{d}_{i.} = \frac{1}{n} \sum_{j=1}^n d_{ij}.$$

The standard deviation, then, is

$$SD = \sigma_d = \sqrt{\sigma_d^2}$$

with estimate

$$\widehat{SD} = \hat{\sigma}_d = \sqrt{\hat{\sigma}_d^2}.$$

Test Statistic

For a two-sided test of the hypotheses

$$H_0: P_T - P_C = 0 \quad \text{vs} \quad H_A: P_T - P_C \neq 0$$

or equivalently

$$H_0: \delta = 0 \quad \text{vs} \quad H_A: \delta \neq 0$$

the power and sample size calculations are based on the test statistic

$$Z = \frac{\hat{\delta}}{\frac{\hat{\sigma}_d}{\sqrt{2n}}}$$

which is asymptotically distributed as standard normal under the null hypothesis. The null hypothesis is rejected in favor of the alternative at level α if

$$\frac{|\hat{\delta}|}{\frac{\hat{\sigma}_d}{\sqrt{2n}}} > Z_{1-\alpha/2}$$

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where $Z_{1-\alpha/2}$ is the upper $1 - \alpha/2$ percentile of the standard normal distribution. One-sided tests reject the null hypothesis at level α if

$$\frac{\frac{|\hat{\delta}|}{\hat{\sigma}_d}}{\sqrt{2n}} > Z_{1-\alpha}$$

where $Z_{1-\alpha}$ is the upper $1 - \alpha$ percentile of the standard normal distribution.

Power Calculation

According to Chow, Shao, Wang, & Lokhnygina (2018) page 83, the power for the two-sided test of $H_0: \delta = 0$ versus $H_A: \delta \neq 0$ is

$$\Phi\left(\frac{\frac{|\delta_1|}{\sigma_d}}{\sqrt{2n}} - Z_{1-\alpha/2}\right)$$

where $\Phi()$ is the standard normal distribution function, δ_1 is a value of the difference under the alternative hypothesis, and $Z_{1-\alpha/2}$ is the upper $1 - \alpha/2$ percentile of the standard normal distribution. The sample size calculation formula for a two-sided test is

$$n = \text{Ceiling}\left\{\frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 \sigma_d^2}{2\delta_1^2}\right\}.$$

The power for a one-sided test is

$$\Phi\left(\frac{\frac{|\delta_1|}{\sigma_d}}{\sqrt{2n}} - Z_{1-\alpha}\right)$$

where $Z_{1-\alpha}$ is the upper $1 - \alpha$ percentile of the standard normal distribution. The sample size calculation formula for a one-sided test is

$$n = \text{Ceiling}\left\{\frac{(Z_{1-\alpha} + Z_{1-\beta})^2 \sigma_d^2}{2\delta_1^2}\right\}.$$

Example 1 – Power Analysis

Suppose you want to consider the power of a balanced cross-over design with a binary endpoint where the test is computed based on the difference for sequence sample sizes between 50 and 200. The difference to detect is 0.2 and the estimated standard deviation of the paired differences is 1. The significance level is 0.05.

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 **Power**
 Alternative Hypothesis **Two-Sided**
 Alpha..... **0.05**
 n (Sample Size per Sequence) **50 to 200 by 50**
 Input Type..... **Differences**
 D1 (Difference|H1 = Pt - Pc) **0.2**
 Standard Deviation (SD)..... **1**

Output

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

Numeric Results

Solve For: **Power**
 Alternative Hypothesis: **Two-Sided**
 Hypotheses: **H0: Pt - Pc = 0 vs. H1: Pt - Pc ≠ 0**

Power	Sample Size		Difference D1	Standard Deviation SD	Alpha
	Sequence n	Total N			
0.51597	50	100	0.2	1	0.05
0.80743	100	200	0.2	1	0.05
0.93373	150	300	0.2	1	0.05
0.97933	200	400	0.2	1	0.05

- Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
- n The sample size in each sequence (or group).
- N The total sample size from both sequences. The sample is divided equally among sequences.
- D1 The difference under the alternative hypothesis.
- SD The standard deviation of paired differences. This is estimated from a previous study.
- Alpha The probability of rejecting a true null hypothesis.

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Summary Statements

A 2x2 cross-over design will be used to test whether the treatment proportion is different from the standard proportion ($H_0: P_t - P_c = 0$ versus $H_1: P_t - P_c \neq 0$). The comparison will be made using a two-sided Z-test, with a Type I error rate (α) of 0.05. The standard deviation of paired differences is assumed to be 1. To detect a proportion difference ($P_t - P_c$) of 0.2 with a sample size of 50 in each sequence (totaling 100 subjects), the power is 0.51597.

Dropout-Inflated Sample Size

Dropout Rate	Sample Size		Dropout-Inflated Enrollment Sample Size		Expected Number of Dropouts	
	n	N	n'	N'	d	D
20%	50	100	63	126	13	26
20%	100	200	125	250	25	50
20%	150	300	188	376	38	76
20%	200	400	250	500	50	100

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 and N	The evaluable group and total sample sizes, respectively, at which power is computed (as entered by the user). If n subjects from each group are evaluated out of the n' subjects that are enrolled in the study, the design will achieve the stated power. $N = 2n$.
n' and N'	The number of subjects that should be enrolled in the study in order to obtain n and N evaluable subjects, based on the assumed dropout rate. 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 Lohknygina, Y. (2018) pages 32-33.). $N' = 2n'$.
d and D	The expected number of group and total dropouts, respectively. $d = n' - n$ and $D = 2d$.

Dropout Summary Statements

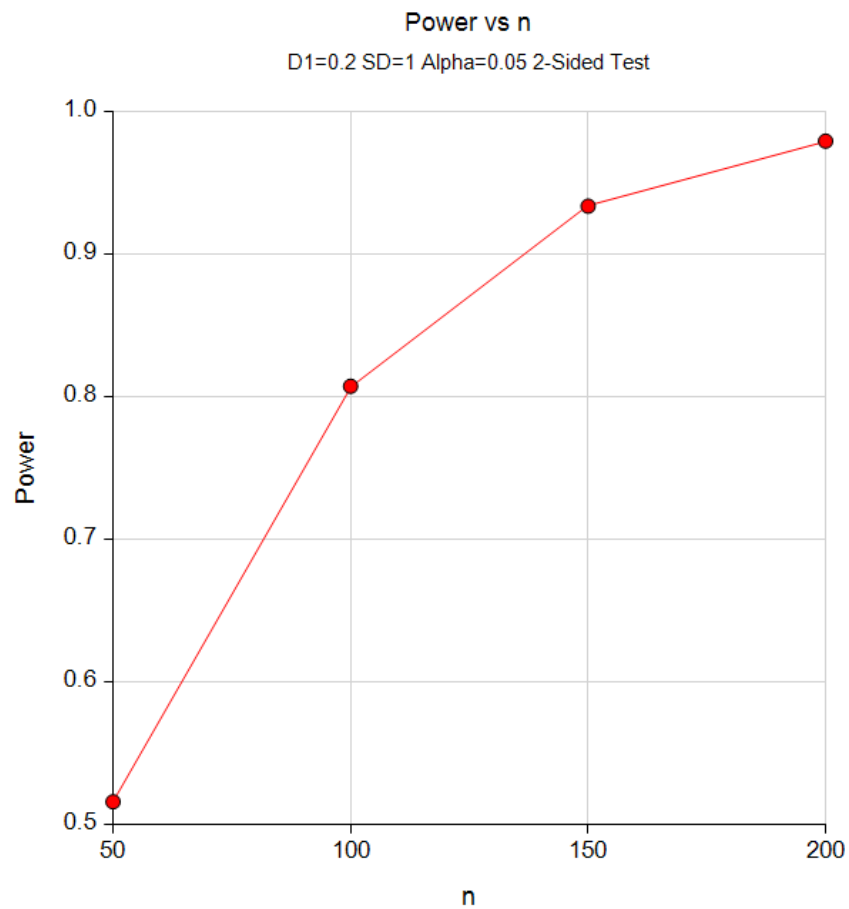
Anticipating a 20% dropout rate, 63 subjects should be enrolled in each group to obtain final sample sizes of 50 subjects per group.

References

Chow, S.C., Shao, J., Wang, H., and Lohknygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.

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Plots



This report shows the values of each of the parameters, one scenario per row. This plot shows the relationship between sample size and power. We see that a sample size of just under 100 per sequence is required to detect a difference of 0.2 with 80% power.

Example 2 – Calculating Sample Size when Estimating the Standard Deviation from a Previous Study

This example demonstrates how to calculate the sample size when estimating the standard deviation of the paired differences from data in a previous study using the method in Chow, Shao, Wang, & Lokhnygina (2018) on pages 82 and 83. In this example we'll find the sample size required to detect a difference of -0.15 with 90% power at a significance level of 0.05, with the standard deviation estimated using cell counts from a previous 2x2 cross-over study with equal sample size per sequence.

Assume that the following results were previously obtained from 280 subjects in a simple 2x2 cross-over trial comparing two inhalation devices, A and B. These results are similar to Table 3.2 of Lui (2016) on page 36 with a slight adjustment to sequence 1 that makes the sample sizes equal per sequence.

SEQUENCE 1 (Control (A) → Treatment (B))					SEQUENCE 2 (Treatment (B) → Control (A))				
		Period 2 (B)					Period 2 (A)		
		Yes	No	Total			Yes	No	Total
Period 1 (A)	Yes	27	41	67	Period 1 (B)	Yes	38	16	54
	No	15	57	72		No	32	54	86
Total		42	98	140	Total		70	70	140

The paired differences of treatment – control for each subject within each sequence are

$$\begin{aligned} d_{ij} &= x_{ijT} - x_{ijC} \\ &= x_{ijB} - x_{ijA} \end{aligned}$$

If x_{ijk} is a binary variable, then d_{ij} can take on the values 0, 1, and -1. If we summarize the results in sequence 1, then there are 15 subjects with $d_{ij} = 1$ (B = "Yes", A = "No"), 41 subjects with $d_{ij} = -1$ (B = "No", A = "Yes"), and $27 + 57 = 84$ subjects with $d_{ij} = 0$ (B = "Yes", A = "Yes" or B = "No", A = "No"). The average paired difference, then, for sequence 1 is

$$\begin{aligned} \bar{d}_{1.} &= \frac{1}{n} \sum_{j=1}^n d_{1j} \\ &= \frac{15(1) + 41(-1) + 84(0)}{140} \\ &= \frac{15 - 41}{140} \\ &= -0.1857. \end{aligned}$$

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Similarly, the average paired difference from sequence 2 is

$$\begin{aligned}\bar{d}_{2.} &= \frac{1}{n} \sum_{j=1}^n d_{2j} \\ &= \frac{16(1) + 32(-1) + 92(0)}{140} \\ &= \frac{16 - 32}{140} \\ &= -0.1143.\end{aligned}$$

The estimated overall treatment - control difference is

$$\begin{aligned}\hat{\delta} &= \frac{1}{2n} \sum_{i=1}^2 \sum_{j=1}^n d_{ij} \\ &= \frac{\bar{d}_{1.} + \bar{d}_{2.}}{2} \\ &= \frac{-0.1857 - 0.1143}{2} \\ &= -0.15.\end{aligned}$$

The estimated variance of paired differences, then, is

$$\begin{aligned}\hat{\sigma}_d^2 &= \frac{1}{2(n-1)} \sum_{i=1}^2 \sum_{j=1}^n (d_{ij} - \bar{d}_{i.})^2 \\ &= \frac{15(1 + 0.1857)^2 + 41(-1 + 0.1857)^2 + 84(0 + 0.1857)^2 + 16(1 + 0.1143)^2 + 32(-1 + 0.1143)^2 + 92(0 + 0.1143)^2}{2(139)} \\ &= 0.3502\end{aligned}$$

with estimated standard deviation

$$\begin{aligned}\widehat{SD} &= \hat{\sigma}_d \\ &= \sqrt{\hat{\sigma}_d^2} \\ &= \sqrt{0.3502} \\ &= 0.5917.\end{aligned}$$

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
Alternative Hypothesis	Two-Sided
Power.....	0.90
Alpha.....	0.05
Input Type.....	Differences
D1 (Difference H1 = Pt - Pc)	-0.15
Standard Deviation (SD).....	0.5917

Output

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

Numeric Results					
Solve For:	Sample Size				
Alternative Hypothesis:	Two-Sided				
Hypotheses:	H0: Pt - Pc = 0 vs. H1: Pt - Pc ≠ 0				
Power	Sample Size		Difference D1	Standard Deviation SD	Alpha
	Sequence n	Total N			
0.90087	82	164	-0.15	0.592	0.05
Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.				
n	The sample size in each sequence (or group).				
N	The total sample size from both sequences. The sample is divided equally among sequences.				
D1	The difference under the alternative hypothesis.				
SD	The standard deviation of paired differences. This is estimated from a previous study.				
Alpha	The probability of rejecting a true null hypothesis.				

This report indicates that the required sample size for 90% power is 82 per sequence for a total of 164.

Example 3 – Calculating Sample Size (Validation using Chow, Shao, Wang, & Likhnygina (2018))

On page 85, Chow, Shao, Wang, & Likhnygina (2018) presents an example of finding the sample size required to detect a difference of 0.2 with 80% power with a significance level of 0.05 when the standard deviation of paired differences is 0.5. They compute the required sample size to be 25 per sequence.

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 3** 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
Power.....	0.80
Alpha.....	0.05
Input Type.....	Differences
D1 (Difference H1 = Pt - Pc)	0.2
Standard Deviation (SD).....	0.5

Output

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

Numeric Results

Solve For:	Sample Size
Alternative Hypothesis:	Two-Sided
Hypotheses:	H0: Pt - Pc = 0 vs. H1: Pt - Pc ≠ 0

Power	Sample Size		Difference D1	Standard Deviation SD	Alpha
	Sequence n	Total N			
0.80743	25	50	0.2	0.5	0.05

The result from **PASS** matches the result from Chow, Shao, Wang, & Likhnygina (2018) exactly.