

## Chapter 204

# Conditional Power of Superiority by a Margin Tests for the Difference Between Two Proportions

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### Introduction

In sequential designs, one or more intermediate analyses of the emerging data are conducted to evaluate whether the experiment should be continued. This may be done to conserve resources or to allow a data monitoring board to evaluate safety and efficacy when subjects are entered in a staggered fashion over a long period of time. *Conditional power* (a frequentist concept) is the probability that the final result will be significant, given the data obtained up to the time of the interim look. *Predictive power* (a Bayesian concept) is the result of averaging the conditional power over the posterior distribution of effect size. Both of these methods fall under the heading of *stochastic curtailment* techniques. Further reading about the theory of these methods can be found in Jennison and Turnbull (2000), Chow and Chang (2007), Chang (2008), Proschan et.al (2006), and Dmitrienko et.al (2005).

This program module computes conditional and predictive power for the case when a two-sample  $z$ -test is used to test superiority by a margin for two proportions.

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### Technical Details

All details and assumptions usually made when using a two-sample  $z$ -test to test the difference between two proportions continue to be in force here.

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### Conditional Power

The power of an experiment indicates whether a study is likely to result in useful results, given the sample size. Low power means that the study is *futile*: little chance of statistical significance even though the alternative hypothesis is true. A study that is futile should not be started. However, futility may be determined only after the study has started. When this happens, the study is *curtailed*.

The futility of a study that is underway can be determined by calculating its *conditional power*: the probability of statistical significance at the completion of the study given the data obtained so far.

It is important to note that conditional power at the beginning of the study before any data are collected is equal to the unconditional power. So, conditional power will be high even if early results are negative. Hence, conditional power will seldom result in study curtailment very early in the study.

### Conditional Power of Superiority by a Margin Tests for the Difference Between Two Proportions

From Jennison and Turnbull (2000) pages 205 to 208, the general upper one-sided conditional power at stage  $k$  for rejecting a null hypothesis about a parameter  $\theta$  at the end of the study, given the observed test statistic,  $Z_k$ , is computed as

$$P_{uk}(\theta) = \Phi\left(\frac{Z_k\sqrt{I_k} - z_{1-\alpha}\sqrt{I_K} + \theta(I_K - I_k)}{\sqrt{I_K - I_k}}\right),$$

and the general lower one-sided conditional power at stage  $k$  is computed as

$$P_{lk}(\theta) = \Phi\left(\frac{-Z_k\sqrt{I_k} - z_{1-\alpha}\sqrt{I_K} - \theta(I_K - I_k)}{\sqrt{I_K - I_k}}\right),$$

where

$\theta$  = the parameter being tested by the hypothesis

$k$  = an interim stage at which the conditional power is computed ( $k = 1, \dots, K - 1$ )

$K$  = the stage at which the study is terminated and the final test computed

$Z_k$  = the test statistic calculated from the observed data that has been collected up to stage  $k$

$I_k$  = the information level at stage  $k$

$I_K$  = the information level at the end of the study

$z_{1-\alpha}$  = the standard normal value for the test with a type I error rate of  $\alpha$ .

Let  $P_1$  and  $P_2$  be the population proportions in groups 1 and 2, respectively. If we define  $\delta = P_2 - P_1$ , such that  $\delta_0 = P_{2,0} - P_1$  is the superiority difference boundary,  $\delta_1 = P_{2,1} - P_1$  is the true population difference under the alternative hypothesis, and  $\hat{\delta}_k = p_{2k} - p_{1k}$  is the estimated proportion difference from the observed data at stage  $k$ , then the parameter  $\theta$  to test the one-sided superiority by a margin alternative hypotheses of  $H_1: \delta > \delta_0$  (higher proportions better) or  $H_1: \delta < \delta_0$  (higher proportions worse) and other conditional power calculation components as outlined in Chang (2008) pages 70 and 71 are

$\theta = \delta_1 - \delta_0$  (the expected difference under the alternative hypothesis)

$Z_k = (\hat{\delta}_k - \delta_0)\sqrt{\hat{I}_k}$  (the superiority  $z$ -statistic computed from the observed data)

$I_k = \frac{1}{\sigma^2} \left( \frac{1}{n_{1k}} + \frac{1}{n_{2k}} \right)^{-1}$  (the interim information level)

$I_K = \frac{1}{\sigma^2} \left( \frac{1}{n_1} + \frac{1}{n_2} \right)^{-1}$  (the final information level)

where

$p_{jk}$  is the sample proportion for group  $j$ , estimating  $P_j$  at stage  $k$

$\hat{I}_k$  is the estimated information from the sample at stage  $k$

$n_{jk}$  is the sample size in group  $j$  at stage  $k$

## Conditional Power of Superiority by a Margin Tests for the Difference Between Two Proportions

$n_j$  is the final sample size in group  $j$

$$\sigma^2 = \bar{p}(1 - \bar{p}) \text{ with } \bar{p} = \frac{P_{1.1} + P_{2.1}}{2}$$

Computing conditional power requires you to set  $P_1$ ,  $P_{2.0}$  or  $\delta_0$ , and  $P_{2.1}$  or  $\delta_1$ . Their values can come from the values used during the planning of the study, from similar studies, or from estimates made from the data that has emerged.

### Futility Index

The *futility index* is  $1 - P_k(\theta)|H_1$ . The study may be stopped if this index is above 0.8 or 0.9 (that is, if conditional power falls below 0.2 or 0.1).

### Predictive Power

*Predictive power* (a Bayesian concept) is the result of averaging the conditional power over the posterior distribution of effect size. From Jennison and Turnbull (2000) pages 210 to 213, the general upper one-sided predictive power at stage  $k$  is given by

$$P_{uk} = \Phi \left( \frac{Z_k \sqrt{I_K} - z_{1-\alpha} \sqrt{I_k}}{\sqrt{I_K - I_k}} \right),$$

and the general lower one-sided predictive power at stage  $k$  is given by

$$P_{lk} = \Phi \left( \frac{-Z_k \sqrt{I_K} - z_{1-\alpha} \sqrt{I_k}}{\sqrt{I_K - I_k}} \right),$$

with all terms defined as in the equations for conditional power.

## 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.

### Test

#### Higher Proportions Are

Use this option to specify the direction of the superiority test. If Higher Proportions are “Better”, the alternative hypothesis is  $H_1: \delta > \delta_0$ , with  $\delta_0 > 0$ . If Higher Proportions are “Worse”, the alternative hypothesis is  $H_1: \delta < \delta_0$ , with  $\delta_0 < 0$ .

## Conditional Power of Superiority by a Margin Tests for the Difference Between Two Proportions

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### Alpha

#### Alpha

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

Values must be between zero and one. Historically, the value of 0.05 has been 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

#### N1 (Group 1 Target Sample Size)

Enter one or more values of the target sample size of group 1, the total number of subjects planned for this group. This value must be an integer greater than one. Note that you may enter a list of values using the syntax *50,100,150,200,250* or *50 to 250 by 50*.

#### N2 (Group 2 Target Sample Size)

Enter a value (or range of values) for the target sample size of group 2 or enter *Use R* to calculate *N2* from *N1*. You may enter a range of values such as *10 to 100 by 10*.

- **Use R**

If *Use R* is entered here, *N2* is calculated using the formula

$$N2 = [R(N1)]$$

where *R* is the Sample Allocation Ratio and the operator  $[Y]$  is the first integer greater than or equal to *Y*. For example, if you want  $N1 = N2$ , select *Use R* and set  $R = 1$ .

#### R (Sample Allocation Ratio)

Enter a value (or range of values) for *R*, the allocation ratio between samples. This value is only used when *N2* is set to *Use R*.

When used, *N2* is calculated from *N1* using the formula:  $N2 = [R(N1)]$  where  $[Y]$  is the next integer greater than or equal to *Y*. Note that setting  $R = 1.0$  forces  $N2 = N1$ .

#### n1k (Group 1 Sample Size at k)

Enter the group 1 sample size obtained through look k. If this value is greater than *N1*, the value of *N1* is increased to this amount.

#### n2k (Group 2 Sample Size at k)

Enter the group 2 sample size obtained through look k. If this value is greater than *N2*, the value of *N2* is increased to this amount.

- **n1k**

If *n1k* is entered here, *n2k* is set equal to *n1k*.

## Conditional Power of Superiority by a Margin Tests for the Difference Between Two Proportions

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### Effect Size

#### Input Type

Indicate what type of values to enter to specify the differences. Regardless of the entry type chosen, the calculations are the same. This option is simply given for convenience in specifying the differences.

The choices are

- **Proportions**

Enter P1 (Group 1 Proportion), P2.0 (Superiority Proportion), and P2.1 (Actual Proportion). The differences  $\delta_0$  (Superiority Difference) and  $\delta_1$  (Actual Difference to Detect) are calculated as

$$\delta_0 = P2.0 - P1,$$

$$\delta_1 = P2.1 - P1.$$

- **Differences**

Enter P1 (Group 1 Proportion),  $\delta_0$  (Superiority Difference), and  $\delta_1$  (Actual Difference to Detect).

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### Effect Size – Group 1 Proportion (Reference)

#### P1 (Group 1 Proportion)

Enter one or more values for the probability of obtaining a success in group 1. This is the proportion of the group 1 population with the trait of interest.

You may enter a range of values such as *0.4 0.5 0.6* or *0.4 to 0.7 by 0.1*. Since this is a proportion, all values must be between 0 and 1.

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### Effect Size – Group 2 Proportion (Treatment)

#### P2.0 (Superiority Proportion)

This is the lower proportion bound used to create the superiority by a margin test hypotheses. The superiority difference,  $\delta_0$ , is calculated from P1 and P2.0 as  $\delta_0 = P2.0 - P1$ .

When Higher Proportions are “Better”,  $P2.0 > P1$  and the alternative hypothesis is  $H1: \delta > \delta_0$ , or equivalently,  $H1: P2 > P2.0$ . You can enter values in the range  $P1 < P2.0 < 1$ .

When Higher Proportions are “Worse”,  $P2.0 < P1$  and the alternative hypothesis is  $H1: \delta < \delta_0$ , or equivalently,  $H1: P2 < P2.0$ . You can enter values in the range  $0 < P2.0 < P1$ .

#### P2.1 (Actual Proportion)

This is the actual group 2 proportion at which conditional power is calculated. The actual difference to detect,  $\delta_1$ , is calculated from P1 and P2.1 as  $\delta_1 = P2.1 - P1$ .

Care should be taken that this value is consistent with the alternative hypothesis.

When Higher Proportions are “Better”, you can enter values in the range  $P2.0 < P2.1 < 1$ .

Since Higher Proportions are “Worse”, you can enter values in the range  $0 < P2.1 < P2.0$ .

## Effect Size – Difference

### $\delta_0$ (Superiority Difference)

This is the difference bound of the superiority by a margin test hypothesis. When Higher Proportions are “Better”, the alternative hypothesis is  $H_1: \delta > \delta_0$  and you can enter values in the range  $0 < \delta_0 < \delta_1 < 1$ . When Higher Proportions are “Worse”, the alternative hypothesis is  $H_1: \delta < \delta_0$  and you can enter values in the range  $-1 < \delta_1 < \delta_0 < 0$ .

### $\delta_1$ (Actual Difference to Detect)

This is the actual difference between the treatment proportion (P2) and the reference proportion (P1) at which conditional power is calculated.

Care should be taken that this value is consistent with the alternative hypothesis.

When Higher Proportions are “Better”,  $0 < \delta_0 < \delta_1 < 1$ .

When Higher Proportions are “Worse”,  $-1 < \delta_1 < \delta_0 < 0$ .

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## Effect Size – Current Test Statistic

### $Z_k$ (Current Test Statistic)

Enter the value of the  $z$ -statistic calculated from the data obtained through stage  $k$ . This value may be positive or negative. Typically, the  $z$ -statistic ranges between -5 and 5.

## Example 1 – Computing Conditional Power

Suppose a study has been planned and is to be analyzed using a one-sided superiority z-test against a lower difference bound of  $\delta_0 = 0.05$  at an alpha of 0.025. The reference group proportion (P1) is 0.6, so the difference bound of  $\delta_0 = 0.05$  corresponds to a superiority proportion of  $P2.0 = P1 + \delta_0 = 0.6 + 0.05 = 0.65$ . The target sample size is 60 per group. An interim analysis is planned after half the data have been collected. The data monitoring board would like to have the conditional power calculated for an actual difference of  $\delta_1 = 0.1$  ( $P2.1 = P1 + \delta_1 = 0.6 + 0.1 = 0.7$ ) and z values of 1, 1.5, 2, 2.5, 3, and 3.5.

### Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Conditional Power of Superiority by a Margin Tests for the Difference Between Two Proportions** procedure window by expanding **Proportions**, then **Two Independent Proportions**, then clicking on **Conditional Power**, and then clicking on **Conditional Power of Superiority by a Margin Tests for the Difference Between Two Proportions**. You may make the appropriate entries as listed below or open **Example 1** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
<b>Design Tab</b>	
Higher Proportions Are .....	<b>Better (H1: <math>\delta &gt; \delta_0</math>)</b>
Alpha.....	<b>0.025</b>
N1 (Group 1 Target Sample Size).....	<b>60</b>
N2 (Group 2 Target Sample Size).....	<b>Use R</b>
R (Sample Allocation Ratio) .....	<b>1.0</b>
n1k (Group 1 Sample Size at Look k).....	<b>30</b>
n2k (Group 2 Sample Size at Look k).....	<b>n1k</b>
Input Type.....	<b>Proportions</b>
P1 (Group 1 Proportion) .....	<b>0.6</b>
P2.0 (Superiority Proportion) .....	<b>0.65</b>
P2.1 (Actual Proportion) .....	<b>0.7</b>
Zk (Current Test Statistic).....	<b>1 1.5 2 2.5 3 3.5</b>

### Annotated Output

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

### Numeric Results

Numeric Results for Two-Sample Z-Test									
Hypotheses: H0: $P2 - P1 \leq \delta_0$ vs. H1: $P2 - P1 > \delta_0$									
Cond. Power	Pred. Power	Total Sample Size		Current Sample Size		Proportions		Test Statistic	
		N1 N2	n1k n2k	P1 P2.0 P2.1	Differences $\delta_0 \delta_1$	Zk	Alpha	Futility	
0.08600	0.29262	60 60	30 30	0.60 0.65 0.70	0.05 0.10	1.000	0.025	0.91400	
0.19330	0.56409	60 60	30 30	0.60 0.65 0.70	0.05 0.10	1.500	0.025	0.80670	
0.35725	0.80743	60 60	30 30	0.60 0.65 0.70	0.05 0.10	2.000	0.025	0.64275	
0.55337	0.94244	60 60	30 30	0.60 0.65 0.70	0.05 0.10	2.500	0.025	0.44663	
0.73702	0.98878	60 60	30 30	0.60 0.65 0.70	0.05 0.10	3.000	0.025	0.26298	
0.87164	0.99860	60 60	30 30	0.60 0.65 0.70	0.05 0.10	3.500	0.025	0.12836	

## Conditional Power of Superiority by a Margin Tests for the Difference Between Two Proportions

### References

Jennison, C., and Turnbull, B.W. 2000. Group Sequential Methods with Applications to Clinical Trials. Chapman & Hall/CRC. New York.  
 Proschan, M., Lan, K.K.G., Wittes, J.T. 2006. Statistical Monitoring of Clinical Trials. Springer. New York.  
 Chang, Mark. 2008. Classical and Adaptive Clinical Trial Designs. John Wiley & Sons. Hoboken, New Jersey.

### Report Definitions

Conditional Power is the probability of rejecting a false null hypothesis at the end of the study given the data that have emerged so far.

Predictive Power is the result of averaging the conditional power over the posterior distribution of the effect size.

$N1|N2$  are the anticipated total sample sizes of groups 1 and 2, respectively.

$n1k|n2k$  are the sample sizes of groups 1 and 2, respectively, obtained through stage k.

$P1$  is the response proportion for group 1.

$P2.0$  is the superiority proportion for group 2 used to compute  $\delta_0$ .

$P2.1$  is the actual proportion for group 2 to detect under the alternative hypothesis used to compute  $\delta_1$ .

$\delta = P2 - P1$  is the difference in proportions.

$\delta_0 = P2.0 - P1$  is the superiority difference used to construct the hypotheses.

$\delta_1 = P2.1 - P1$  is the actual difference to detect under the alternative hypothesis at which conditional power is calculated.

$Z_k$  is the value of the test statistic from the observed data at stage k.

Alpha is the probability of rejecting a true null hypothesis.

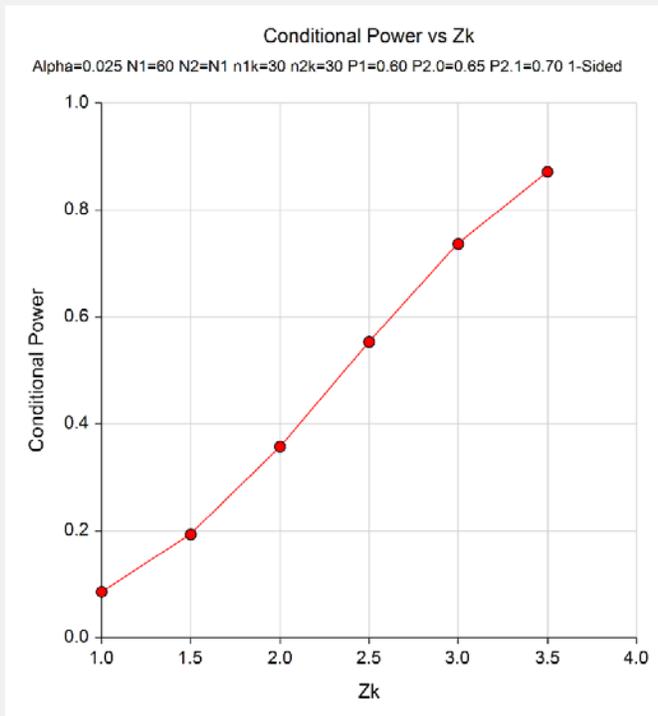
Futility is one minus the conditional power. A value greater than 0.9 or 0.8 indicates the study should be stopped because there is little chance of achieving statistical significance.

### Summary Statements

The first 30 of 60 subjects in group 1 and 30 of 60 subjects in group 2 achieve 8.600% conditional power to detect a difference of  $\delta_1 = P2.1 - P1 = 0.70 - 0.60 = 0.10$  using a Z-test for superiority by a margin with a difference bound of  $\delta_0 = P2.0 - P1 = 0.65 - 0.60 = 0.05$  and a significance level of  $\alpha = 0.025$ . The value of the test statistic from data that have emerged so far is  $Z_k = 1.000$ . The futility index is 0.91400.

This report shows the values of each of the parameters, one scenario per row. The definitions of each column are given in the Report Definitions section.

## Plots Section



This plot shows the relationship between conditional power and  $Z_k$ .

## Example 2 – Validation

We could not find an example of a conditional power calculation for a one-sided superiority by a margin proportions test in the literature. Since the calculations are relatively simple, we will validate the calculation of the third scenario ( $Z_k = 2$ ) of Example 1 by hand.

In this case

$$\bar{p} = \frac{P_1 + P_{2.1}}{2} = \frac{0.6 + 0.7}{2} = 0.65$$

$$\sigma^2 = \bar{p}(1 - \bar{p}) = 0.65(0.35) = 0.2275$$

$$I_k = \frac{1}{\sigma^2} \left( \frac{1}{n_{1k}} + \frac{1}{n_{2k}} \right)^{-1} = \frac{1}{0.2275} \left( \frac{1}{30} + \frac{1}{30} \right)^{-1} = 65.9341$$

$$I_K = \frac{1}{\sigma^2} \left( \frac{1}{n_1} + \frac{1}{n_2} \right)^{-1} = \frac{1}{0.2275} \left( \frac{1}{60} + \frac{1}{60} \right)^{-1} = 131.8681$$

$$\begin{aligned} P_{uk}(\theta) &= \Phi \left( \frac{Z_k \sqrt{I_k} - Z_{1-\alpha} \sqrt{I_K} + \theta(I_K - I_k)}{\sqrt{I_K - I_k}} \right) \\ &= \Phi \left( \frac{2\sqrt{65.9341} - 1.9599640\sqrt{131.8681} + 0.05(131.8681 - 65.9341)}{\sqrt{131.8681 - 65.9341}} \right) \\ &= \Phi(-0.36581) \\ &= 0.35725 \end{aligned}$$

This value matches the third line of the report in Example 1.