

Chapter 461

Conditional Power and Sample Size Reestimation of One-Sample T-Tests for Non-Inferiority

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 predicted power for the case when a one-sample *t*-test is used to test whether the mean of a population is greater than or less than a specific non-inferiority bound. It also provides *sample size reestimation* to achieve a specified conditional power value.

Technical Details

All details and assumptions usually made when using a one-sample non-inferiority *t*-test continue to be in force here.

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 and Sample Size Reestimation of One-Sample T-Tests for Non-Inferiority

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 θ 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

θ = 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 α .

If we define μ_R as the population reference, standard, or baseline mean, NIM as the non-inferiority margin, and μ_1 as the actual mean under the alternative hypothesis, then the parameter θ to test the one-sided non-inferiority alternative hypotheses of $H_1: \mu > \mu_0$ (higher means better with $\mu_0 = \mu_R - |NIM|$) or $H_1: \mu < \mu_0$ (higher means worse with $\mu_0 = \mu_R + |NIM|$) and other conditional power calculation components as outlined in Chang (2008) page 69 are

$$\theta = \mu_1 - \mu_0 \quad (\text{the expected difference under the alternative hypothesis})$$

$$Z_k = (\bar{x}_k - \mu_0) \sqrt{\hat{I}_k} \quad (\text{the } t\text{-statistic computed from the observed data})$$

$$I_k = \frac{n_k}{\sigma^2} \quad (\text{the interim information level})$$

$$I_K = \frac{N}{\sigma^2} \quad (\text{the final information level})$$

where

\bar{x}_k is the sample mean, estimating μ_1 at stage k

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

n_k is the sample size at stage k

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N is the total sample size

σ^2 is the variance of X (estimated by the sample variance).

Computing conditional power requires you to set σ^2 , μ_0 , and μ_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.

Converting from a T-Statistic to a Z-Statistic

A common problem is that the procedure requires a Z-statistic, but the results from an analysis usually provide a T-statistic with a given degrees of freedom. So, the T-statistic must be transformed to a Z-statistic. One way to do this is to use the associated p-value. This is accomplished using the following steps:

Step 1. Find the p-value associated with the t-statistic

For example, suppose we have a t-statistic of 2.33 with 30 degrees of freedom. Using the **PASS** Probability Calculator, the probability for Student's T distribution is $\text{Prob}(t \geq T) = 0.0133616$.

Step 2. Convert this p-value to a z-statistic

Continuing the example, we can use the Normal distribution in the **PASS** Probability Calculator to determine that the z-score associated with a p-value of 0.0133616 is -2.215537403212. Since the t-statistic was positive, we use $z = 2.215537403212$.

Step 3. Enter the z-statistic for Z_k (Current Test Statistic)

Continuing the example, we would enter 2.2155374 for Z_k (Current Test Statistic).

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.

Sample Size Reestimation

As Chang (2014) points out, after an interim analysis, it is often desirable to recalculate the target sample size using updated values for various nuisance parameters such as the variance. This process is known as *sample size reestimation*.

One method of calculating an adjusted sample size estimate is to search for the sample size that results in a predetermined value of conditional power. **PASS** conducts a binary search using the conditional power as the criterion. The result is called the *target sample size*.

Example 1 – Computing Conditional Power

Suppose a study has been planned and is to be analyzed using a one-sided non-inferiority t -test at an alpha of 0.025. The reference mean is known to be 6 and the test will have a non-inferiority margin of 1. The test will have a lower bound of $\mu_0 = \mu_R - \text{NIM} = 6 - 1 = 5$. The sample size is 50. The standard deviation is expected to be about 1.8. An interim analysis is run after half the data have been collected. This analysis yields a t -test value of 2.12. The data monitoring board would like to have the conditional power calculated for actual mean values of 5, 5.5, 6, and 6.5.

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 **Conditional Power**
 Higher Means Are **Better (H1: $\mu > \mu_0$)**
 Alpha **0.025**
 N (Target Sample Size) **50**
 nk (Sample Size at Look k) **25**
 μ_0 (Non-Inferiority Mean) **5**
 μ_1 (Actual Mean to Detect) **5 5.5 6 6.5**
 σ (Standard Deviation) **1.8**
 Test Statistic Input Type **Tk**
 Tk (Current Test Statistic) **2.12**

Output

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

Numeric Reports

Numeric Results

Solve For: [Conditional Power](#)
 Test Type: One-Sample T-Test
 Higher Means Are: Better
 Hypotheses: $H_0: \mu \leq \mu_0$ vs. $H_1: \mu > \mu_0$

Power		Sample Size		Mean		Mean Difference δ_1	Standard Deviation σ	Test Statistic Tk	Alpha	Futility
Conditional	Predictive	Target N	Look k nk	Non-Inferiority μ_0	Actual μ_1					
0.22278	0.81089	50	25	5	5.0	0.0	1.8	2.12	0.025	0.77722
0.73436	0.81089	50	25	5	5.5	0.5	1.8	2.12	0.025	0.26564
0.97805	0.81089	50	25	5	6.0	1.0	1.8	2.12	0.025	0.02195
0.99967	0.81089	50	25	5	6.5	1.5	1.8	2.12	0.025	0.00033

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Conditional Power	The probability of rejecting a false null hypothesis at the end of the study given the data that have emerged so far.
Predictive Power	The result of averaging the conditional power over the posterior distribution of the effect size.
N	The target sample size.
n_k	The sample size obtained through stage k.
μ_0	The non-inferiority mean used to construct the hypotheses.
μ_1	The actual mean to detect under the alternative hypothesis at which conditional power is calculated.
δ_1	The mean difference that is to be detected by the completed study. $\delta_1 = \mu_1 - \mu_0$.
σ	The standard deviation of the response.
T_k	The value of the test statistic from the observed data at stage k.
Alpha	The probability of rejecting a true null hypothesis.
Futility	Equal to 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

A single-group design will be used to test whether the mean (μ) is non-inferior, based on a non-inferiority mean of 5 ($H_0: \mu \leq 5$ versus $H_1: \mu > 5$). The comparison will be made using a one-sided, one-sample t-test, with a Type I error rate (α) of 0.025. The standard deviation is assumed to be 1.8. To detect a mean of $\mu_1 = 5$ (or $\delta_1 = \mu_1 - \mu_0 = 0$), with a current sample size of 25 out of a target sample size of 50, and with a current t-test statistic of 2.12, the conditional power is 0.22278. The predictive power is 0.81089, and the futility index is 0.77722.

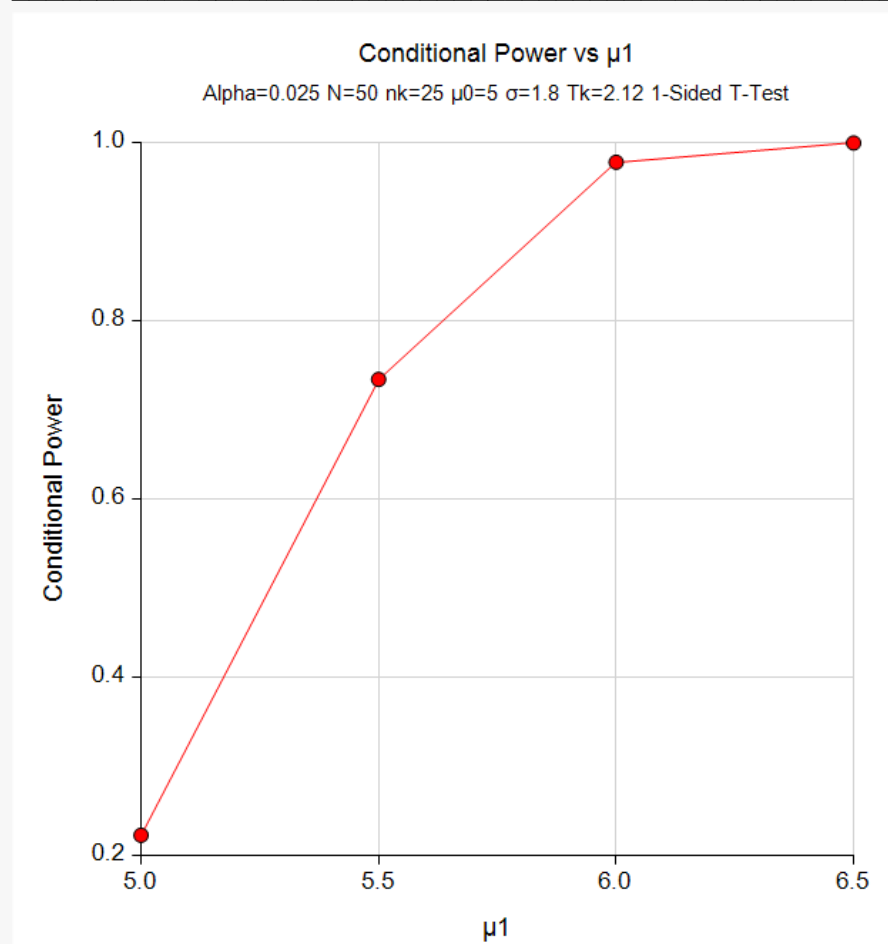
References

- 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.
- Chang, Mark. 2014. Adaptive Design Theory and Implementation Using SAS and R. CRC Press. New York.
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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

Plots



This plot shows the relationship between conditional power and μ_1 .

Example 2 – Validation

We could not find an example of a conditional power calculation for a one-sample non-inferiority t -test in the literature. Since the calculations are relatively simple, we will validate the calculation by hand.

Suppose a study has been planned and is to be analyzed using a one-sided non-inferiority t -test at an alpha of 0.025. The reference mean is known to be 6 and the test will have a non-inferiority margin of 1. The test will have a lower bound of $\mu_0 = 5$. The sample size is 50. The standard deviation is expected to be about 1.8. An interim analysis is run after half the data have been collected. This analysis yields a z -test value of 2.12.

In this case

$$\begin{aligned} I_k &= \frac{n_k}{\sigma^2} & I_K &= \frac{N}{\sigma^2} \\ &= \frac{25}{1.8^2} & &= \frac{50}{1.8^2} \\ &= 7.7160494 & &= 15.432099 \end{aligned}$$

$$\begin{aligned} P_{uk}(\theta) &= \Phi\left(\frac{Z_k\sqrt{I_k} - Z_{1-\alpha}\sqrt{I_K} + \theta(I_K - I_k)}{\sqrt{I_K - I_k}}\right) \\ &= \Phi\left(\frac{2.12\sqrt{7.7160494} - 1.959964\sqrt{15.432099} + (6 - 5)(15.432099 - 7.7160494)}{\sqrt{15.432099 - 7.7160494}}\right) \\ &= \Phi\left(\frac{5.905473}{2.777777}\right) \\ &= \Phi(2.125970) \\ &= 0.983247 \end{aligned}$$

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 **Conditional Power**
 Higher Means Are **Better ($H_1: \mu > \mu_0$)**
 Alpha **0.025**
 N (Target Sample Size) **50**
 nk (Sample Size at Look k) **25**
 μ_0 (Non-Inferiority Mean) **5**
 μ_1 (Actual Mean to Detect) **6**
 σ (Standard Deviation) **1.8**
 Test Statistic Input Type **Zk**
 Zk (Current Test Statistic) **2.12**

Output

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

Numeric Results

Solve For: [Conditional Power](#)
 Test Type: One-Sample T-Test
 Higher Means Are: Better
 Hypotheses: $H_0: \mu \leq \mu_0$ vs. $H_1: \mu > \mu_0$

Power		Sample Size		Mean		Mean Difference δ_1	Standard Deviation σ	Test Statistic Zk	Alpha	Futility
Conditional	Predictive	Target N	Look k nk	Non-Inferiority μ_0	Actual μ_1					
0.98325	0.8504	50	25	5	6	1	1.8	2.12	0.025	0.01675

The conditional power of 0.98325 matches the value calculated by hand.

Example 3 – Sample Size Reestimation

Suppose a study has started. It is being conducted to detect a difference of 0.6 using a one-sided non-inferiority t -test at an alpha of 0.025. The reference mean is thought to be 6 and the test will have a non-inferiority margin of 1. The test will have a lower bound of $\mu_0 = \mu_R - \text{NIM} = 6 - 1 = 5$. The target sample size is 50. The standard deviation is expected to be about 1.8.

An interim analysis was run after half the data were collected. This analysis yields a z -test value of 2.12. This test value was the result of transforming the p -value of the t -test with the inverse, standard normal distribution. The sample standard deviation was 3.27.

The data monitoring board would like to have the sample size reestimated to obtain a conditional power of 0.8.

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 Reestimation**
 Higher Means Are **Better ($H_1: \mu > \mu_0$)**
 Conditional Power **0.8**
 Alpha **0.025**
 n_k (Sample Size at Look k) **25**
 μ_0 (Non-Inferiority Mean) **5**
 μ_1 (Actual Mean to Detect) **5.6**
 σ (Standard Deviation) **3.27**
 Test Statistic Input Type **Zk**
 Zk (Current Test Statistic) **2.12**

Output

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

Numeric Results

Solve For: [Sample Size Reestimation](#)
 Test Type: One-Sample T-Test
 Higher Means Are: Better
 Hypotheses: $H_0: \mu \leq \mu_0$ vs. $H_1: \mu > \mu_0$

Power		Sample Size		Mean		Mean Difference δ_1	Standard Deviation σ	Test Statistic Zk	Alpha	Futility
Conditional	Predictive	Target N	Look k n_k	Non-Inferiority μ_0	Actual μ_1					
0.8014	0.92561	149	25	5	5.6	0.6	3.27	2.12	0.025	0.1986

Notice that the target sample size has increased from 50 to 149.