Chapter 742

Non-Inferiority Tests for Simple Linear Regression

Introduction

This procedure computes power and sample size for non-inferiority tests of the slope in simple linear regression. Simple linear regression is a commonly used procedure in statistical analysis to model a linear relationship between a dependent variable Y and an independent variable X.

The details of sample size calculation for simple linear regression are presented in the *Non-Zero Null Tests for Simple Linear Regression* chapter and they will not be duplicated here. This chapter only discusses those changes necessary for non-inferiority tests.

Difference between Simple Linear Regression and Correlation

The correlation coefficient is used when *X* and *Y* are from a bivariate normal distribution. That is, *X* is assumed to be a random variable whose distribution is normal. The values of X will not be known until the study is completed. In the simple linear regression context, no statement is made about the distribution of *X*. In fact, *X* does not have to be a random variable. In this procedure the distribution of Y is conditioned on X.

Fixed or Random X

Gatsonis and Sampson (1989) present power analysis results for two approaches: *unconditional* and *conditional*. This procedure provides a calculation for the *conditional* (fixed X) approach.

The *unconditional* approach assumes that X is normally distributed and is based on the correlation coefficient. The normality assumption might occasionally be met, but not frequently. Our impression is that usually, the values of X will not be known at the planning stage and they will not follow (even approximately) the normal distribution. Hence, the only option available is to proceed with the sample size calculation using the *conditional* approach and then estimate the standard deviation of the X's as best you can.

Technical Details

Suppose that the dependence of a variable *Y* on another variable *X* can be modeled using the simple linear equation

$$Y = A + BX$$

In this equation, *A* is the *Y*-intercept, *B* is the slope, *Y* is the dependent variable, and *X* is the independent variable.

The nature of the relationship between *Y* and *X* is studied using a sample of *N* observations. Each observation consists of a data pair: the *X* value and the *Y* value. The values of *A* and *B* are estimated from these observations using the method of least squares. Using these estimated values, each data pair may be modeled using the equation

$$Y_i = a + bX_i + e_i$$

Note that *a* and *b* are the least squares estimates of the population parameters *A* and *B*. The *e* values represent the discrepancies between the estimated values (*a* + *bX*) and the actual values *Y*. They are called the errors or residuals.

If it is assumed that these *e* values are normally distributed, tests of hypotheses about *A* and *B* can be constructed. Specifically, we can employ a T-test to test the non-inferiority of B compared to a non-inferiority boundary *B0*.

Linear Regression Slope T-Test Statistic

It is anticipated that a one-sided *t*-test of a regression coefficient will be used to conduct the test. Hence, the formula of the test statistic is

$$t_{N-2} = \frac{b - B0}{s_b}$$

where *N* is the sample size, *b* is the estimate of *B*, and s_b is the standard error of *b*.

The Statistical Hypotheses

Non-inferiority and superiority tests are examples of directional (one-sided) tests and their power and sample size could be calculated using the *Non-Zero Null Tests for Simple Linear Regression* procedure. However, at the urging of our users, we have developed this procedure which provides the input and output options that are convenient for non-inferiority tests. This section will review the specifics of non-inferiority testing.

Remember that in the usual simple linear regression setting, the null (H0) and alternative (H1) hypotheses for one-sided upper-tail tests are defined as

$$H0{:}\, B \le B0 \quad \text{versus} \quad H1{:}\, B > B0$$

Rejecting H0 implies that the slope is larger than the value B0. This test is called an *upper-tail test* because H0 is rejected in samples in which the sample slope is larger than B0.

The corresponding *lower-tail test* is

$$H1{:}\, B \ge B0 \quad \text{versus} \quad H1{:}\, B < B0$$

Non-inferiority tests are special cases of the above directional tests. It will be convenient to adopt the following specialize notation for the discussion of these tests.

Parameter	Interpretation	
B	*Population slope*.	This parameter will be estimated using the method of least squares.
B1	*Actual population slope at which power is calculated*.	
		This is the assumed population slope used in all calculations.
B0	*Non-Inferiority Slope*.	This is the smallest (or largest) value of the slope for which the new treatment will still be considered non-inferior to the current reference value.
B_R	*Reference value*.	Usually, this is the slope in the reference population.
NIM	*Margin of non-inferiority*.	
		This is a tolerance value that defines the magnitude of slope that is not of practical importance. This may be thought of as the largest difference from the reference value that is considered to be trivial.

Non-Inferiority Tests

A *non-inferiority test* tests that the slope is not worse than that of the baseline (reference) population by more than a small non-inferiority margin. The actual direction of the hypothesis depends on the whether higher values of the response are good or bad.

Case 1: High Values Good

In this case, higher values are better. The hypotheses are arranged so that rejecting the null hypothesis implies that the slope is no less than a small amount below the reference value. Equivalent sets of the null and alternative hypotheses are

$H0: B \leq B0$ versus $H1: B > B0$

$H0: B \leq B_R - NIM$ versus $H1: B > B_R - NIM$

Case 2: High Values Bad

In this case, lower values are better. The hypotheses are arranged so that rejecting the null hypothesis implies that the mean of the treatment group is no more than a small amount above the reference value. Equivalent sets of the null and alternative hypotheses are

$H0: B \geq B0$ versus $H1: B < B0$

$H0: B \geq B_R + NIM$ versus $H1: B < B_R + NIM$

Power Calculation of the Non-Inferiority Test of the Regression Coefficient, B

The following presentation is based on the standard results for a t-test as shown by Neter, Wasserman, and Kutner (1983) pages 71 and 72.

The power for a non-inferiority test in which higher values of B are better is calculated as follows for a one-tailed test in which the statistical hypotheses are H0: $B \leq B0$ vs. H1: $B > B0$.

1. Find $t_{1-\alpha}$ such that $T_{df}(t_{1-\alpha}) = 1 - \alpha$, where $T_{df}(x)$ is the area under a central-*t* curve to the left of *x* and *df* = *N* – 2.
2. Calculate: $X_0 = (t_{1-\alpha})\sigma_e/\sqrt{N}$.
3. Calculate the noncentrality parameter: $\lambda = \sqrt{N}(B1 - B0)\sigma_X/\sigma_e$, where σ_X is the standard deviation of the X values in the regression and *B1* is the slope at which the power is to be calculated.
4. Calculate: $t_1 = \left(X_0 - (B1 - B0)\sigma_X\sqrt{N}/\sigma_e\right) + \lambda$.
5. Power = $1 - T'_{df,\lambda}(t_1)$, where $T'_{df,\lambda}(x)$ is the area to the left of *x* under a noncentral-*t* curve with degrees of freedom *df* and noncentrality parameter λ.

The power for the case in which lower values of B are better is calculated using a test in which $H1\colon B < B0$.

The sample size can be easily found using a binary search with this power formula.

Calculation of σ_X

The above calculation requires the value of σ_X, the (population) standard deviation of the X values in the regression analysis. Except for the occasional experimental design that includes a specification of the X values (e.g., doses), the specific X values are unknown in the planning phase. Hence, a reasonable estimate must be found. PASS includes a special tool called the *Standard Deviation Estimator* that will aid in your search for accurate estimates of this parameter.

The following table provides examples of typical data configurations and their corresponding standard deviations.

σ_X	X Values	σ_X	X Values	σ_X	X Values	σ_X	X Values
0.500	1, 2	0.816	1, 2, 3	1.118	1, 2, 3, 4	1.414	1, 2, 3, 4, 5
1.000	1, 3	1.633	1, 3, 5	2.236	1, 3, 5, 7	2.828	1, 3, 5, 7, 9
1.500	1, 4	2.449	1, 4, 7	3.354	1, 4, 7, 10	4.243	1, 4, 7, 10, 13
2.000	1, 5	3.266	1, 5, 9	4.472	1, 5, 9, 13	5.657	1, 5, 9, 13, 17
4.000	1, 9	6.532	1, 9, 17	8.944	1, 9, 17, 25	11.314	1, 9, 17, 25, 33

Because of the direct impact on the power and sample size, it will be important to spend some time determining appropriate values for this parameter.

One final note: when a basic pattern is repeated, its population standard deviation remains the same. For example, the standard deviation of the values 1, 2, 1, 2, 1, 2, 1, 2 is 0.5. This is also the standard deviation of 1, 2 or 1, 2, 1, 2.

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. Under most situations, you will select either *Power* for a power analysis or *Sample Size* for sample size determination.

Select *Sample Size* when you want to calculate the sample size needed to achieve a given power and alpha level.

Select *Power* when you want to calculate the power of an experiment.

Non-Inferiority Test

Higher Slopes Are

Use this option to specify whether higher values of B (slope) are interpreted to be *better* or *worse* than lower values. This in turn determines the direction of the hypothesis test.

- **Better**

  If B2 > B3, then B2 is better than B3. The higher, the better. The statistical hypothesis tested is H0: B ≤ B0 vs. H1: B > B0.

- **Worse**

  If B2 < B3, then B2 is better than B3. The lower, the better. The statistical hypothesis tested is H0: B ≥ B0 vs. H1: B < B0.

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 commonly used.

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

Alpha

This option specifies one or more values for the probability of a type-I error (alpha). A type-I error occurs when you reject the null hypothesis when in fact it is true.

Values of alpha must be between zero and one. Historically, the value of 0.05 has been used for alpha. This means that about one test in twenty will falsely reject the null hypothesis. You should pick a value for alpha that represents the risk of a type-I error you are willing to take in your experimental situation.

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 (Sample Size)

Enter one or more values for the number of observations (e.g., subjects) in the study.

Effect Size – Slope

B0 (Non-Inferiority Slope) when Higher is Better

Enter one or more values for B0, the non-inferiority boundary in the case when higher slope values are desired.

Suppose B_R is the reference slope value. The non-inferiority test requires us to state how much lower than B_R a slope can be and we are still willing to conclude that the slope value is non-inferior to B_R. In this case, B0 + |NIM| = B_R where NIM is the non-inferiority margin.

B0 is set to a value slightly less than B_R and the alternative hypothesis is that B > B0.

The statistical hypothesis tested is *H0: B ≤ B0 vs. H1: B > B0.*

Note that neither B_R or NIM is entered in the analysis.

For example, suppose B_R = 10. We might set B0 to 8 or 9.

Range

B0 can be any value, positive or negative, so long as B0 < B_R.

This value must be in the same scale as σx.

B0 (Non-Inferiority Slope) when Higher is Worse

Enter one or more values for B0, the non-inferiority boundary in the case when lower slope values are desired.

Suppose B_R is the reference slope value. The non-inferiority test requires us to state how much higher than B_R a slope can be and we are still willing to conclude that the slope value is non-inferior to B_R. In this case, B0 - |NIM| = B_R where NIM is the non-inferiority margin.

B0 is set to a value slightly greater than B_R and the alternative hypothesis is that B < B0.

The statistical hypothesis tested is *H0: B ≥ B0 vs. H1: B < B0.*

Note that neither B_R or NIM is entered in the analysis.

For example, suppose B_R = 10. We might set B0 to 11 or 12.

Range

B0 can be any value, positive or negative, so long as B0 > B_R.

B1 (Slope|H1) when Higher is Better

Enter one or more values of the slope assumed by the alternative hypothesis, B1. This represents the actual value of B at which the power is computed.

You should make sure than B1 > B0.

You can enter a single value such as ‘1’ or a series of values such as ‘1 2 3’ or ‘1 to 10 by 1”.

B1 (Slope|H1) when Higher is Worse

Enter one or more values of the slope assumed by the alternative hypothesis, B1. This represents the actual value of B at which the power is computed.

You should make sure than B1 < B0.

You can enter a single value such as ‘1’ or a series of values such as ‘1 2 3’ or ‘1 to 10 by 1”.

Effect Size – Standard Deviation of X

σx Input Type

Select the method you want to use to enter the value(s) of σx. Your choices are

- **σx (Std Dev of X)**
  Enter one or more values for σx directly.

- **List of X Values**
  Enter a list of two or more numbers from which the standard deviation is to be calculated.

σx (Standard Deviation of X)

Enter one or more values for σx, the *population* standard deviation of the X values that will occur in a sample.

Usually, the actual X values are not known at the planning stage. When they are not known, you will have to estimate this value. You can press the *Standard Deviation Estimator* button at the right to obtain help in determining appropriate values for this parameter. Just be sure to use the *population*, not the *sample*, formula. That is, divide the sum of squares by N, not N-1.

The individual numbers can be any numeric value: positive, negative, or zero.

Fixed Xs

Determine the standard deviation of a typical set of fixed Xs. For example, suppose the X values will be five -1's and five 1's. The population standard deviation of these values (dividing by N, not N - 1) is 1.0. This is the value of σx. Note that '1 2' will result in the same σx as '1 2 1 2', '1 1 1 2 2 2', '-1 -2', or '11 12'.

Random Xs

Estimate one or more values of σx, the standard deviation of X, from your knowledge of X. If nothing else is available, you can use the likely range divided by 4, 5, or 6.

List of X Values

Enter a list of values from which the value of σx will be calculated. For example, entering "1, 3" results in σx = 1.0. Note that this calculation assumes that the N observations are allocated equally among the X's.

Effect Size – σe (Standard Deviation of Residuals)

σe Input Type

Select the method to use to enter σe (the standard deviation of the residuals).

- **σe (Std Dev of Residuals)**
  Specify σe directly.

- **σY (Std Dev of Y)**
  Specify σY. Calculate: $\sigma e^2 = \sigma Y^2 - B1^2 (\sigma x^2)$

σe (Std Dev of Residuals)

Enter one or more values of the standard deviation of the residuals from the regression of Y on X. The possible range is 0 < σe.

σY (Std Dev of Y)

Enter one or more values for the standard deviation of Y, ignoring the independent variable X. The value of σY is converted to σe using the formula: $\sigma e^2 = \sigma Y^2 - B1^2 (\sigma x^2)$. The allowable range is $0 < |B1(\sigma x)| < \sigma Y$.

Example 1 – Calculating the Power

Suppose a power analysis is required for a simple linear regression study that will perform a non-inferiority test the relationship between two variables, *Y* and *X*. Further suppose that in the past, the slope has been 1 and it will be advantageous to show that it is now at least 0.8.

The analysis will look at the power of several sample sizes between 20 and 180. A non-inferiority test will be used with a significance level of 0.025. Based on previous studies, σe will be assumed to be 0.6. The value of σx will assume that X is binary with equally-likely values of 1 and 2. The power will be computed at B1 = 0.9, 1, 1.1, and 1.2.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Non-Inferiority Tests for Simple Linear Regression** 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	**Power**
Higher Slopes Are	**Better (H1: B > B0)**
Alpha	**0.025**
N (Sample Size)	**20 60 100 140 180**
B0 (Non-Inferiority Slope)	**0.8**
B1 (Slope|H1)	**0.9 1 1.1 1.2**
σx Input Type	**List of X Values**
List of X Values	**1 2**
σe Input Type	**σe (Std Dev of Residuals)**
σe (Std Dev of Residuals)	**0.6**

Annotated Output

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

Numeric Results
Hypotheses: H0: B ≤ B0 vs. H1: B > B0

Power	Sample Size N	Non-Inferiority Slope B0	Actual Slope B1	Std Dev of X σx	Std Dev of Y σY	Std Dev of Resids σe	R^2	Alpha
0.0541	20	0.800	0.900	0.500	0.750	0.600	0.360	0.025
0.1050	20	0.800	1.000	0.500	0.781	0.600	0.410	0.025
0.1838	20	0.800	1.100	0.500	0.814	0.600	0.457	0.025
0.2917	20	0.800	1.200	0.500	0.849	0.600	0.500	0.025
0.0926	60	0.800	0.900	0.500	0.750	0.600	0.360	0.025
0.2450	60	0.800	1.000	0.500	0.781	0.600	0.410	0.025
0.4778	60	0.800	1.100	0.500	0.814	0.600	0.457	0.025
0.7187	60	0.800	1.200	0.500	0.849	0.600	0.500	0.025
0.1282	100	0.800	0.900	0.500	0.750	0.600	0.360	0.025
0.3784	100	0.800	1.000	0.500	0.781	0.600	0.410	0.025
0.6969	100	0.800	1.100	0.500	0.814	0.600	0.457	0.025
0.9100	100	0.800	1.200	0.500	0.849	0.600	0.500	0.025
0.1633	140	0.800	0.900	0.500	0.750	0.600	0.360	0.025
0.4993	140	0.800	1.000	0.500	0.781	0.600	0.410	0.025

(report continues)

References

Dupont, W.D. and Plummer, W.D. Jr. 1998. 'Power and Sample Size Calculations for Studies Involving Linear Regression'. Controlled Clinical Trials, Vol. 19, Pages 589-601.
Sampson, Allan R. 1974. 'A Tale of Two Regressions'. JASA, Vol. 69, No. 347, Pages 682-689.
Neter, J., Wasserman, W., and Kutner, M. 1983. Applied Linear Regression Models. Richard D. Irwin, Inc. Chicago, Illinois.

Report Definitions

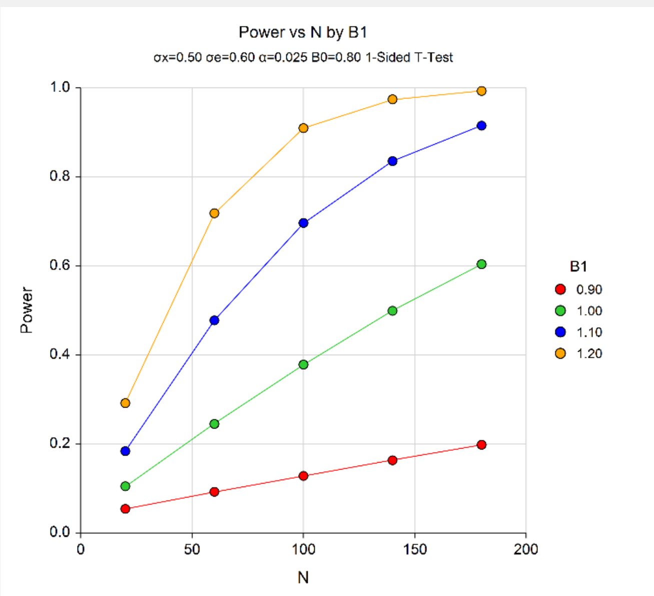
Power is the probability of rejecting a false null hypothesis. It should be close to one.
N is the size of the sample drawn from the population. To conserve resources, it should be small.
B0 is the non-inferiority slope (boundary) in the case in which HIGHER slope values are desired.
B1 is the slope at which the power is calculated.
σx is the standard deviation of the X values.
σY is the standard deviation of Y (ignoring X).
σe is the standard deviation of the residuals.
R^2 is the R-squared when Y is regressed on X.
Alpha is the probability of rejecting a true null hypothesis.

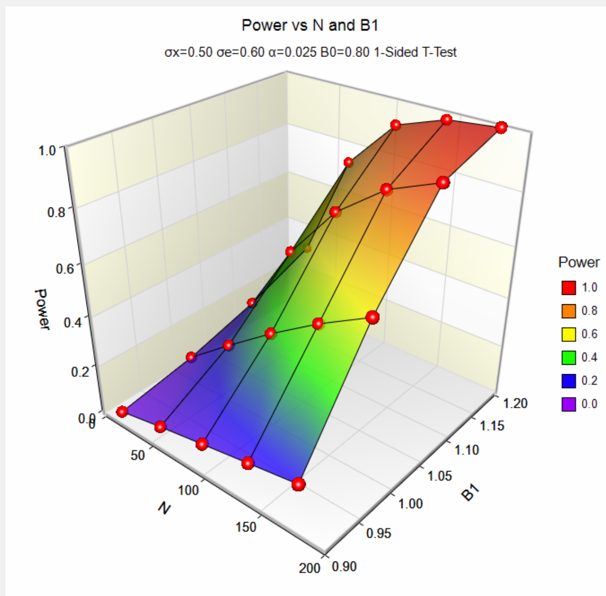
Summary Statements

A non-inferiority test is planned in which HIGHER slope values are desired. A sample size of 20 achieves 5% power to detect a change in slope from 0.800 under the null hypothesis to 0.900 under the alternative hypothesis when the statistical hypothesis is one-sided, the significance level is 0.025, the standard deviation of X is 0.500, the standard deviation of Y is 0.750, the standard deviation of residuals is 0.600, and R^2 is 0.360.

This report shows the calculated power for each of the scenarios.

Plots Section





These plots show the power versus the sample size for the three values of B1.

Example 2 – Validation using Another PASS Procedure

We could not find a validation example for this procedure in the literature. But since this procedure was derived from the **Non-Zero Null Tests for Simple Linear Regression** procedure, we will use an example from that previously validated procedure to validate this procedure.

In the other procedure, set the *Solve For* parameter to Sample Size. Also, set the *Alternative Hypothesis* to One-Sided (H1: B > B0). Also, set $Power = 0.9, B0 = 0.8, B1 = 0.9, \alpha = 0.05, \sigma_X = 0.5, \sigma_e = 0.6$.

The sample size is calculated as 1234.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Non-Inferiority Tests for Simple Linear Regression** 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**
Higher Slopes Are	**Better (H1: B > B0)**
Power	**0.90**
Alpha	**0.05**
B0 (Non-Inferiority Slope)	**0.8**
B1 (Slope|H1)	**0.9**
σx Input Type	**σx (Std Dev of X)**
σx (Std Dev of X)	**0.5**
σe Input Type	**σe (Std Dev of Residuals)**
σe (Std Dev of Residuals)	**0.6**

Output

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

Numeric Results

Hypotheses: H0: B ≤ B0 vs. H1: B > B0

Power	Sample Size N	Non-Inferiority Slope B0	Actual Slope B1	Std Dev of X σx	Std Dev of Y σY	Std Dev of Resids σe	R^2	Alpha
0.9001	1234	0.800	0.900	0.500	0.750	0.600	0.360	0.050

The sample size of 1234 matches the result from the other procedure.