

## Chapter 517

# One-Sample Z-Tests for Equivalence

## Introduction

This procedure allows you to study the power and sample size of  $z$ -tests of equivalence of one mean with a value (e.g. a historical control or gold standard). Schuirmann's (1987) two one-sided tests (TOST) approach is used to test equivalence. The  $z$ -test assumes that the population standard deviation is known.

## Outline of an Equivalence Test

PASS follows the *two one-sided tests* approach described by Schuirmann (1987) and Phillips (1990). It will be convenient to adopt the following specialized notation for the discussion of these tests.

<u>Parameter</u>	<u>PASS Input/Output</u>	<u>Interpretation</u>
$E_L, E_U$	EL, EU	<i>Lower and Upper Equivalence Limits.</i> If the actual mean is between $E_L$ and $E_U$ , the treatment is said to be <i>equivalent</i> to the reference value.
$\mu$	$\mu$	<i>Population mean.</i> If the data are paired differences, this is the mean of those differences. This parameter will be estimated by the study.
$\mu_1$	$\mu_1$	<i>Actual population mean at which power is calculated.</i> This is the assumed population mean used in all calculations.

With  $E_L < E_U$ , the null hypothesis of non-equivalence is

$$H_0: \mu \leq E_L \text{ or } \mu \geq E_U.$$

The alternative hypothesis of equivalence is

$$H_1: E_L < \mu < E_U.$$

## One-Sample Z-Test Statistic

A one-sample  $z$ -test is used to analyze the data when the standard deviation is known. The test assumes that the data are a simple random sample from a population of normally-distributed values that have the same known variance. This assumption implies that the observations are continuous and normal. The calculation of the two, one-sided  $z$ -tests proceeds as follows

$$z_L = \frac{\bar{x} - E_L}{\sigma/\sqrt{N}}$$

$$z_U = \frac{\bar{x} - E_U}{\sigma/\sqrt{N}}$$

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where  $\sigma$  is the known standard deviation of the measurements. The test is usually calculated using a  $100(1 - 2\alpha)\%$  confidence interval of the mean. If the both limits of this confidence interval are between  $E_L$  and  $E_U$ , equivalence is concluded.

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### Power Calculation

The power of this test is

$$\Pr(z_L \geq z_{1-\alpha} \text{ and } z_U \leq z_\alpha)$$

where  $z_L$  and  $z_U$  are distributed as standard normal.

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### 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.

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#### Design Tab

The Design tab contains the parameters associated with this test such as the means, sample sizes, alpha, and power.

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#### 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 that has already been run.

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#### 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 also 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. 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 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*.

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### Sample Size

#### N (Sample Size)

This option specifies one or more values of the sample size, the number of individuals in the study (total subjects). This value must be an integer greater than one.

You may enter a list of values using the syntax *50,100,150,200,250* or *50 to 250 by 50*.

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### Effect Size – Equivalence Limits

#### EU (Upper Equivalence Limit)

Enter the upper limit on equivalence. Mean differences outside EL and EU are not considered equivalent. Differences between them are considered equivalent.

Note that you must have  $EL < \mu_1 < EU$ .

#### EL (Lower Equivalence Limit)

Enter the lower limit on equivalence. Differences outside EL and EU are not considered equivalent. Differences between them are.

If you want symmetric limits about zero, enter “-Upper Limit” for EL to force  $EL = -|EU|$ .

Note that you must have  $EL < \mu_1 < EU$ . Finally, the scale of these numbers must match the scale of  $\sigma$ .

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### Effect Size – Mean

#### $\mu_1$ (Actual Mean)

Enter one or more values for the actual value of the mean at which power and sample size will be calculated.

This value can be any number. For paired data, this value is often set to zero, but it can be non-zero as long as  $EL < \mu_1 < EU$ .

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### Effect Size – Standard Deviation

#### $\sigma$ (Standard Deviation)

This option specifies one or more values of the known standard deviation. This must be a positive value.

PASS includes a special module for estimating the standard deviation. This module may be loaded by pressing the *SD* button. Refer to the Standard Deviation Estimator chapter for further details.

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## Example 1 – Finding Power

A one-group design is to be used to compare the impact on diastolic blood pressure of a new drug with the known standard drug. The average diastolic blood pressure after administration of the reference drug is 96 mmHg. Researchers believe this average may drop to 92 mmHg with the use of a new drug. The known  $\sigma$  is 25.

Following FDA guidelines, the researchers want to show that the diastolic blood pressure with the new drug is within 20% of the diastolic blood pressure with the standard drug. Thus, the equivalence limits of the mean difference of the two drugs are  $96 - 19.2 = 76.8$  and  $96 + 19.2 = 115.2$ . They decide to calculate the power for a range of sample sizes between 5 and 50. The significance level is 0.05.

### Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **One-Sample Z-Tests for Equivalence** procedure window by expanding **Means**, then **One Mean**, selecting **Equivalence**, and then clicking on **One-Sample Z-Tests for Equivalence**. 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**.

<u>Option</u>	<u>Value</u>
<b>Design Tab</b>	
Solve For .....	<b>Power</b>
Alpha.....	<b>0.05</b>
N (Sample Size).....	<b>5 10 15 20 30 40 50</b>
EU (Upper Equivalence Limit) .....	<b>115.2</b>
EL (Lower Equivalence Limit) .....	<b>76.8</b>
$\mu_1$ (Actual Mean) .....	<b>92</b>
$\sigma$ (Standard Deviation) .....	<b>25</b>

### Annotated Output

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

### Numeric Results

Numeric Results						
Hypotheses: $H_0: \mu \leq EL \text{ or } \mu \geq EU$ vs. $H_1: EL < \mu < EU$						
	Sample Size	Lower Equiv Limit	Upper Equiv Limit	Actual Mean	Standard Deviation	
Power	N	EL	EU	$\mu_1$	$\sigma$	Alpha
0.05418	5	76.800	115.200	92.000	25.000	0.050
0.51085	10	76.800	115.200	92.000	25.000	0.050
0.73549	15	76.800	115.200	92.000	25.000	0.050
0.85252	20	76.800	115.200	92.000	25.000	0.050
0.95374	30	76.800	115.200	92.000	25.000	0.050
0.98610	40	76.800	115.200	92.000	25.000	0.050
0.99603	50	76.800	115.200	92.000	25.000	0.050

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### 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.
- Mathews, Paul. 2010. Sample Size Calculations - Practical Methods for Engineers and Scientists. Mathews Malnar and Bailey. Fairport Harbor, OH.
- Blackwelder, W.C. 1998. 'Equivalence Trials.' In Encyclopedia of Biostatistics, John Wiley and Sons. New York. Volume 2, 1367-1372.

### Report Definitions

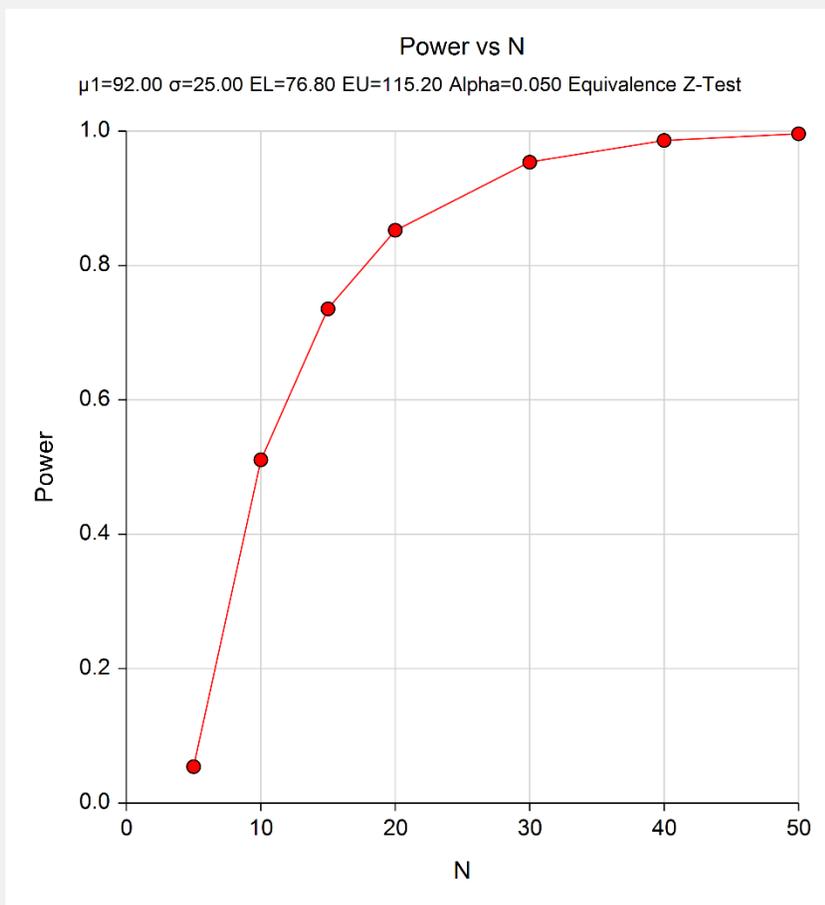
- Power is the probability of rejecting the null hypothesis when it is false. It should be close to one.
- N is the sample size, the number of subjects (or pairs) in the study.
- EL is the minimum allowable mean that still results in equivalence.
- EU is the maximum allowable mean that still result in equivalence.
- $\mu_1$  is the actual value of the mean at which the power and sample size are computed.
- $\sigma$  is the standard deviation of the response (or standard deviation of differences for paired data). It measures the variability in the population.
- Alpha is the probability of rejecting the null hypothesis when it is true. It should be small.

### Summary Statements

In an equivalence test of one mean using two one-sided z-tests, a sample size of 5 achieves 5% power at a 5.0% significance level when the actual mean is 92.000, the known standard deviation is 25.000, and the equivalence limits are 76.800 and 115.200.

This report shows the power for the indicated scenarios. Note that if they want 90% power, they will require a sample of around 30 subjects.

## Plots Section



This plot shows the power versus the sample size.

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## Example 2 – Validation using Chow, Shao, Wang, and Lokhnygina (2018)

Chow, Shao, Wang, and Lokhnygina (2018) presents an example on pages 46 and 47 of a one-sample equivalence z-test sample size calculation in which  $EU = 0.05$ ,  $EL = -0.05$ ,  $\mu_1 = 0.0$ ,  $\sigma = 0.1$ ,  $\alpha = 0.05$ , and  $\text{power} = 0.80$ . They obtain a sample size of 35.

### Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **One-Sample Z-Tests for Equivalence** procedure window by expanding **Means**, then **One Mean**, selecting **Equivalence**, and then clicking on **One-Sample Z-Tests for Equivalence**. 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**.

<u>Option</u>	<u>Value</u>
<b>Design Tab</b>	
Solve For .....	<b>Sample Size</b>
Power .....	<b>0.80</b>
Alpha .....	<b>0.05</b>
EU (Upper Equivalence Limit) .....	<b>0.05</b>
EL (Lower Equivalence Limit) .....	<b>-0.05</b>
$\mu_1$ (Actual Mean) .....	<b>0</b>
$\sigma$ (Standard Deviation) .....	<b>0.1</b>

### Output

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

<b>Numeric Results</b>						
Hypotheses: $H_0: \mu \leq EL \text{ or } \mu \geq EU$ vs. $H_1: EL < \mu < EU$						
	Sample Size N	Lower Equiv Limit EL	Upper Equiv Limit EU	Actual Mean $\mu_1$	Standard Deviation $\sigma$	Alpha
Power	35	-0.050	0.050	0.000	0.100	0.050

The sample size of 35 matches Chow, Shao, Wang, and Lokhnygina (2018) exactly.