

Chapter 498

Paired Z-Tests for Superiority by a Margin

Introduction

This procedure computes power and sample size for superiority by a margin tests in paired designs in which the paired differences are distributed as a normal random variable and the standard deviation is known.

The details of sample size calculation for the paired design are presented in the Paired Z-Tests chapter and they will not be duplicated here. This chapter only discusses those changes necessary for superiority by a margin tests. Sample size formulas for superiority by a margin tests of a single mean are presented in Chow et al. (2018) page 43.

The *one-sample z-test* is used to test whether a population mean is different from a specific value. When the data are differences between paired values, this test is known as the *paired z-test*.

Paired Designs

Paired data may occur because two measurements are made on the same subject or because measurements are made on two subjects that have been matched according to other variables. Hypothesis tests on paired data can be analyzed by considering the difference between the paired items as the response. The distribution of differences is usually symmetric. In fact, the distribution must be symmetric if the individual distributions of the two items are identical. Hence, the paired *t*-test is appropriate for paired data even when the distributions of the individual items are not normal.

The Statistical Hypotheses

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

Remember that in the usual *t*-test setting with δ defined as the mean paired difference, the null (H_0) and alternative (H_1) hypotheses for one-sided upper-tail tests are defined as

$$H_0: \delta \leq \delta_0 \quad \text{versus} \quad H_1: \delta > \delta_0$$

Rejecting H_0 implies that the mean is larger than the value δ_0 . This test is called an *upper-tail test* because H_0 is rejected in samples in which the sample mean is larger than δ_0 .

The *lower-tail test* is

$$H_0: \delta \geq \delta_0 \quad \text{versus} \quad H_1: \delta < \delta_0$$

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Superiority by a margin tests are special cases of the above directional tests. It will be convenient to adopt the following specialized notation for the discussion of these tests.

Parameter	PASS Input/Output	Interpretation
δ	δ	<i>Population mean paired difference.</i> This is the mean of paired differences in the population. This parameter will be estimated by the study.
δ_1	$\delta 1$	<i>Actual paired difference at which power is calculated.</i> This is the value of the mean paired difference at which power is calculated.
M_S	SM	<i>Margin of superiority.</i> This is a tolerance value that defines the magnitude of difference that is required for practical importance. This may be thought of as the largest difference that is considered to be trivial. The sign is determined by the specific design. This value is used to compute the bound, δ_0 .

Superiority by a Margin Tests

A *superiority by a margin test* tests that the mean of paired differences is greater than (or less than) zero by more than a small superiority margin. The actual direction of the hypothesis depends on 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 mean paired difference is greater than zero by at least the margin of superiority. The value of δ at which power is calculated must be greater than $|M_S|$. The null and alternative hypotheses with $\delta_0 = |M_S|$ are

$$H_0: \delta \leq |M_S| \quad \text{versus} \quad H_1: \delta > |M_S|$$

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 is less than the reference value by at least the margin of superiority. The value of δ at which power is calculated must be less than $-|M_S|$. The null and alternative hypotheses with $\delta_0 = -|M_S|$ are

$$H_0: \delta \geq -|M_S| \quad \text{versus} \quad H_1: \delta < -|M_S|$$

Paired Z-Test Statistic

The paired z-test assumes that the paired differences, X_i , are a simple random sample from a population of normally distributed difference values that all have the same mean and variance (known). This assumption implies that the data are continuous, and their distribution is symmetric. The calculation of the z-test proceeds as follows

$$z = \frac{\bar{X} - \delta_0}{\sigma/\sqrt{n}}$$

where

$$\bar{X} = \frac{\sum_{i=1}^n X_i}{n}$$

and δ_0 is the value of the mean hypothesized by the null hypothesis which depends on the magnitude and sign of M_S .

The significance of the test statistic is determined by computing the p-value. If this p-value is less than a specified level (usually 0.05), the hypothesis is rejected. Otherwise, no conclusion can be reached.

Population Size

This is the number of subjects in the population. Usually, you assume that samples are drawn from a very large (infinite) population. Occasionally, however, situations arise in which the population of interest is of limited size. In these cases, appropriate adjustments must be made.

When a finite population size is specified, the standard deviation is reduced according to the formula:

$$\sigma'^2 = \left(1 - \frac{n}{N}\right) \sigma^2$$

where n is the sample size, N is the population size, σ is the original standard deviation, and σ' is the new standard deviation.

The quantity n/N is often called the sampling fraction. The quantity $\left(1 - \frac{n}{N}\right)$ is called the *finite population correction factor*.

The Standard Deviation of Paired Differences (σ)

If you know the standard deviation of paired differences (σ), enter it directly. If you know the standard deviations of the paired variables (σ_1 and σ_2) and the Pearson correlation between the paired variables (ρ), the standard deviation of paired differences (σ) may be calculated using the equation

$$\sigma^2 = \sigma_1^2 + \sigma_2^2 - 2\rho\sigma_1\sigma_2$$

such that

$$\sigma = \sqrt{\sigma_1^2 + \sigma_2^2 - 2\rho\sigma_1\sigma_2}.$$

If $\sigma_1 = \sigma_2 = \sigma_x$, then this formula reduces to

$$\sigma^2 = 2\sigma_x^2(1 - \rho)$$

such that

$$\sigma = \sqrt{2\sigma_x^2(1 - \rho)}.$$

If you know the within-subject population standard deviation (σ_w), then σ may be calculated using the equation

$$\sigma^2 = 2\sigma_w^2$$

such that

$$\sigma = \sqrt{2\sigma_w^2}.$$

σ_w is often estimated by the square root of the within mean square error (WMSE) from a repeated measures ANOVA.

Power Calculation for the Paired Z-Test

When the standard deviation is known, the power is calculated as follows for a directional alternative (one-tailed test) in which $\delta_1 > \delta_0$.

1. Find z_α such that $1 - \Phi(z_\alpha) = \alpha$, where $\Phi(x)$ is the area to the left of x under the standardized normal curve.
2. Calculate: $X_1 = \delta_0 + z_\alpha \frac{\sigma}{\sqrt{n}}$.
3. Calculate: $z_1 = \frac{X_1 - \delta_1}{\frac{\sigma}{\sqrt{n}}}$.
4. Power = $1 - \Phi(z_1)$.

Example 1 – Power Analysis

Suppose that a test is to be conducted to determine if a new cancer treatment improves the mean bone density. The adjusted mean bone density (AMBD) in the population of interest is 0.002300 gm/cm. Clinicians decide that if the treatment increases AMBD by more than 5% (0.000115 gm/cm), it generates a significant health benefit. They also want to consider what would happen if the margin of superiority is set to 2.5% (0.0000575 gm/cm). The standard deviation of paired differences is 0.000300 gm/cm.

The analysis will be a superiority test using the paired z-test at the 0.025 significance level. Power is to be calculated assuming that the new treatment has 7.5% improvement on AMBD. Several sample sizes between 20 and 300 will be analyzed. The researchers want to achieve a power of at least 90%. All numbers have been multiplied by 10000 to make the reports and plots easier to read.

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
Higher Means Are	Better (H1: $\delta > SM$)
Population Size	Infinite
Alpha	0.025
N (Sample Size)	20 40 60 80 100 150 200 300
SM (Superiority Margin)	0.575 1.15
δ_1 (Mean of Paired Differences)	1.725
Standard Deviation Input Type	Enter the SD of Paired Differences
σ (SD of Paired Differences)	3

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Output

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

Numeric Results

Solve For: Power
 Higher Means Are: Better
 Hypotheses: $H_0: \delta \leq SM$ vs. $H_1: \delta > SM$

Power	Sample Size N	Paired Differences			Alpha	Beta
		Superiority Margin SM	Mean δ	Standard Deviation σ		
0.40298	20	0.575	1.725	3	0.025	0.59702
0.67884	40	0.575	1.725	3	0.025	0.32116
0.84359	60	0.575	1.725	3	0.025	0.15641
0.92904	80	0.575	1.725	3	0.025	0.07096
0.96949	100	0.575	1.725	3	0.025	0.03051
0.99688	150	0.575	1.725	3	0.025	0.00312
0.99973	200	0.575	1.725	3	0.025	0.00027
1.00000	300	0.575	1.725	3	0.025	0.00000
0.13506	20	1.150	1.725	3	0.025	0.86494
0.22730	40	1.150	1.725	3	0.025	0.77270
0.31728	60	1.150	1.725	3	0.025	0.68272
0.40298	80	1.150	1.725	3	0.025	0.59702
0.48273	100	1.150	1.725	3	0.025	0.51727
0.65079	150	1.150	1.725	3	0.025	0.34921
0.77356	200	1.150	1.725	3	0.025	0.22644
0.91305	300	1.150	1.725	3	0.025	0.08695

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
 N The sample size, the number of subjects (or pairs) in the study.
 SM The magnitude of the margin of superiority. Since higher means are better, this value is positive and is the distance above the reference value that is required to be considered superior.
 δ The population mean of paired differences.
 δ 1 The value of the mean of paired differences at which power and sample size are calculated.
 σ The standard deviation of paired differences for the population.
 Alpha The probability of rejecting a true null hypothesis.
 Beta The probability of failing to reject the null hypothesis when the alternative hypothesis is true.

Summary Statements

A paired design (where higher means are considered to be better) will be used to test whether treatment 1 is superior to treatment 2 by a margin by testing whether the paired mean difference (δ) is greater than 0.575 ($H_0: \delta \leq 0.575$ versus $H_1: \delta > 0.575$). The comparison will be made using a one-sided, paired-difference Z-test, with a Type I error rate (α) of 0.025. The (known) standard deviation of paired differences is assumed to be 3. To detect a paired mean difference of 1.725 with a sample size of 20 pairs, the power is 0.40298.

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Dropout-Inflated Sample Size

Dropout Rate	Sample Size N	Dropout- Inflated Enrollment Sample Size N'	Expected Number of Dropouts D
20%	20	25	5
20%	40	50	10
20%	60	75	15
20%	80	100	20
20%	100	125	25
20%	150	188	38
20%	200	250	50
20%	300	375	75

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	The evaluable sample size at which power is computed (as entered by the user). If N subjects are evaluated out of the N' subjects that are enrolled in the study, the design will achieve the stated power.
N'	The total number of subjects that should be enrolled in the study in order to obtain 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 Lokhnygina, Y. (2018) pages 32-33.)
D	The expected number of dropouts. $D = N' - N$.

Dropout Summary Statements

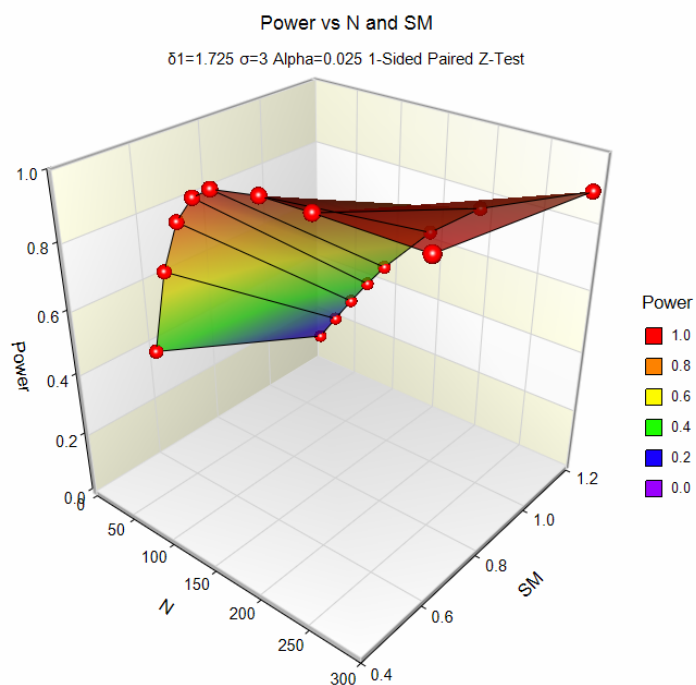
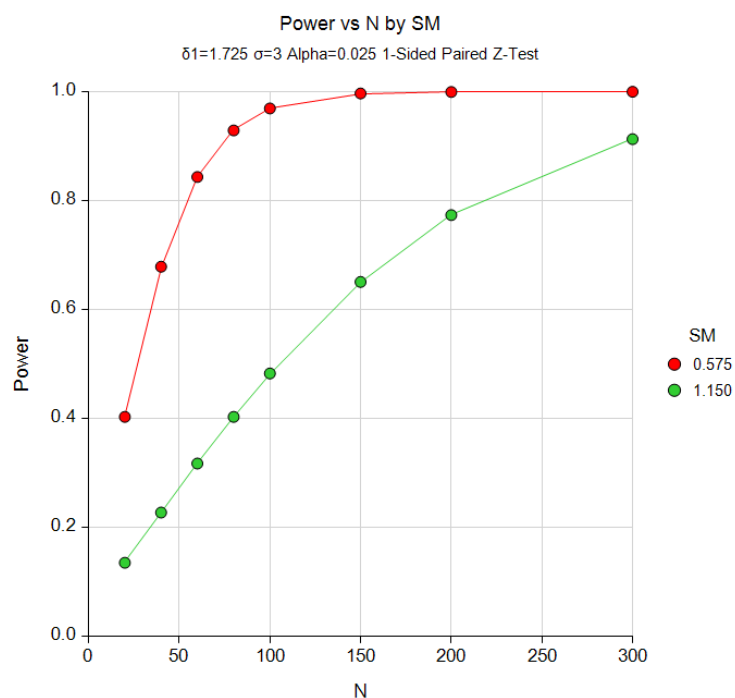
Anticipating a 20% dropout rate, 25 subjects should be enrolled to obtain a final sample size of 20 subjects.

References

- Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. 2018. Sample Size Calculations in Clinical Research, Third Edition. Taylor & Francis/CRC. Boca Raton, Florida.
- Julious, Steven A. 2004. 'Tutorial in Biostatistics. Sample sizes for clinical trials with Normal data.' Statistics in Medicine, 23:1921-1986.

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Plots



The above report shows that for $SM = 1.15$, the sample size necessary to obtain 90% power is just under 300. However, if $SM = 0.575$, the required sample size is only about 75.

Example 2 – Finding the Sample Size

Continuing with Example 1, the researchers want to know the exact sample size for each value of SM to achieve 90% power.

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**
 Higher Means Are **Better (H1: $\delta > SM$)**
 Population Size **Infinite**
 Power **0.90**
 Alpha **0.025**
 SM (Superiority Margin) **0.575 1.15**
 δ_1 (Mean of Paired Differences) **1.725**
 Standard Deviation Input Type **Enter the SD of Paired Differences**
 σ (SD of Paired Differences) **3**

Output

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

Numeric Results

Solve For: **Sample Size**
 Higher Means Are: **Better**
 Hypotheses: **H0: $\delta \leq SM$ vs. H1: $\delta > SM$**

Power	Sample Size N	Paired Differences			Alpha	Beta
		Superiority Margin SM	Mean δ_1	Standard Deviation σ		
0.90195	72	0.575	1.725	3	0.025	0.09805
0.90097	287	1.150	1.725	3	0.025	0.09903

This report shows the exact sample size requirement for each value of SM.

Example 3 – Validation

This procedure uses the same mechanics as the *Paired Z-Tests for Non-Inferiority* procedure. We refer the user to Example 3 of Chapter 494 for the validation.