Chapter 512

Paired Z-Tests for Equivalence

Introduction

This procedure allows you to study the power and sample size of tests of equivalence of means of two correlated (paired) variables. Schuirmann's (1987) two one-sided tests (TOST) approach is used to test equivalence. The paired z-test may be used in this situation when the standard deviation of paired differences is known.

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, often demographic, variables. Hypothesis tests on paired data can be analyzed by considering the differences between the paired items. The distribution of these 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 definition of equivalence has been refined in recent years using the concepts of prescribability and switchability. *Prescribability* refers to ability of a physician to prescribe either of two drugs at the beginning of the treatment. However, once prescribed, no other drug can be substituted for it. *Switchability* refers to the ability of a patient to switch from one drug to another during treatment without adverse effects. Prescribability is associated with equivalence of location and variability. Switchability is associated with the concept of individual equivalence. This procedure analyzes average equivalence. Thus, it partially analyzes prescribability. It does not address equivalence of variability or switchability.

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.

Parameter	PASS Input/Output	Interpretation
δ	δ	*Population mean of paired differences*. This is the mean of paired differences, $X_1 - X_2$, in the population. This parameter will be estimated by the study.
δ_1	$\delta 1$	*Actual paired difference at which power is calculated*. This is the value of the mean paired difference at which power is calculated.
E_L, E_U	EL, EU	*Lower* and *Upper Equivalence Limits.* If the average paired difference is between these two limits, the treatment is said to be *equivalent* to the reference.

With $E_L < 0$ and $E_U > 0$, the null hypothesis of non-equivalence is

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

The alternative hypothesis of equivalence is

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

Paired Z-Test Statistic

A paired *z*-test is used to analyze the data when the standard deviation of paired differences 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 differences are continuous and normal. The calculation of the two, one-sided *z*-tests proceeds as follows:

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

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

where σ is the known standard deviation of the paired differences. The test is usually calculated using a 100(1 – 2α)% confidence interval of the mean difference. If both limits of this confidence interval are between E_L and E_U, equivalence is concluded.

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

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.

Example 1 – Finding Power

A paired design is to be used to compare the impact of two drugs on diastolic blood pressure. The average diastolic blood pressure after administration of the reference drug is known to be 96 mmHg. Researchers believe this average may drop to 92 mmHg with the use of a new drug. The known σ 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 reference drug. Thus, the equivalence limits of the mean difference of the two drugs are -19.2 and 19.2. They decide to calculate the power for a range of sample sizes between 5 and 50. The significance level is 0.05.

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**
Alpha.. **0.05**
N (Sample Size).. **5 10 15 20 30 40 50**
EU (Upper Equivalence Limit)........................ **19.2**
EL (Lower Equivalence Limit) .... **-Upper Limit**
δ1 (Mean of Paired Differences).................... **-4**
Standard Deviation Input Type .... **Enter the SD of Paired Differences**
σ (SD of Paired Differences).......................... **25**

Output

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

Numeric Reports

Numeric Results

Solve For: Power
Hypotheses: H0: $\delta \le$ EL or $\delta \ge$ EU vs. H1: EL < δ < EU

		Paired Differences				
		Equivalence Limits				
Power	Sample Size N	Lower EL	Upper EU	Mean δ1	Standard Deviation σ	Alpha
0.05418	5	-19.2	19.2	-4	25	0.05
0.51085	10	-19.2	19.2	-4	25	0.05
0.73549	15	-19.2	19.2	-4	25	0.05
0.85252	20	-19.2	19.2	-4	25	0.05
0.95374	30	-19.2	19.2	-4	25	0.05
0.98610	40	-19.2	19.2	-4	25	0.05
0.99603	50	-19.2	19.2	-4	25	0.05

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.
EL The minimum allowable mean that still results in equivalence.
EU The maximum allowable mean that still result in equivalence.
δ The population mean of paired differences.
δ1 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.

Summary Statements

A paired design will be used to test whether the treatment 1 mean (μ1) is equivalent to the treatment 2 mean (μ2), with lower and upper mean difference equivalence limits of -19.2 and 19.2 (H0: δ ≤ -19.2 or δ ≥ 19.2 versus H1: -19.2 < δ < 19.2, δ = μ1 - μ2). The comparison will be made using two one-sided, paired-difference Z-tests, with an overall Type I error rate (α) of 0.05. The (known) standard deviation of paired differences is assumed to be 25. To detect a paired mean difference of -4 with a sample size of 5 pairs, the power is 0.05418.

Dropout-Inflated Sample Size

Dropout Rate	Sample Size N	Dropout-Inflated Enrollment Sample Size N'	Expected Number of Dropouts D
20%	5	7	2
20%	10	13	3
20%	15	19	4
20%	20	25	5
20%	30	38	8
20%	40	50	10
20%	50	63	13

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, 7 subjects should be enrolled to obtain a final sample size of 5 subjects.

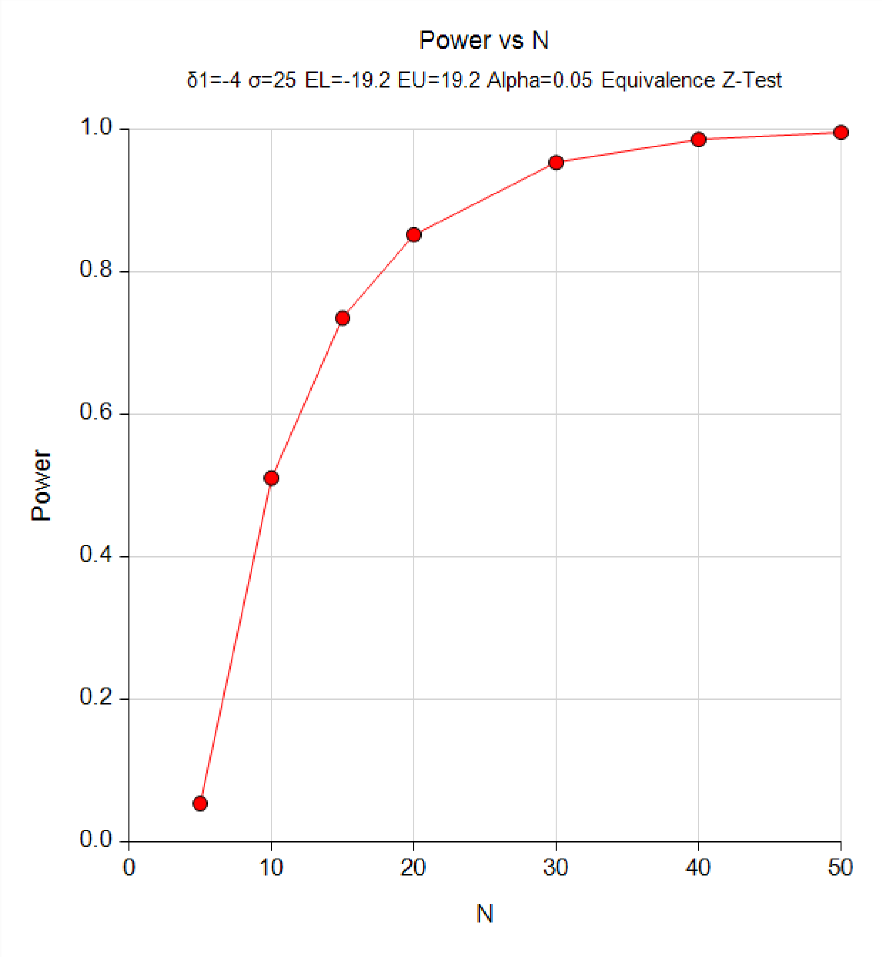
References

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.
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.

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

Plots



This plot shows the power versus the sample size.

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 paired equivalence *z*-test sample size calculation in which EU = 0.05, EL = -0.05, δ1 = 0.0, σ = 0.1, alpha = 0.05, and power = 0.80. They obtain a sample size of 35.

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**
Power.. **0.80**
Alpha.. **0.05**
EU (Upper Equivalence Limit)....................... **0.05**
EL (Lower Equivalence Limit) .... **-Upper Limit**
δ1 (Mean of Paired Differences)................... **0**
Standard Deviation Input Type .... **Enter the SD of Paired Differences**
σ (SD of Paired Differences).......................... **0.1**

Output

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

Numeric Results

Solve For: Sample Size
Hypotheses: H0: δ ≤ EL or δ ≥ EU vs. H1: EL < δ < EU

		Paired Differences				
		Equivalence Limits				
Power	Sample Size N	Lower EL	Upper EU	Mean δ1	Standard Deviation σ	Alpha
0.81088	35	-0.05	0.05	0	0.1	0.05

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