Chapter 520

Equivalence Tests for the Difference Between Two Means in a 2x2 Cross-Over Design

Introduction

This procedure calculates power and sample size of statistical tests of equivalence of the means of a 2x2 cross-over design which is analyzed with a t-test. Schuirmann's (1987) two one-sided tests (TOST) approach is used to test equivalence. Only a brief introduction to the subject will be given here. For a comprehensive discussion on the subject, refer to Chow and Liu (1999) and Julious (2004).

Measurements are made on individuals that have been randomly assigned to one of two sequences. The first sequence receives the treatment followed by the reference (AB). The second sequence receives the reference followed by the treatment (BA). This *cross-over* design may be analyzed by a TOST equivalence test to show that the two means do not differ by more than a small amount, called the margin of equivalence.

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.

Cross-Over Designs

Senn (2002) defines a *cross-over* design as one in which each subject receives all treatments, and the objective is to study differences among the treatments. The name *cross-over* comes from the most common case in which there are only two treatments. In this case, each subject *crosses over* from one treatment to the other. It is assumed that there is a *washout* period between treatments during which the response returns back to its baseline value. If this does not occur, there is said to be a *carryover* effect.

A 2x2 cross-over design contains to two *sequences* (treatment orderings) and two time periods (occasions). One sequence receives treatment A followed by treatment B. The other sequence receives B and then A. The design includes a washout period between responses to make certain that the effects of the first drug do not carry over to the second. Thus, the groups in this design are defined by the sequence in which the drugs are administered, not by the treatments they receive. Indeed, higher-order cross-over designs have been used in which the same treatment is used on both occasions.

Cross-over designs are employed because, if the no-carryover assumption is met, treatment differences are measured within a subject rather than between subjects—making a more precise measurement. Examples of the situations that might use a cross-over design are the comparison of anti-inflammatory drugs in arthritis and the comparison of hypotensive agents in essential hypertension. In both of these cases, symptoms are expected to return to their usual baseline level shortly after the treatment is stopped.

Cross-Over Analysis

The following discussion summarizes the presentation of Chow and Liu (1999). The general linear model for the standard 2x2 cross-over design is

$$Y_{ijk} = \mu + S_{ik} + P_j + \mu_{(j,k)} + C_{(j-1,k)} + e_{ijk}$$

where *i* represents a subject (1 to N_k), *j* represents the period (1 or 2), and *k* represents the sequence (1 or 2). The S_{ik} represent the random effects of the subjects. The P_j represent the effects of the two periods. The $\mu_{(j,k)}$ represent the means of the two treatments. In the case of the 2x2 cross-over design

$$\mu_{(j,k)} = \begin{cases} \mu_1 & \text{if } k = j \\ \mu_2 & \text{if } k \neq j \end{cases}$$

where the subscripts 1 and 2 represent treatments A and B, respectively.

The $C_{(j-1,k)}$ represent the carry-over effects. In the case of the 2x2 cross-over design

$$C_{(j-1,k)} = \begin{cases} C_1 & \text{if } j = 2, k = 1 \\ C_2 & \text{if } j = 2, k = 2 \\ 0 & \text{otherwise} \end{cases}$$

where the subscripts 1 and 2 represent treatments A and B, respectively.

Assuming that the average effect of the subjects is zero, the four means from the 2x2 cross-over design can be summarized using the following table.

Sequence	Period 1	Period 2
1 (AB)	$\mu_{11} = \mu + P_1 + \mu_1$	$\mu_{21} = \mu + P_2 + \mu_2 + C_1$
2 (BA)	$\mu_{12} = \mu + P_1 + \mu_2$	$\mu_{22} = \mu + P_2 + \mu_1 + C_2$

where $P_1 + P_2 = 0$ and $C_1 + C_2 = 0$.

Advantages of Cross-Over Designs

A comparison of treatments on the same subject is expected to be more precise. The increased precision often translates into a smaller sample size. Also, patient enrollment into the study may be easier because each patient will receive both treatments. Finally, it is often more difficult to obtain a subject than to obtain a measurement.

Disadvantages of Cross-Over Designs

The statistical analysis of a cross-over experiment is more complex than a parallel-group experiment and requires additional assumptions. It may be difficult to separate the treatment effect from the period effect, the carry-over effect of the previous treatment, and the interaction between period and treatment.

The design cannot be used when the treatment (or the measurement of the response) alters the subject permanently. Hence, it should not be used to compare treatments that are intended to provide a cure.

Because subjects must be measured at least twice, it is often more difficult to keep patients enrolled in the study. It is arguably simpler to measure a subject once than to obtain their measurement twice. This is particularly true when the measurement process is painful, uncomfortable, embarrassing, or time consuming.

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 specialize notation for the discussion of these tests.

Parameter	PASS Input/Output	Interpretation
μ_T	Not used	*Treatment mean*. This is the treatment mean.
μ_R	Not used	*Reference mean*. This is the mean of a reference population.
ε_U, ε_L	EU, EL	*Equivalence Limits.* These are the tolerance values that define the maximum changes that are not of practical importance. These may be thought of as the largest changes from the baseline that are considered to be trivial.
δ	δ1	*True difference*. This is the value of $\mu_T - \mu_R$, the difference between the treatment and reference means. This is the value at which the power is calculated.

Note that the actual values of μ_T and μ_R are not needed. Only their difference is needed for power and sample size calculations.

The null hypothesis of non-equivalence is

$$H_0: \delta \leq \varepsilon_L \quad \text{or} \quad \delta \geq \varepsilon_U, \quad \text{where} \quad \varepsilon_L < 0, \varepsilon_U > 0.$$

and the alternative hypothesis of equivalence is

$$H_1: \varepsilon_L < \delta < \varepsilon_U$$

Test Statistic

This section describes the test statistic that is used to perform the hypothesis test.

T-Test

A *t*-test is used to analyze the data. The test assumes that the data are a simple random sample from a population of normally distributed values that have the same variance. This assumption implies that the differences are continuous and normal. The calculation of the two, one-sided t-tests proceeds as follow

$$T_L = \frac{(\bar{x}_T - \bar{x}_R) - \varepsilon_L}{\hat{\sigma}_w\sqrt{\frac{2}{N}}} \quad \text{and} \quad T_U = \frac{(\bar{x}_T - \bar{x}_R) - \varepsilon_U}{\hat{\sigma}_w\sqrt{\frac{2}{N}}}$$

where $\hat{\sigma}_w^2$ is the within mean square error from the appropriate ANOVA table.

The significance of each test statistic is determined by computing the p-value. If this p-value is less than a specified level (usually 0.05), the null hypothesis is rejected.

Computing the Within-Subject Variance (σ_w^2)

The ANOVA F-test is calculated using a standard repeated-measures analysis of variance table in which the between factor is the sequence and the within factor is the treatment. The within mean square error provides an estimate of the within-subject variance, σ_w^2, where

$$\sigma_w^2 = \text{Variance}\left(e_{ijk}\right)$$

If prior studies used a *t*-test rather than an ANOVA to analyze the data, you may not have a direct estimate of σ_w^2. Instead, you may have an estimate of the variance of the period differences from the *t*-test ($\hat{\sigma}_P^2$), an estimate of the variance of the paired differences ($\hat{\sigma}_D^2$), or an estimate of the variances of the paired variables ($\hat{\sigma}_1^2$ and $\hat{\sigma}_2^2$) and the correlation between the paired variables ($\hat{\rho}$). The within-subject variance, σ_w^2, is functionally related to these other variances as described below. Any of these different variances may be entered directly into this procedure.

Using the Variance of the Period Differences (σ_P^2)

The variance of the period differences for each subject within each sequence (σ_P^2) is defined as

$$\sigma_P^2 = \text{Variance}\left(\frac{Y_{i2k} - Y_{i1k}}{2}\right).$$

σ_P^2 has a functional relationship with the within-subject population variance (σ_w^2), namely

$$\sigma_P^2 = \frac{\sigma_w^2}{2},$$

such that

$$\sigma_w^2 = 2\sigma_P^2 .$$

The within-subject standard deviation (σ_w) is then

$$\sigma_w = \sqrt{2\sigma_P^2}\,.$$

Using the Variance of the Paired Differences (σ_D^2)

The variance of the paired differences (σ_D^2) is defined as

$$\sigma_D^2 = \text{Variance}(Y_{i2k} - Y_{i1k})\,.$$

σ_D^2 has a functional relationship with the within-subject population variance (σ_w^2), namely

$$\sigma_D^2 = 2\sigma_w^2\,,$$

such that

$$\sigma_w^2 = \frac{\sigma_D^2}{2}.$$

The within-subject standard deviation (σ_w) is then

$$\sigma_w = \sqrt{\frac{\sigma_D^2}{2}}.$$

Using the Variances of the Paired Variables (σ_1^2 and σ_2^2) and the Correlation Between the Paired Variables (ρ)

The variances of the paired variables (σ_1^2 and σ_2^2) and the correlation between the paired variables (ρ) are defined as

$$\sigma_1^2 = \text{Variance}(Y_{i1k})$$

$$\sigma_2^2 = \text{Variance}(Y_{i2k})$$

$$\rho = \text{Correlation}(Y_{i1k}, Y_{i2k})$$

The variance of paired differences (σ_D^2) can be computed from σ_1^2, σ_2^2 and ρ as

$$\sigma_D^2 = \sigma_1^2 + \sigma_2^2 - 2\rho\sigma_1\sigma_2\,,$$

such that the within-subject population variance (σ_w^2) can be computed as

$$\sigma_w^2 = \frac{\sigma_D^2}{2} = \frac{\sigma_1^2 + \sigma_2^2 - 2\rho\sigma_1\sigma_2}{2}.$$

The within-subject standard deviation (σ_w) is then

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

If $\sigma_1^2 = \sigma_2^2 = \sigma_x^2$, then with

$$\sigma_x^2 = \text{Variance}\left(Y_{ijk}\right),$$

the formula for σ_w^2 reduces to

$$\sigma_w^2 = \sigma_x^2(1-\rho).$$

The within-subject standard deviation (σ_w) is then

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

Computing the Power

The power of this test is given by

$$\Pr(T_L \geq t_{1-\alpha,N-2} \quad \text{and} \quad T_U \leq -t_{1-\alpha,N-2})$$

where T_L and T_U are distributed as the bivariate, noncentral *t* distribution with noncentrality parameters Δ_L and Δ_U given by

$$\Delta_L = \frac{\delta - \varepsilon_L}{\sigma_w\sqrt{\frac{2}{N}}}$$

$$\Delta_U = \frac{\delta - \varepsilon_U}{\sigma_w\sqrt{\frac{2}{N}}}$$

Example 1 – Finding Power

A cross-over 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 within mean square error of similar studies is 324. Its square root is 18.

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 6 and 100. 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 (Total Sample Size)	**6 10 16 20 40 60 80 100**
EU (Upper Equivalence Limit)	**19.2**
EL (Lower Equivalence Limit)	**-Upper Limit**
δ1 (Actual Difference to Detect)	**-4**
Standard Deviation Input Type	**Enter the Within-Subject Population SD**
σw (Within-Subject Population SD)	**18**

Output

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

Numeric Reports

Numeric Results

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

Power	Total Sample Size N	Equivalence Limits Lower EL	Equivalence Limits Upper EU	Actual Difference δ1	Standard Deviation σw	Alpha	Beta
0.14704	6	-19.2	19.2	-4	18	0.05	0.85296
0.38731	10	-19.2	19.2	-4	18	0.05	0.61269
0.69965	16	-19.2	19.2	-4	18	0.05	0.30035
0.81045	20	-19.2	19.2	-4	18	0.05	0.18955
0.98042	40	-19.2	19.2	-4	18	0.05	0.01958
0.99828	60	-19.2	19.2	-4	18	0.05	0.00172
0.99987	80	-19.2	19.2	-4	18	0.05	0.00013
0.99999	100	-19.2	19.2	-4	18	0.05	0.00001

Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N	The total sample size drawn from all sequences. The sample is divided equally among sequences.
EL and EU	The lower and upper equivalence limits, respectively, which are the maximum allowable differences that still result in equivalence.
δ	The difference in means. Difference (δ) = Treatment Mean (μT) - Reference Mean (μR).
δ1	The actual mean difference under the alternative hypothesis at which the power is computed.
σw	The within-subject population standard deviation. σw = √[var(e_ijk)]. σw is estimated as the square root of the within mean square error (WMSE) (i.e., σw = √[WMSE]) from a repeated measures ANOVA analysis of a prior cross-over design.
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 2×2 cross-over design will be used to test whether the treatment mean (μT) is equivalent to the reference mean (μR), with 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 = μT - μR). The comparison will be made using two one-sided t-tests, with an overall Type I error rate (α) of 0.05. The within-subject population standard deviation is assumed to be 18. To detect a difference in means (μT - μR) of -4, with a total sample size of 6 (allocated equally to the two sequences), the power is 0.14704.

Dropout-Inflated Sample Size

Dropout Rate	Sample Size N	Dropout-Inflated Enrollment Sample Size N'	Expected Number of Dropouts D
20%	6	8	2
20%	10	13	3
20%	16	20	4
20%	20	25	5
20%	40	50	10
20%	60	75	15
20%	80	100	20
20%	100	125	25

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, 8 subjects should be enrolled to obtain a final sample size of 6 subjects.

References

Blackwelder, W.C. 1998. 'Equivalence Trials.' In Encyclopedia of Biostatistics, John Wiley and Sons. New York. Volume 2, 1367-1372.

Chow, S.C. and Liu, J.P. 1999. Design and Analysis of Bioavailability and Bioequivalence Studies. Marcel Dekker. New York

Chow, S.C., Shao, J., and Wang, H. 2003. Sample Size Calculations in Clinical Research. Marcel Dekker. New York.

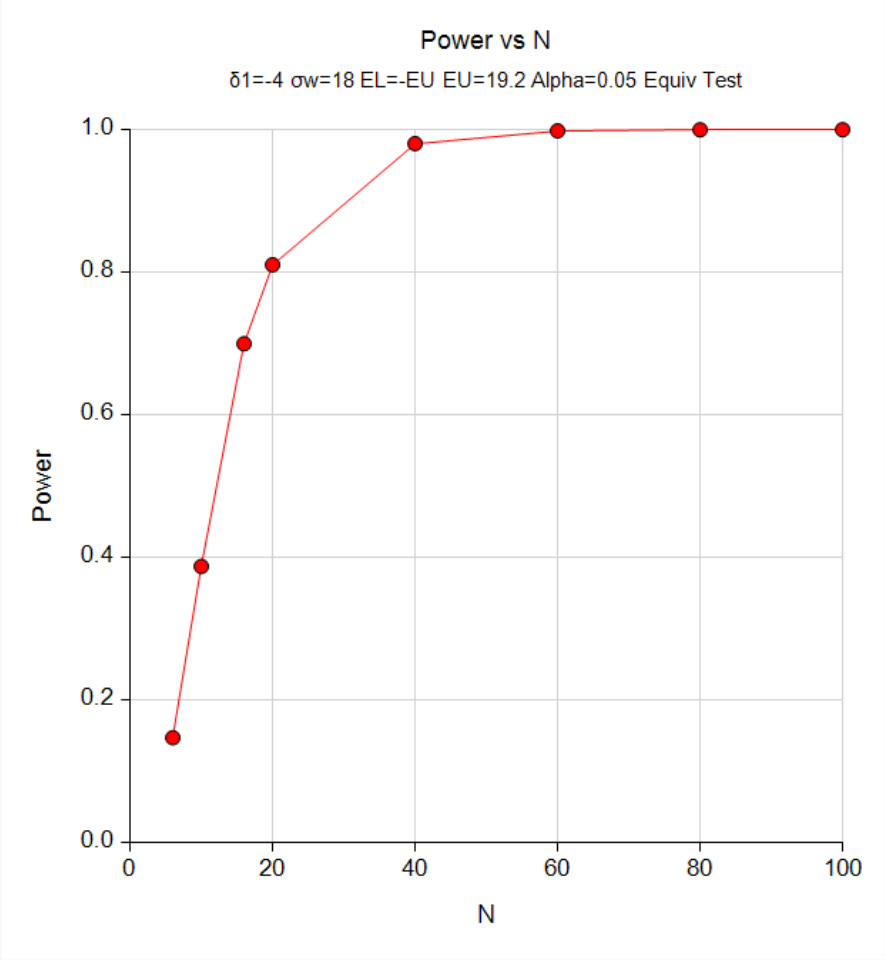
Julious, Steven A. 2004. 'Tutorial in Biostatistics. Sample sizes for clinical trials with Normal data.' Statistics in Medicine, 23:1921-1986.

Senn, Stephen. 2002. Cross-over Trials in Clinical Research. Second Edition. John Wiley & Sons. New York.

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 – Finding Sample Size

Continuing with Example 1, the researchers want to find the exact sample size needed to achieve both 80% power and 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**
Power	**0.80 0.90**
Alpha	**0.05**
EU (Upper Equivalence Limit)	**19.2**
EL (Lower Equivalence Limit)	**-Upper Limit**
δ1 (Actual Difference to Detect)	**-4**
Standard Deviation Input Type	**Enter the Within-Subject Population SD**
σw (Within-Subject Population SD)	**18**

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

Power	Total Sample Size N	Equivalence Limits Lower EL	Equivalence Limits Upper EU	Actual Difference δ1	Standard Deviation σw	Alpha	Beta
0.81045	20	-19.2	19.2	-4	18	0.05	0.18955
0.90321	26	-19.2	19.2	-4	18	0.05	0.09679

We note that 20 subjects are needed to achieve 80% power and 26 subjects are needed to achieve 90% power.

Example 3 – Validation using Phillips (1990)

Phillips (1990) page 142 presents a table of sample sizes for various parameter values. In this table, the treatment mean, standard deviation, and equivalence limits are all specified as percentages of the reference mean. We will reproduce the second line of the table in which the square root of the within mean square error is 20%; the equivalence limits are 20%; the treatment mean is 100%, 95%, 90%, and 85%; the power is 70%; and the significance level is 0.05. Phillips reports total sample size as 16, 20, 40, and 152 corresponding to the four treatment mean percentages. We will now setup this example in **PASS**.

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**
Power	**0.7**
Alpha	**0.05**
EU (Upper Equivalence Limit)	**20**
EL (Lower Equivalence Limit)	**-Upper Limit**
δ1 (Actual Difference to Detect)	**0 -5 -10 -15**
Standard Deviation Input Type	**Enter the Within-Subject Population SD**
σw (Within-Subject Population SD)	**20**

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

Power	Total Sample Size N	Equivalence Limits: Lower EL	Equivalence Limits: Upper EU	Actual Difference δ1	Standard Deviation σw	Alpha	Beta
0.70012	152	-20	20	-15	20	0.05	0.29988
0.70922	40	-20	20	-10	20	0.05	0.29078
0.72205	20	-20	20	-5	20	0.05	0.27795
0.70310	16	-20	20	0	20	0.05	0.29690

Note that **PASS** obtains the same samples sizes as Phillips (1990).

Example 4 – Validation using Machin et al. (1997)

Machin *et al.* (1997) page 107 present an example of determining the sample size for a cross-over design in which the reference mean is 35.03, the treatment mean is 35.03, the standard deviation, entered as the square root of the within mean square error, is 40% of the reference mean, the limits are plus or minus 20% of the reference mean, the power is 80%, and the significance level is 0.10. Machin *et al.* calculate the total sample size to be 54.

When the parameters are given as percentages of the reference mean, it is easy enough to calculate the exact amounts by applying those percentages. However, the percentages can all be entered directly as long as all parameters (EU, EL, D, and Sw) are specified as percentages.

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 4** 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	**0.10**
EU (Upper Equivalence Limit)	**20**
EL (Lower Equivalence Limit)	**-Upper Limit**
δ1 (Actual Difference to Detect)	**0**
Standard Deviation Input Type	**Enter the Within-Subject Population SD**
σw (Within-Subject Population SD)	**40**

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

Power	Total Sample Size N	Equivalence Limits: Lower EL	Equivalence Limits: Upper EU	Actual Difference δ1	Standard Deviation σw	Alpha	Beta
0.80497	54	-20	20	0	40	0.1	0.19503

Note that **PASS** also has obtained a sample size of 54.

Example 5 – Validation using Chow and Liu (1999)

Chow and Liu (1999) page 153 present an example of determining the sample size for a cross-over design in which the reference mean is 82.559, the treatment mean is 82.559, the standard deviation, entered as the square root of the within mean square error, is 15.66%, the limits are plus or minus 20%, the power is 80%, and the significance level is 0.05. They calculate a sample size of 12. **PASS** calculates a sample size of 13. To see why **PASS** has increased the sample size by one, we will evaluate the power at sample sizes of 10, 12, 13, 14, and 16.

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 5** 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 (Total Sample Size)	**10 12 13 14 16**
EU (Upper Equivalence Limit)	**20**
EL (Lower Equivalence Limit)	**-Upper Limit**
δ1 (Actual Difference to Detect)	**0**
Standard Deviation Input Type	**Enter the Within-Subject Population SD**
σw (Within-Subject Population SD)	**15.66**

Output

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

Numeric Results

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

	Total Sample Size	Equivalence Limits		Actual Difference	Standard Deviation		
Power	N	Lower EL	Upper EU	δ1	σw	Alpha	Beta
0.66435	10	-20	20	0	15.66	0.05	0.33565
0.79317	12	-20	20	0	15.66	0.05	0.20683
0.83634	13	-20	20	0	15.66	0.05	0.16366
0.87523	14	-20	20	0	15.66	0.05	0.12477
0.92578	16	-20	20	0	15.66	0.05	0.07422

The power for *N* = 12 is 0.79317. The power for *N* = 13 is 0.83634. Hence, to achieve better than 80% power, a sample size of 13 is necessary. However, 0.7932 is sufficiently close to 0.800 to make *N* = 12 a reasonable choice (as Chow and Liu did).

Example 6 – Validation using Senn (1993)

Senn (1993) page 217 presents an example of determining the sample size for a cross-over design in which the reference mean is equal to the treatment mean, the standard deviation, entered as the square root of the within mean square error, is 45, the equivalence limits are plus or minus 30, the power is 80%, and the significance level is 0.05. He calculates a sample size of 40.

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 6** 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)	**30**
EL (Lower Equivalence Limit)	**-Upper Limit**
δ1 (Actual Difference to Detect)	**0**
Standard Deviation Input Type	**Enter the Within-Subject Population SD**
σw (Within-Subject Population SD)	**45**

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

Power	Total Sample Size N	Equivalence Limits Lower EL	Equivalence Limits Upper EU	Actual Difference δ1	Standard Deviation σw	Alpha	Beta
0.80045	40	-30	30	0	45	0.05	0.19955

PASS also calculates a sample size of 40.