Chapter 282

Assurance for Two-Sample T-Tests for Equivalence Allowing Unequal Variance

Introduction

This procedure calculates assurance and sample size of *equivalence* tests of the means of two independent groups using the two-sample unequal-variance *t*-test. The outcome is a continuous normal random variable and the variances of the two groups (populations) are assumed to be equal. 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, refer to Chow and Liu (1999).

Measurements are made on individuals that have been randomly assigned to one of two groups. This *parallel-groups* design may be analyzed by a TOST equivalence test to show that the means of the two groups 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.

The methods for assurance calculation in this procedure are based on O'Hagan, Stevens, and Campbell (2005).

Assurance

The assurance of a design is the expected value of the power with respect to one or more prior distributions of the design parameters. Assurance is also referred to as *Bayesian assurance*, *expected power*, *average power*, *statistical assurance*, *hybrid classical-Bayesian procedure,* or *probability of success*.

The power of a design is the probability of rejecting the null hypothesis, conditional on a given set of design attributes, such as the test statistic, the significance level, the sample size, and the effect size to be detected. As the effect size parameters are typically unknown quantities, the stated power may be very different from the true power if the specified parameter values are inaccurate.

While power is conditional on individual design parameter values, and is highly sensitive to those values, assurance is the average power across a presumed prior distribution of the effect size parameters. Thus, assurance adds a Bayesian element to the frequentist framework, resulting in a hybrid approach to the probability of trial or study success. It should be noted that when it comes time to perform the statistical test on the resulting data, these methods for calculating assurance assume that the traditional (frequentist) tests will be used.

The next section describes some of the ways in which the prior distributions for effect size parameters may be determined.

Elicitation

In order to calculate assurance, a suitable prior distribution for the effect size parameters must be determined. This process is called the *elicitation* of the prior distribution.

The elicitation may be as simple as choosing a distribution that seems plausible for the parameter(s) of interest, or as complex as combining the informed advice of several experts based on experience in the field, available pilot data, or previous studies. The accuracy of the assurance value depends on the accuracy of the elicited prior distribution. The assumption (or hope) is that an informed prior distribution will produce a more accurate estimate of the probability of trial success than a single value estimate. Because clinical trials and other studies are often costly, many institutions now routinely require an elicitation step.

Two reference texts that focus on elicitation are O'Hagan, Buck, Daneshkhah, Eiser, Garthwaite, Jenkinson, Oakley, and Rakow (2006) and Dias, Morton, and Quigley (2018).

Equivalence Tests Hypotheses

PASS follows the *two one-sided tests* approach described by Schuirmann (1987) and Phillips (1990). Let $\mu_1 = \mu_T$ be the test group mean, $\mu_2 = \mu_R$ be the reference group mean, and E_L and E_U be the lower and upper bounds, respectively, on $\delta = \mu_1 - \mu_2 = \mu_T - \mu_R$ that define the region of equivalence.

It will be convenient to adopt the following specialized notation for the discussion of these tests.

Parameter	PASS Input/Output	Interpretation
μ_1 or μ_T	Not used	*Mean* of population 1. Population 1 is assumed to consist of those who have received the new treatment.
μ_2 or μ_R	Not used	*Mean* of population 2. Population 2 is assumed to consist of those who have received the reference treatment.
E_L, E_U	EL, EU	*Lower* and *Upper Equivalence Limits.* If the difference is between these two limits, the new treatment is said to be *equivalent* to the reference.
δ	δ	*Actual difference*. This is the value of $\mu_1 - \mu_2$, the difference between the means. This is the value at which the power is calculated.

Note that the actual values of μ_1 and μ_2 are not needed. Only their difference is needed for power and sample size calculations.

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

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

Test Statistics

Welch (1938) proposed the following test when the two variances are not assumed to be equal. The calculation of the two one-sided test statistics uses the following equations.

$$t_L^* = \frac{(\bar{X}_1 - \bar{X}_2) - E_L}{s_{\bar{X}_1 - \bar{X}_2}^*}$$

$$t_U^* = \frac{(\bar{X}_1 - \bar{X}_2) - E_U}{s_{\bar{X}_1 - \bar{X}_2}^*}$$

where

$$\bar{X}_k = \frac{\sum_{i=1}^{N_k} X_{ki}}{N_k},$$

$$s_k = \sqrt{\left(\frac{\sum_{i=1}^{N_k}(X_{ki} - \bar{X}_k)^2}{(N_k - 1)}\right)},$$

$$s_{\bar{X}_1 - \bar{X}_2}^* = \sqrt{\frac{s_1^2}{N_1} + \frac{s_2^2}{N_2}},$$

$$df = \frac{{s_{\bar{X}_1 - \bar{X}_2}^*}^4}{\frac{s_1^4}{N_1^2(N_1 - 1)} + \frac{s_2^4}{N_2^2(N_2 - 1)}},$$

The null hypothesis is rejected if t_L^* and $-t_U^*$ are both greater than or equal to $t_{1-\alpha, df}$.

Power Calculation

When $\sigma_1 \neq \sigma_2$, the power for Welch's unequal-variance t-test is calculated as follows.

$$\Pr\left(t_L^* \geq t_{1-\alpha, df} \text{ and } t_U^* \leq -t_{1-\alpha, df} \,|\, \mu_1, \mu_2, \sigma_1, \sigma_2\right)$$

where t_L^* and t_U^* are distributed as the bivariate, noncentral t distribution with noncentrality parameters Δ_L and Δ_U given by

$$\Delta_L = \frac{\delta - E_L}{\sqrt{\frac{\sigma_1^2}{N_1} + \frac{\sigma_2^2}{N_2}}}$$

$$\Delta_U = \frac{\delta - E_U}{\sqrt{\frac{\sigma_1^2}{N_1} + \frac{\sigma_2^2}{N_2}}}$$

and

$$df = \frac{\left(\sqrt{\frac{\sigma_1^2}{N_1} + \frac{\sigma_2^2}{N_2}}\right)^4}{\frac{\sigma_1^4}{N_1^2(N_1 - 1)} + \frac{\sigma_2^4}{N_2^2(N_2 - 1)}}.$$

Assurance Calculation

This assurance computation described here is based on O'Hagan, Stevens, and Campbell (2005).

Let $P_1(H|\delta, \sigma_1, \sigma_2)$ be the power function described above where H is the event that null hypothesis is rejected conditional on the values of the parameters. The specification of $\delta, \sigma_1,$ and σ_2 is critical to the power calculation, but their actual values are seldom known. This uncertainty has led to the development of another quantity that is useful in sample size determination: *assurance*. Assurance is defined as the expected power where the expectation is with respect to a joint prior distribution for $\delta, \sigma_1,$ and σ_2. Hence, assurance is

$$Assurance = E_{\delta, \sigma_1, \sigma_2}\big(P_1(H|\delta, \sigma_1, \sigma_2)\big) = \iiint P_1(H|\delta, \sigma_1, \sigma_2) f(\delta, \sigma_1, \sigma_2) d\delta d\sigma_1 d\sigma_2$$

where $f(\delta, \sigma_1, \sigma_2)$ is the joint prior distribution of $\delta, \sigma_1,$ and σ_2.

In **PASS**, the joint prior distribution can be specified as either a discrete approximation to the joint prior distribution, or as individual prior distributions, one for each parameter.

Specifying a Joint Prior Distribution

If the joint prior distribution is to be specified directly, the distribution is specified in **PASS** using a discrete approximation to the function $f(\delta, \sigma_1, \sigma_2)$. This provides flexibility in specifying the joint prior distribution. In the three-parameter case, four columns are entered on the spreadsheet: three for the parameters and a fourth for the probability. Each row gives a value for each parameter and the corresponding parameter-combination probability. The accuracy of the distribution approximation is controlled by the number of points (spreadsheet rows) that are used.

An example of entering a joint prior distribution is included at the end of the chapter.

Specifying Individual Prior Distributions

Ciarleglio, Arendt, and Peduzzi (2016) suggest that more flexibility is available if the joint prior distribution is separated into three independent univariate distributions as follows:

$$f(\delta, \sigma_1, \sigma_2) = f_1(\delta) f_2(\sigma_1) f_3(\sigma_2)$$

where $f_1(\delta)$ is the prior distribution of δ, $f_2(\sigma_1)$ is the prior distribution of σ_1, and $f_3(\sigma_2)$ is the prior distribution of σ_2. This method is also available in **PASS**. In this case, the definition of assurance becomes

$$Assurance = E_{\delta, \sigma_1, \sigma_2}\big(P_1(H|\delta, \sigma_1, \sigma_2)\big) = \iiint P_1(H|\delta, \sigma_1, \sigma_2) f_1(\delta) f_2(\sigma_1) f_3(\sigma_2) d\delta d\sigma_1 d\sigma_2$$

Using this definition, the assurance can be calculated using numerical integration. There are a variety of pre-programmed, univariate prior distributions available in **PASS**.

Fixed Values (No Prior) and Custom Values

For any given parameter, **PASS** also provides the option of entering a single fixed value for the prior distribution, or a series of values and corresponding probabilities (using the spreadsheet), rather than one of the pre-programmed distributions.

Numerical Integration in PASS (and Notes on Computation Speed)

When the prior distribution is specified as independent univariate distributions, **PASS** uses a numerical integration algorithm to compute the assurance value as follows:

The domain of each prior distribution is divided into M intervals. Since many of the available prior distributions are unbounded on one (e.g., Gamma) or both (e.g., Normal) ends, an approximation is made to make the domain finite. This is accomplished by truncating the distribution to a domain between the two quantiles: $q_{0.001}$ and $q_{0.999}$.

The value of M controls the accuracy and speed of the algorithm. If only one parameter is to be given a prior distribution, then a value of M between 50 and 100 usually gives an accurate result in a timely manner. However, if two parameters are given priors, the number of iterations needed increases from M to M^2. For example, if M is 100, 10000 iterations are needed. Reducing M from 100 to 50 reduces the number of iterations from 10000 to 2500.

The algorithm runtime increases when searching for sample size rather than solving for assurance, as a search algorithm is employed in this case. When solving for sample size, we recommend reducing M to 20 or less while exploring various scenarios, and then increasing M to 50 or more for a final, more accurate, result.

List of Available Univariate Prior Distributions

This section lists the univariate prior distributions that may be used for any of the applicable parameters when the Prior Entry Method is set to Individual.

No Prior

If 'No Prior' is chosen for a parameter, the parameter is assumed to take on a single, fixed value with probability one.

Beta (Shape 1, Shape 2, a, c)

A random variable X that follows the beta distribution is defined on a finite interval [a, c]. Two shape parameters (α and β) control the shape of this distribution. Two location parameters a and c give the minimum and maximum of X.

The probability density function of the beta distribution is

$$f(x|\alpha,\beta,a,c) = \frac{\left(\frac{x-a}{c-a}\right)^{\alpha-1}\left(\frac{c-x}{c-a}\right)^{\beta-1}}{(c-a)B(\alpha,\beta)}$$

where $B(\alpha,\beta) = \Gamma(\alpha)\,\Gamma(\beta)/\,\Gamma(\alpha+\beta)$ and $\Gamma(z)$ is the gamma function.

The mean of X is

$$\mu_X = \frac{\alpha c + \beta a}{\alpha + \beta}$$

Various distribution shapes are controlled by the values of α and β. These include

Symmetric and Unimodal

$\alpha = \beta > 1$

U Shaped

$\alpha = \beta < 1$

Bimodal

$\alpha, \beta < 1$

Uniform

$\alpha = \beta = 1$

Parabolic

$\alpha = \beta = 2$

Bell-Shaped

$\alpha = \beta > 2$

Gamma (Shape, Scale)

A random variable X that follows the gamma distribution is defined on the interval $(0, \infty)$. A shape parameter, κ, and a scale parameter, θ, control the distribution.

The probability density function of the gamma distribution is

$$f(x|\kappa, \theta) = \frac{x^{\kappa-1} e^{-\frac{x}{\theta}}}{\theta^\kappa \Gamma(\kappa)}$$

where $\Gamma(z)$ is the gamma function.

The mean of X is

$$\mu_X = \frac{\kappa}{\theta}$$

A truncated version of the distribution is constructed by dividing the density by $1 - \text{Prob}(Min \leq X \leq Max)$ where *Min* and *Max* are two truncation bounds.

Inverse-Gamma (Shape, Scale)

A random variable X that follows the inverse-gamma distribution is defined on the interval $(0, \infty)$. If $Y \sim$ gamma, then $X = 1 / Y \sim$ inverse-gamma. A shape parameter, α, and a scale parameter, β, control the distribution.

The probability density function of the inverse-gamma distribution is

$$f(x|\alpha, \beta) = \frac{\beta^{\alpha} x^{\alpha-1} e^{-\frac{\beta}{x}}}{\Gamma(\alpha)}$$

where $\Gamma(z)$ is the gamma function.

The mean of X is

$$\mu_X = \frac{\beta}{\alpha - 1} \; for \; \alpha > 1$$

A truncated version of the distribution is constructed by dividing the density by $1 - \text{Prob}(Min \leq X \leq Max)$ where Min and Max are two truncation bounds.

Logistic (Location, Scale)

A random variable X that follows the logistic distribution is defined on the interval $(-\infty, \infty)$. A location parameter, μ, and a scale parameter, s, control the distribution.

The probability density function of the logistic distribution is

$$f(x|\mu, s) = \frac{e^{-\frac{x-\mu}{s}}}{s\left(1 + e^{-\frac{x-\mu}{s}}\right)^2}$$

The mean of X is

$$\mu_X = \mu$$

A truncated version of the distribution is constructed by dividing the density by $1 - \text{Prob}(Min \leq X \leq Max)$ where Min and Max are two truncation bounds.

Lognormal (Mean, SD)

A random variable X that follows the lognormal distribution is defined on the interval $(0, \infty)$. A location parameter, $\mu_{\log(X)}$, and a scale parameter, $\sigma_{\log(X)}$, control the distribution. If $Z \sim$ standard normal, then $X = e^{\mu + \sigma Z} \sim$ lognormal. Note that $\mu_{\log(X)} = E(\log(X))$ and $\sigma_{\log(X)} = Standard\ Deviation(\log(X))$.

The probability density function of the lognormal distribution is

$$f(x|\mu, \sigma) = \frac{e^{-\frac{1}{2}\left(\frac{\log x - \mu}{\sigma}\right)^2}}{x\sigma\sqrt{2\pi}}$$

The mean of X is

$$\mu_X = e^{\mu + \frac{\sigma^2}{2}}$$

A truncated version of the distribution is constructed by dividing the density by $1 - \text{Prob}(Min \leq X \leq Max)$ where Min and Max are two truncation bounds.

LogT (Mean, SD)

A random variable X that follows the logT distribution is defined on the interval $(0, \infty)$. A location parameter, $\mu_{\log(X)}$, a scale parameter, $\sigma_{\log(X)}$, and a shape parameter, ν, control the distribution. Note that ν is referred to as the *degrees of freedom*.

If t ~ Student's t, then $X = e^{\mu + \sigma t} \sim$ logT.

The probability density function of the logT distribution is

$$f(x|\mu, \sigma, \nu) = \frac{\Gamma\left(\frac{\nu+1}{2}\right)}{x\Gamma\left(\frac{\nu}{2}\right)\sigma\sqrt{\nu\pi}}\left(1 + \frac{1}{\nu}\left(\frac{\log x - \mu}{\sigma}\right)^2\right)^{\left(\frac{-\nu-1}{2}\right)}$$

The mean of X is not defined.

A truncated version of the distribution is constructed by dividing the density by $1 - \text{Prob}(Min \leq X \leq Max)$ where *Min* and *Max* are two truncation bounds.

Normal (Mean, SD)

A random variable X that follows the normal distribution is defined on the interval $(-\infty, \infty)$. A location parameter, μ, and a scale parameter, σ, control the distribution.

The probability density function of the normal distribution is

$$f(x|\mu, \sigma) = \frac{e^{-\frac{1}{2}\left(\frac{x-\mu}{\sigma}\right)^2}}{\sigma\sqrt{2\pi}}$$

The mean of X is

$$\mu_X = \mu$$

A truncated version of the distribution is constructed by dividing the density by $1 - \text{Prob}(Min \leq X \leq Max)$ where *Min* and *Max* are two truncation bounds.

T (Mean, SD, DF)

A random variable X that follows Student's t distribution is defined on the interval $(-\infty, \infty)$. A location parameter, μ, a scale parameter, σ, and a shape parameter, ν, control the distribution. Note that ν is referred to as the *degrees of freedom* or *DF*.

The probability density function of the Student's t distribution is

$$f(x|\mu, \sigma, \nu) = \frac{\Gamma\left(\frac{\nu+1}{2}\right)}{\Gamma\left(\frac{\nu}{2}\right)\sigma\sqrt{\nu\pi}}\left(1 + \frac{1}{\nu}\left(\frac{x - \mu}{\sigma}\right)^2\right)^{\left(\frac{-\nu-1}{2}\right)}$$

The mean of X is μ if $\nu > 1$.

A truncated version of the distribution is constructed by dividing the density by $1 - \text{Prob}(Min \leq X \leq Max)$ where *Min* and *Max* are two truncation bounds.

Triangle (Mode, Min, Max)

Let a = minimum, b = maximum, and c = mode. A random variable X that follows a triangle distribution is defined on the interval (a, b).

The probability density function of the triangle distribution is

$$f(x|a, b, c) = \begin{cases} \dfrac{2(x - a)}{(b - a)(c - a)} & \text{for } a \leq x < c \\ \dfrac{2}{b - a} & \text{for } x = c \\ \dfrac{2(b - x)}{(b - a)(b - c)} & \text{for } c < x \leq b \end{cases}$$

The mean of X is

$$\frac{a + b + c}{3}$$

Uniform (Min, Max)

Let a = minimum and b = maximum. A random variable X that follows a uniform distribution is defined on the interval $[a, b]$.

The probability density function of the uniform distribution is

$$f(x|a, b) = \begin{cases} \dfrac{1}{b - a} & \text{for } a \leq x \leq b \end{cases}$$

The mean of X is

$$\frac{a + b}{2}$$

Weibull (Shape, Scale)

A random variable X that follows the Weibull distribution is defined on the interval $(0, \infty)$. A shape parameter, κ, and a scale parameter, λ, control the distribution.

The probability density function of the Weibull distribution is

$$f(x|\kappa, \lambda) = \frac{\kappa}{\lambda} \left(\frac{x}{\lambda}\right)^{\kappa - 1} e^{-\left(\frac{x}{\lambda}\right)^{\kappa}}$$

The mean of X is

$$\mu_X = \kappa \Gamma \left(1 + \frac{1}{\kappa}\right)$$

A truncated version of the distribution is constructed by dividing the density by $1 - \text{Prob}(Min \leq X \leq Max)$ where *Min* and *Max* are two truncation bounds.

Custom (Values and Probabilities in Spreadsheet)

This custom prior distribution is represented by a set of user-specified points and associated probabilities, entered in two columns of the spreadsheet. The points make up the entire set of values that are used for this parameter in the calculation of assurance. The associated probabilities should sum to one. Note that custom values and probabilities can be used to approximate any continuous distribution.

For example, a prior distribution of X might be

X_i P_i
10   0.2
20   0.2
30   0.3
40   0.2
50   0.1

In this example, the mean of X is

$$\mu_X = \sum_{i=1}^{5} X_i P_i$$

Example 1 – Assurance Over a Range of Sample Sizes

Suppose a parallel-group design is to be used to compare the influence of two drugs on diastolic blood pressure. Previous studies have shown the diastolic blood pressure to be close to 96 mmHg with the reference drug and is thought to be 92 mmHg with the experimental drug. The within-group standard deviation is assumed to be 18mmHg for group 1 and 15mmHg for group 2.

The researchers want to show that the diastolic blood pressure with the experimental drug is within 20% of the diastolic blood pressure with the reference drug. Note that 20% of 96 is 19.2. The significance level is 0.05. A power analysis calculated the necessary sample size as 16 per group (see Example 2 of the *Two-Sample T-Tests for Equivalence Allowing Unequal Variance* procedure).

To complete their sample size study, the researchers want to run an assurance analysis for a range of group sample sizes from 10 to 100. An elicitation exercise determined that a reasonable prior distribution of the mean difference should be normal with mean -4 and standard deviation 10. The elicitation also concluded that the prior distribution of the group 1 standard deviation should be normal with mean 18 and standard deviation 5. The prior distribution of the group 2 standard deviation should be normal with mean 15 and standard deviation 4.

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	**Assurance**
Prior Entry Method..	**Individual (Enter a prior distribution for each applicable parameter)**
Alpha..	**0.05**
Group Allocation	**Equal (N1 = N2)**
Sample Size Per Group	**10 15 20 40 60 80 100**
EU (Upper Equivalence Limit)........................	**19.2**
EL (Lower Equivalence Limit)	**-19.2**
Prior Distribution of δ	**Normal (Mean, SD)**
Mean..	**-4**
SD...	**10**
Truncation Boundaries..................................	**None**
Prior Distribution of σ1	**Normal (Mean, SD)**
Mean..	**18**
SD...	**5**
Truncation Boundaries..................................	**None**
Prior Distribution of σ2	**Normal (Mean, SD)**
Mean..	**15**
SD...	**4**
Truncation Boundaries..................................	**None**

Options Tab
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Number of Computation Points for each........**20**
  Prior Distribution
Maximum N1 in Sample Size Search **5000**

Output

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

Numeric Reports

Numeric Results
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Solve For: Assurance
Difference: $\delta = \mu_1 - \mu_2 = \mu_T - \mu_R$
Hypotheses: H0: $\delta \le$ EL or $\delta \ge$ EU   vs.   H1: EL $< \delta <$ EU
Prior Type: Independent Univariate Distributions

Prior Distributions
δ: Normal (Mean = -4, SD = 10).
σ_1:   Normal (Mean = 18, SD = 5).
σ_2:   Normal (Mean = 15, SD = 4).
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| | | | | | Equivalence Limits | | Expected Mean Diff | Group 1 Std Dev | Group 2 Std Dev | |
| | | | | | Lower EL | Upper EU | | | | |
Assurance*	Power‡	N1	N2	N	Lower EL	Upper EU	E(δ)	E(σ_1)	E(σ_2)	Alpha
0.36848	0.55247	10	10	20	-19.2	19.2	-4	18	15	0.05
0.51486	0.77233	15	15	30	-19.2	19.2	-4	18	15	0.05
0.59980	0.88100	20	20	40	-19.2	19.2	-4	18	15	0.05
0.73879	0.99238	40	40	80	-19.2	19.2	-4	18	15	0.05
0.78918	0.99959	60	60	120	-19.2	19.2	-4	18	15	0.05
0.81567	0.99998	80	80	160	-19.2	19.2	-4	18	15	0.05
0.83222	1.00000	100	100	200	-19.2	19.2	-4	18	15	0.05
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* The number of points used for computation of the prior(s) was 20.
‡ Power was calculated using $\delta = E(\delta) = -4$, $\sigma_1 = E(\sigma_1) = 18$, and $\sigma_2 = E(\sigma_2) = 15$.

Assurance	The expected power where the expectation is with respect to the prior distribution(s).
Power	The power calculated using the means of the prior distributions as the values of the corresponding parameters.
N1	The number of subjects in group 1.
N2	The number of subjects in group 2.
N	The total sample size. N = N1 + N2.
EL	The lower equivalence limit. Equivalence is concluded if EL < Difference < EU.
EU	The upper equivalence limit.
E(δ)	The expected value over its prior distribution of the difference in the group means assumed by the alternative hypothesis. Note that $\delta = \mu_1 - \mu_2$.
E(σ_1)	The expected value over its prior distribution of the group 1 standard deviation.
E(σ_2)	The expected value over its prior distribution of the group 2 standard deviation.
Alpha	The probability of rejecting a true null hypothesis.

Summary Statements
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An equivalence test of means using two one-sided unequal-variance t-tests with sample sizes of 10 in group 1 (treatment) and 10 in group 2 (reference or control) achieves 0.36848 assurance. The significance level (alpha) of the test is 0.05. The equivalence limits are -19.2 and 19.2. The prior distribution used for the mean difference is Normal (Mean = -4, SD = 10). The prior distribution used for the group 1 standard deviation is Normal (Mean = 18, SD = 5). The prior distribution used for the group 2 standard deviation is Normal (Mean = 15, SD = 4).
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Dropout-Inflated Sample Size
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	Sample Size			Dropout-Inflated Enrollment Sample Size			Expected Number of Dropouts		
Dropout Rate	N1	N2	N	N1'	N2'	N'	D1	D2	D
20%	10	10	20	13	13	26	3	3	6
20%	15	15	30	19	19	38	4	4	8
20%	20	20	40	25	25	50	5	5	10
20%	40	40	80	50	50	100	10	10	20
20%	60	60	120	75	75	150	15	15	30
20%	80	80	160	100	100	200	20	20	40
20%	100	100	200	125	125	250	25	25	50

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.
N1, N2, and N   The evaluable sample sizes at which power is computed (as entered by the user). If N1 and N2 subjects
                  are evaluated out of the N1' and N2' subjects that are enrolled in the study, the design will achieve the
                  stated power.
N1', N2', and N' The number of subjects that should be enrolled in the study in order to obtain N1, N2, and N evaluable
                  subjects, based on the assumed dropout rate. N1' and N2' are calculated by inflating N1 and N2 using the
                  formulas N1' = N1 / (1 - DR) and N2' = N2 / (1 - DR), with N1' and N2' 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.)
D1, D2, and D   The expected number of dropouts. D1 = N1' - N1, D2 = N2' - N2, and D = D1 + D2.

Dropout Summary Statements
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Anticipating a 20% dropout rate, 13 subjects should be enrolled in Group 1, and 13 in Group 2, to obtain final group sample sizes of 10 and 10, respectively.
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References
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O'Hagan, A., Stevens, J.W., and Campbell, M.J. 2005. 'Assurance in clinical trial design'. Pharmaceutical Statistics, Volume 4, Pages 187-201.
Ciarleglio, M.M., Arendt, C.D., and Peduzzi, P.N. 2016. 'Selection of the effect size for sample size determination for a continuous response in a superiority clinical trial using a hybrid classical and Bayesian procedure'. Clinical Trials, Volume 13(3), pages 275-285.
Dias, L.C., Morton, A., and Quigley, J. 2018. Elicitation, The Science and Art of Structuring Judgement. Springer.
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, S. A. 2010. Sample Sizes for Clinical Trials. Chapman & Hall/CRC. Boca Raton, FL.
Blackwelder, W.C. 1998. 'Equivalence Trials.' In Encyclopedia of Biostatistics, John Wiley and Sons. New York. Volume 2, 1367-1372.
Phillips, Kem F. 1990. 'Power of the Two One-Sided Tests Procedure in Bioequivalence', Journal of Pharmacokinetics and Biopharmaceutics, Volume 18, No. 2, pages 137-144.
Schuirmann, Donald. 1987. 'A Comparison of the Two One-Sided Tests Procedure and the Power Approach for Assessing the Equivalence of Average Bioavailability', Journal of Pharmacokinetics and Biopharmaceutics, Volume 15, Number 6, pages 657-680.
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This report shows the assurance values obtained by each sample size.

Plots Section
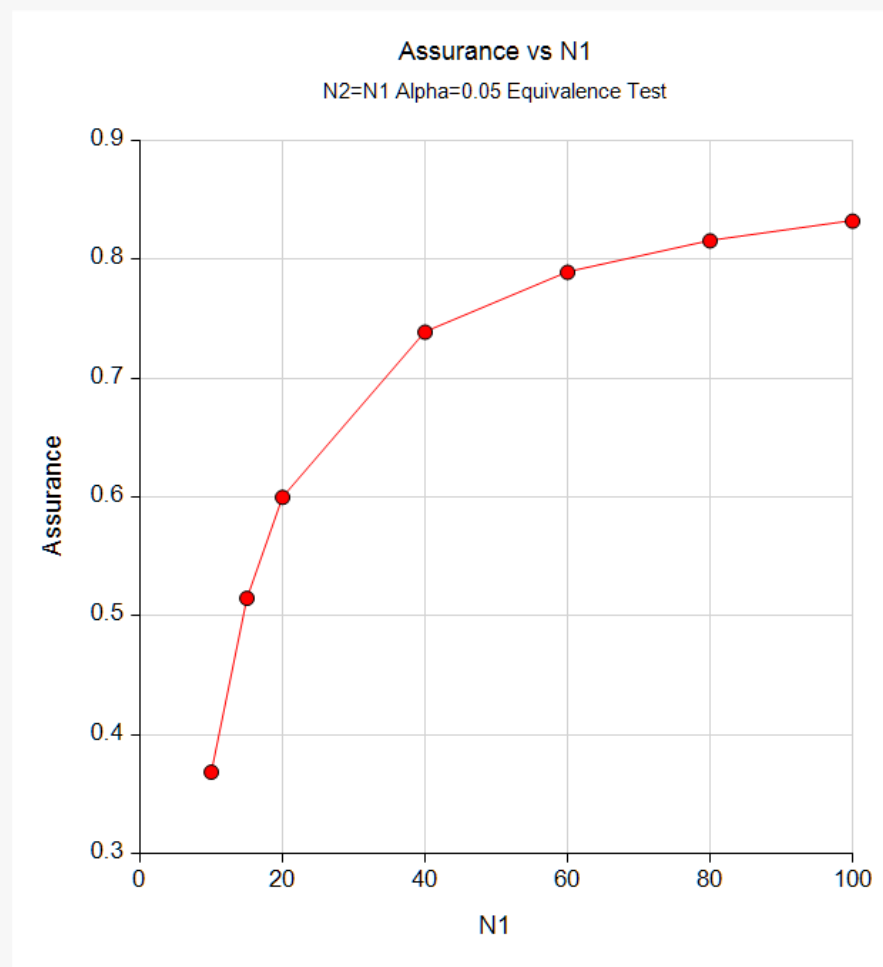
Plots
_____

This plot shows the relationship between the assurance and sample size.

Comparison Plots Section

Comparison Plots
_____

This plot shows the relationship of assurance, power, and sample size.

Example 2 – Validation using Hand Computation

We could not find a validation example in the literature, so we have developed a validation example of our own. Suppose an equivalence test will be used in which N1 = N2 = 30 and the significance level is 0.05. The equivalence limits were -19.2 and 19.2.

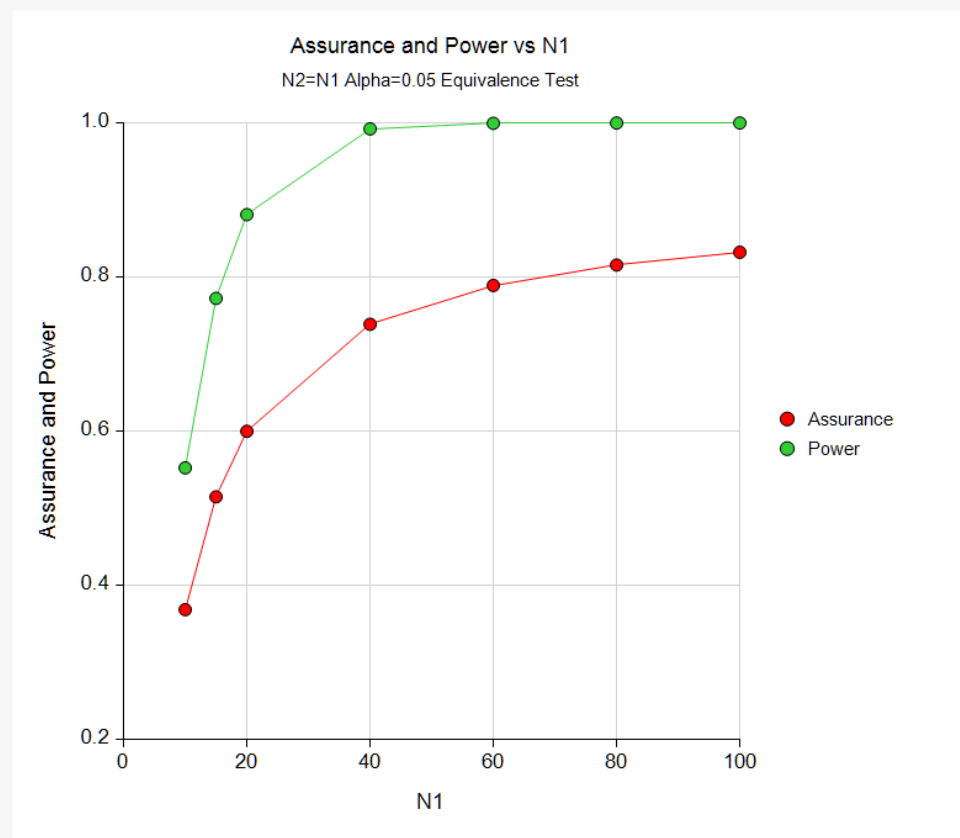The prior distribution of the difference will be approximated by the following table.

δ	Prob
-8	0.3
0	0.4
8	0.3

The prior distribution of the group 1 standard deviation will be approximated by the following table.

σ_1	Prob
16	0.2
21	0.6
26	0.2

The prior distribution of the group 2 standard deviation will be approximated by the following table.

σ_2	Prob
12	0.2
17	0.6
22	0.2

Note that in all three of these tables, the parameter values are equi-spaced. This is important when using a discrete approximation such as we have here.

The *Two-Sample T-Tests for Equivalence Allowing Unequal Variance* procedure is used compute the power for each of the 27 combinations of $\delta, \sigma_1,$ and σ_2. The results of these calculations were as follows.

Numeric Results for Two One-Sided Unequal-Variance T-Tests

Solve For: Power
Difference: δ = µ1 - µ2 = µT - µR
Hypotheses: H0: δ ≤ EL or δ ≥ EU   vs.   H1: EL < δ < EU

Power	N1	N2	N	Lower Equiv Limit EL	Upper Equiv Limit EU	δ	σ1	σ2	Alpha
0.91858	30	30	60	-19.2	19.2	-8	16	12	0.05
0.83229	30	30	60	-19.2	19.2	-8	16	17	0.05
0.71924	30	30	60	-19.2	19.2	-8	16	22	0.05
0.79900	30	30	60	-19.2	19.2	-8	21	12	0.05
0.72790	30	30	60	-19.2	19.2	-8	21	17	0.05
0.64031	30	30	60	-19.2	19.2	-8	21	22	0.05
0.67626	30	30	60	-19.2	19.2	-8	26	12	0.05
0.62424	30	30	60	-19.2	19.2	-8	26	17	0.05
0.54657	30	30	60	-19.2	19.2	-8	26	22	0.05
0.99963	30	30	60	-19.2	19.2	0	16	12	0.05
0.99516	30	30	60	-19.2	19.2	0	16	17	0.05
0.97003	30	30	60	-19.2	19.2	0	16	22	0.05
0.99126	30	30	60	-19.2	19.2	0	21	12	0.05
0.97277	30	30	60	-19.2	19.2	0	21	17	0.05
0.92568	30	30	60	-19.2	19.2	0	21	22	0.05
0.95024	30	30	60	-19.2	19.2	0	26	12	0.05

0.91277	30	30	60	-19.2	19.2	0	26	17	0.05
0.83773	30	30	60	-19.2	19.2	0	26	22	0.05
0.91858	30	30	60	-19.2	19.2	8	16	12	0.05
0.83229	30	30	60	-19.2	19.2	8	16	17	0.05
0.71924	30	30	60	-19.2	19.2	8	16	22	0.05
0.79900	30	30	60	-19.2	19.2	8	21	12	0.05
0.72790	30	30	60	-19.2	19.2	8	21	17	0.05
0.64031	30	30	60	-19.2	19.2	8	21	22	0.05
0.67626	30	30	60	-19.2	19.2	8	26	12	0.05
0.62424	30	30	60	-19.2	19.2	8	26	17	0.05
0.54657	30	30	60	-19.2	19.2	8	26	22	0.05

The assurance calculation is made by summing the quantities $\left[(power_{i,j,k})(p(\delta_i))\left(p(\sigma_{1j})\right)\left(p(\sigma_{2k})\right) \right]$ as follows

$$Assurance = (0.91858 \times 0.3 \times 0.2) + (0.83229 \times 0.3 \times 0.6) + \cdots + (0.54657 \times 0.3 \times 0.2) = 0.81818.$$

To run this example, the spreadsheet will need to be loaded with the following four columns in which the first two are for the difference, δ, and the second two are for the standard deviation, σ.

C1	C2	C3	C4	C5	C6
-8	0.3	16	0.2	12	0.2
0	0.4	21	0.6	17	0.6
8	0.3	26	0.2	22	0.2

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 ....**Assurance**
Prior Entry Method..**Individual (Enter a prior distribution for each**
                                                          applicable parameter)
Alpha...**0.05**
Group Allocation ....**Equal (N1 = N2)**
Sample Size Per Group **30**
EU (Upper Equivalence Limit).......................**19.2**
EL (Lower Equivalence Limit) ....**-19.2**
Prior Distribution of δ ....**Custom (Values and Probabilities in Spreadsheet)**
Column of Values **C1**
Column of Pr(Values)....................................**C2**
Prior Distribution of σ1 ....**Custom (Values and Probabilities in Spreadsheet)**
Column of Values **C3**
Column of Pr(Values)....................................**C4**
Prior Distribution of σ2 ....**Custom (Values and Probabilities in Spreadsheet)**
Column of Values **C5**
Column of Pr(Values)....................................**C6**

Options Tab

Number of Computation Points for each **20**
  Prior Distribution
Maximum N1 in Sample Size Search **5000**

Input Spreadsheet Data

Row	C1	C2	C3	C4	C5	C6
1	-8	0.3	16	0.2	12	0.2
2	0	0.4	21	0.6	17	0.6
3	8	0.3	26	0.2	22	0.2

Output

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

Numeric Results

Solve For: Assurance
Difference: $\delta = \mu_1 - \mu_2 = \mu_T - \mu_R$
Hypotheses: H0: $\delta \leq EL$ or $\delta \geq EU$ vs. H1: $EL < \delta < EU$
Prior Type: Independent Univariate Distributions

Prior Distributions
δ: Point List (Values = C1, Probs = C2).
  C1: -8 0 8
  C2: 0.3 0.4 0.3
σ_1:   Point List (Values = C3, Probs = C4).
  C3: 16 21 26
  C4: 0.2 0.6 0.2
σ_2:   Point List (Values = C5, Probs = C6).
  C5: 12 17 22
  C6: 0.2 0.6 0.2

					Equivalence Limits		Expected Mean Diff	Group 1 Std Dev	Group 2 Std Dev	
Assurance	Power‡	N1	N2	N	Lower EL	Upper EU	E(δ)	E(σ_1)	E(σ_2)	Alpha
0.81818	0.97277	30	30	60	-19.2	19.2	0	21	17	0.05

‡ Power was calculated using δ = E(δ) = 0, σ_1 = E(σ_1) = 21, and σ_2 = E(σ_2) = 17.

PASS has also calculated the assurance as 0.81818 which validates the procedure.

Example 3 – Finding the Sample Size Needed to Achieve a Specified Assurance

Continuing with Example 1, the researchers want to investigate the sample sizes necessary to achieve assurances of 0.5, 0.6, and 0.7.

In order to reduce the runtime during this exploratory phase of the analysis, the number of points in the prior computation is reduced to 20. This slightly reduces the accuracy, but greatly reduces the runtime.

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**
Prior Entry Method..**Individual (Enter a prior distribution for each**
	applicable parameter)
Assurance..**0.5 0.6 0.7**
Alpha..**0.05**
Group Allocation ....**Equal (N1 = N2)**
EU (Upper Equivalence Limit).......................**19.2**
EL (Lower Equivalence Limit) ....**-19.2**
Prior Distribution of δ ....**Normal (Mean, SD)**
Mean..**-4**
SD..**10**
Truncation Boundaries..................................**None**
Prior Distribution of σ1 ....**Normal (Mean, SD)**
Mean..**18**
SD..**5**
Truncation Boundaries..................................**None**
Prior Distribution of σ2 ....**Normal (Mean, SD)**
Mean..**15**
SD..**4**
Truncation Boundaries..................................**None**

Options Tab

Number of Computation Points for each........**10**
Prior Distribution	
Maximum N1 in Sample Size Search **5000**

Output

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

Numeric Reports

Numeric Results
_____

Solve For: Sample Size
Difference: δ = μ1 - μ2 = μT - μR
Hypotheses: H0: δ ≤ EL or δ ≥ EU   vs.   H1: EL < δ < EU
Prior Type: Independent Univariate Distributions

Prior Distributions
δ: Normal (Mean = -4, SD = 10).
σ1:   Normal (Mean = 18, SD = 5).
σ2:   Normal (Mean = 15, SD = 4).
_____

Assurance*						Equivalence Limits		Expected Mean Diff	Group 1 Std Dev	Group 2 Std Dev	
Actual	Target	Power‡	N1	N2	N	Lower EL	Upper EU	E(δ)	E(σ1)	E(σ2)	Alpha
0.51502	0.5	0.77233	15	15	30	-19.2	19.2	-4	18	15	0.05
0.61144	0.6	0.89542	21	21	42	-19.2	19.2	-4	18	15	0.05
0.70162	0.7	0.97553	32	32	64	-19.2	19.2	-4	18	15	0.05

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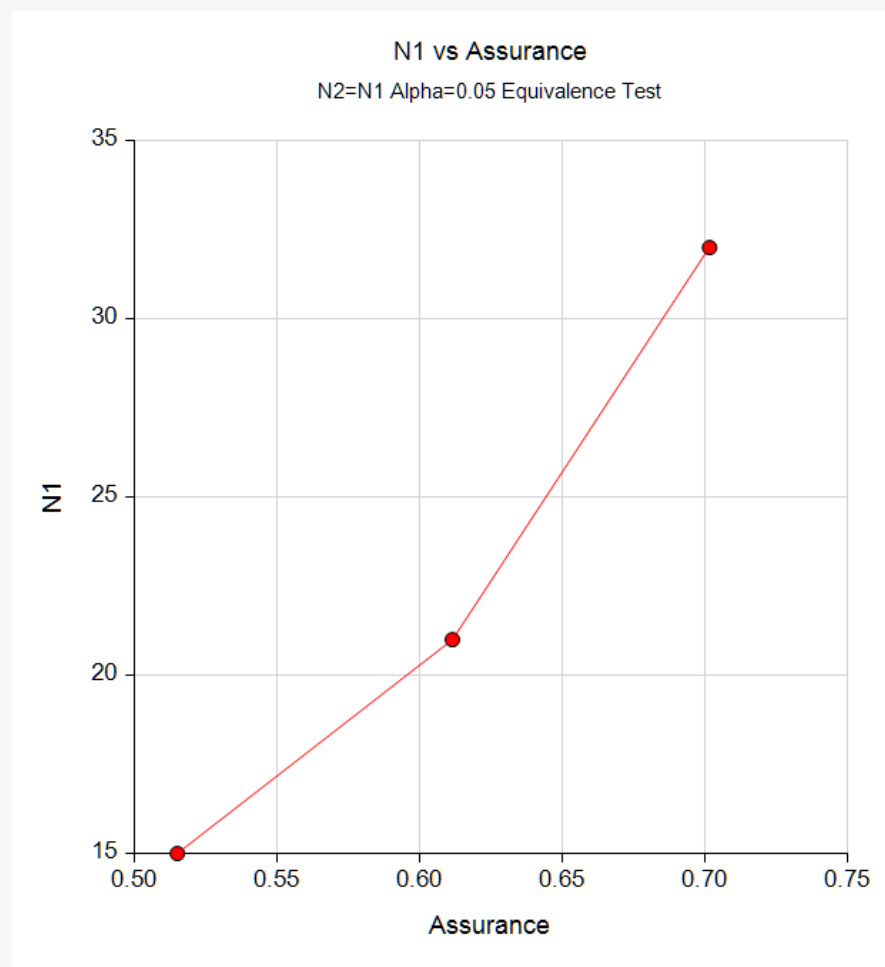* The number of points used for computation of the prior(s) was 10.
‡ Power was calculated using δ = E(δ) = -4, σ1 = E(σ1) = 18, and σ2 = E(σ2) = 15.

This report shows the required sample size for each assurance target.

Plots Section

Plots
_____

This plot shows the relationship between the sample size and assurance.

Example 4 – Joint Prior Distribution

The following example shows the complexity required to specify a joint distribution for three or more parameters.

Suppose two-sample Welch's unequal-variance equivalence test will be used in which N1 = N2 = 100 and the significance level is 0.05. The equivalence limits were -19.2 and 19.2.

Further suppose that the joint prior distribution of the difference and group standard deviations is approximated by the following table. In a real study, the values in this table would be provided by an elicitation study.

Note that the program will rescale the probabilities so they sum to one.

δ	σ1	σ2	Prob
-6	21	24	0.1
-4	20	23	0.1
-3	23	25	0.2
-2	22	24	0.2
-1	25	28	0.1
0	24	27	0.1
2	25	29	0.3
3	24	27	0.3
6	27	31	0.5
7	25	28	0.5
8	29	33	0.3
9	28	32	0.3
12	35	39	0.1
13	34	37	0.1
15	39	42	0.2
16	38	40	0.2
21	43	47	0.1
23	42	45	0.1

To run this example, the spreadsheet will need to be loaded with the following four columns.

C1	C2	C3	C4
-6	21	24	0.1
-4	20	23	0.1
-3	23	25	0.2
-2	22	24	0.2
-1	25	28	0.1
0	24	27	0.1
2	25	29	0.3
3	24	27	0.3
6	27	31	0.5
7	25	28	0.5
8	29	33	0.3
9	28	32	0.3
12	35	39	0.1
13	34	37	0.1
15	39	42	0.2

16	38	40	0.2
21	43	47	0.1
23	42	45	0.1

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 ....**Assurance**
Prior Entry Method.......................................**Combined (Enter parameter values and probabilities on spreadsheet)**
Alpha...**0.05**
Group Allocation ....**Equal (N1 = N2)**
Sample Size Per Group **100**
EU (Upper Equivalence Limit).......................**19.2**
EL (Lower Equivalence Limit) ....**-19.2**
Column of δ Values **C1**
Column of σ1 Values **C2**
Column of σ2 Values **C3**
Column of Pr(Values).....................................**C4**

Options Tab

Number of Computation Points for each........**10**
  Prior Distribution
Maximum N1 in Sample Size Search **5000**

Input Spreadsheet Data

Row	C1	C2	C3	C4
1	-6	21	24	0.1
2	-4	20	23	0.1
3	-3	23	25	0.2
4	-2	22	24	0.2
5	-1	25	28	0.1
6	0	24	27	0.1
7	2	25	29	0.3
8	3	24	27	0.3
9	6	27	31	0.5
10	7	25	28	0.5
11	8	29	33	0.3
12	9	28	32	0.3
13	12	35	39	0.1
14	13	34	37	0.1
15	15	39	42	0.2
16	16	38	40	0.2
17	21	43	47	0.1
18	23	42	45	0.1

Output

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

Numeric Results

Solve For: Assurance
Difference: $\delta = \mu_1 - \mu_2 = \mu_T - \mu_R$
Hypotheses: H0: $\delta \le EL$ or $\delta \ge EU$ vs. H1: $EL < \delta < EU$
Prior Type: Joint Multivariate Distribution

Prior Distribution
Point Lists
δ: C1: -6 -4 -3 -2 -1 0 2 3 6 7 8 9 12 13 15 16 21 23
σ_1:   C2: 21 20 23 22 25 24 25 24 27 25 29 28 35 34 39 38 43 42
σ_2:   C3: 24 23 25 24 28 27 29 27 31 28 33 32 39 37 42 40 47 45
Prob: C4: 0.1 0.1 0.2 0.2 0.1 0.1 0.3 0.3 0.5 0.5 0.3 0.3 0.1 0.1 0.2 0.2 0.1 0.1

| | | | | | Equivalence Limits | | Expected Mean Diff | Group 1 Std Dev | Group 2 Std Dev | |
| | | | | | Lower EL | Upper EU | | | | |
Assurance	Power‡	N1	N2	N	EL	EU	E(δ)	E(σ_1)	E(σ_2)	Alpha
0.77823	0.92007	100	100	200	-19.2	19.2	6.34211	28.05263	31.31579	0.05

‡ Power was calculated using $\delta = E(\delta) = 6.34211$, $\sigma_1 = E(\sigma_1) = 28.05263$, and $\sigma_2 = E(\sigma_2) = 31.31579$.

PASS has calculated the assurance as 0.77823.

Example 5 – Joint Prior Validation

The problem given in Example 2 will be used to validate the joint prior distribution method. This will be done by running the independent-prior scenario used in that example through the joint-prior method and checking that the assurance values match.

In Example 2, the prior distributions of the difference, the group 1 standard deviation, and the group 2 standard deviation are

δ	Prob
-8	0.3
0	0.4
8	0.3

σ_1	Prob
12	0.2
16	0.6
20	0.2

σ_2	Prob
15	0.2
19	0.6
23	0.2

The joint prior distribution can be found by multiplying the three independent probabilities in each row. This results in the following discrete probability distribution.

δ	σ1	σ2	Prob
-8	16	12	0.012
-8	16	17	0.036
-8	16	22	0.012
-8	21	12	0.036
-8	21	17	0.108
-8	21	22	0.036
-8	26	12	0.012
-8	26	17	0.036
-8	26	22	0.012
0	16	12	0.016
0	16	17	0.048
0	16	22	0.016
0	21	12	0.048
0	21	17	0.144
0	21	22	0.048
0	26	12	0.016
0	26	17	0.048
0	26	22	0.016
8	16	12	0.012
8	16	17	0.036
8	16	22	0.012
8	21	12	0.036
8	21	17	0.108
8	21	22	0.036

8	26	12	0.012
8	26	17	0.036
8	26	22	0.012

To run this example, the spreadsheet is loaded with the following four columns.

C1	C2	C3	C4
-8	16	12	0.012
-8	16	17	0.036
-8	16	22	0.012
-8	21	12	0.036
-8	21	17	0.108
-8	21	22	0.036
-8	26	12	0.012
-8	26	17	0.036
-8	26	22	0.012
0	16	12	0.016
0	16	17	0.048
0	16	22	0.016
0	21	12	0.048
0	21	17	0.144
0	21	22	0.048
0	26	12	0.016
0	26	17	0.048
0	26	22	0.016
8	16	12	0.012
8	16	17	0.036
8	16	22	0.012
8	21	12	0.036
8	21	17	0.108
8	21	22	0.036
8	26	12	0.012
8	26	17	0.036
8	26	22	0.012

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 ....**Assurance**
Prior Entry Method.......................................**Combined (Enter parameter values and**
                                         probabilities on spreadsheet)
Alpha..**0.05**
Group Allocation ....**Equal (N1 = N2)**
Sample Size Per Group **30**
EU (Upper Equivalence Limit).......................**19.2**
EL (Lower Equivalence Limit) ....**-19.2**
Column of δ Values **C1**
Column of σ1 Values **C2**
Column of σ2 Values **C3**
Column of Pr(Values)....................................**C4**

Options Tab
_____

Number of Computation Points for each........**10**
  Prior Distribution
Maximum N1 in Sample Size Search **5000**

Input Spreadsheet Data
_____

Row	C1	C2	C3	C4
1	-8	16	12	0.012
2	-8	16	17	0.036
3	-8	16	22	0.012
4	-8	21	12	0.036
5	-8	21	17	0.108
6	-8	21	22	0.036
7	-8	26	12	0.012
8	-8	26	17	0.036
9	-8	26	22	0.012
10	0	16	12	0.016
11	0	16	17	0.048
12	0	16	22	0.016
13	0	21	12	0.048
14	0	21	17	0.144
15	0	21	22	0.048
16	0	26	12	0.016
17	0	26	17	0.048
18	0	26	22	0.016
19	8	16	12	0.012
20	8	16	17	0.036
21	8	16	22	0.012
22	8	21	12	0.036
23	8	21	17	0.108
24	8	21	22	0.036

25	8	26	12	0.012
26	8	26	17	0.036
27	8	26	22	0.012

Output

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

Numeric Results

Solve For: Assurance
Difference: $\delta = \mu1 - \mu2 = \mu T - \mu R$
Hypotheses: H0: $\delta \le$ EL or $\delta \ge$ EU   vs.   H1: EL $< \delta <$ EU
Prior Type: Joint Multivariate Distribution

Prior Distribution
Point Lists
δ: C1:   -8 -8 -8 -8 -8 -8 -8 -8 -8 0 0 0 0 0 0 0 0 0 8 8 8 8 8 8 8 8 8
$\sigma1$:   C2:   16 16 16 21 21 21 26 26 26 16 16 16 21 21 21 26 26 26 16 16 16 21 21 21 26 26 26
$\sigma2$:   C3:   12 17 22 12 17 22 12 17 22 12 17 22 12 17 22 12 17 22 12 17 22 12 17 22
Prob: C4:   0.012 0.036 0.012 0.036 0.108 0.036 0.012 0.036 0.012 0.016 0.048 0.016 0.048 0.144 0.048
            0.016 0.048 0.016 0.012 0.036 0.012 0.036 0.108 0.036 0.012 0.036 0.012

					Equivalence Limits		Expected Mean Diff	Group 1 Std Dev	Group 2 Std Dev	
					Lower EL	Upper EU				
Assurance	Power‡	N1	N2	N			E(δ)	E($\sigma1$)	E($\sigma2$)	Alpha
0.81818	0.97277	30	30	60	-19.2	19.2	0	21	17	0.05

‡ Power was calculated using δ = E(δ) = 0, $\sigma1$ = E($\sigma1$) = 21, and $\sigma2$ = E($\sigma2$) = 17.

PASS has also calculated the assurance as 0.81818 which matches Example 2 and thus validates the procedure.