Chapter 278

Assurance for Two-Sample T-Tests for Superiority by a Margin Assuming Equal Variance

Introduction

This procedure calculates the assurance of superiority by a margin two-sample t-tests in which the outcome is a continuous normal random variable and the variances of the two groups (populations) are assumed to be equal. The calculation is based on a user-specified prior distribution of the effect size parameters. This procedure may also be used to determine the needed sample size to obtain a specified assurance.

The methods for this procedure are based on the assurance discussion given in O'Hagan, Stevens, and Campbell (2005). Sample size formulas for superiority by a margin tests of two means are presented in Chow et al. (2018) pages 50-51.

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).

Superiority by a Margin, Two-Sample T-Test

A *superiority by a margin test* tests that the treatment mean is better than the reference mean by more than a superiority margin. The actual direction of the hypothesis depends on the response variable being studied. The word *SM* refers to the superiority margin.

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

$H_0: \mu_1 \le \mu_2 + |SM|$ versus $H_1: \mu_1 > \mu_2 + |SM|$

$H_0: \mu_1 - \mu_2 \le |SM|$ versus $H_1: \mu_1 - \mu_2 > |SM|$

$H_0: \delta \le |SM|$ versus $H_1: \delta > |SM|$

Case 2: High Values Bad

In this case, higher values are worse. The hypotheses are arranged so that rejecting the null hypothesis implies that the treatment mean is less than the reference mean by at least the margin of superiority. The value of δ at which power is calculated must be less than $-|SM|$. The null and alternative hypotheses with $\delta_0 = -|SM|$ are

$H_0: \mu_1 \ge \mu_2 - |SM|$ versus $H_1: \mu_1 < \mu_2 - |SM|$

$H_0: \mu_1 - \mu_2 \ge -|SM|$ versus $H_1: \mu_1 - \mu_2 < -|SM|$

$H_0: \delta \ge -|SM|$ versus $H_1: \delta < -|SM|$

Test Statistic

Under the null hypothesis, this test assumes that the two groups of data are simple random samples from a single population of normally distributed values that all have the same mean and variance. This assumption implies that the data are continuous, and their distribution is symmetric. The calculation of the test statistic for the case when higher response values are better is as follows.

$$t_{df} = \frac{(\bar{X}_1 - \bar{X}_2) - \delta_0}{s_{\bar{X}_1 - \bar{X}_2}}$$

where

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

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

$$s_{\bar{X}_1 - \bar{X}_2} = \sqrt{\frac{(N_1 - 1)s_1^2 + (N_2 - 1)s_2^2}{N_1 + N_2 - 2}\left(\frac{1}{N_1} + \frac{1}{N_2}\right)},$$

$$df = N_1 + N_2 - 2,$$

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

The null hypothesis is rejected if the computed p-value is less than a specified level (usually 0.05). Otherwise, no conclusion can be reached.

Power Calculation

The power is calculated from N_1 and N_2, α, the assumed $\delta = \mu_1 - \mu_2$, and the assumed common standard deviation, $\sigma_1 = \sigma_2 = \sigma$.

The steps for calculating the power are as follows:

1. Find t_α such that $1 - T_{df}(t_\alpha) = \alpha$, where $T_{df}(x)$ is the area to the left of x under a central-t distribution with degrees of freedom, $df = N_1 + N_2 - 2$.

2. Calculate: $\sigma_{\bar{X}} = \sigma\sqrt{\frac{1}{N_1} + \frac{1}{N_2}}$.

3. Calculate the noncentrality parameter: $\lambda = \frac{\delta - \delta_0}{\sigma_{\bar{X}}}$.

4. Calculate: $Power = 1 - T'_{df,\lambda}(t_\alpha)$, where $T'_{df,\lambda}(x)$ is the area to the left of x under a noncentral-t distribution with degrees of freedom, $df = N_1 + N_2 - 2$, and noncentrality parameter, λ.

The algorithms for calculating power for the opposite direction and the two-sided hypotheses are analogous to this method.

Assurance Calculation

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

Let $P_1(H|\delta,\sigma)$ 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 δ and σ is critical to the power calculation, but the actual values are seldom known. Assurance is defined as the expected power where the expectation is with respect to a joint prior distribution for the parameters δ and σ. Hence, the definition of assurance is

$$Assurance = E_{\delta,\sigma}\big(P_1(H|\delta,\sigma)\big) = \iint P_1(H|\delta,\sigma)f(\delta,\sigma)d\delta \, d\sigma$$

where $f(\delta,\sigma)$ is the joint prior distribution of δ and σ.

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 $f(\delta,\sigma)$. This provides flexibility in specifying the joint prior distribution. In the two-parameter case, three columns are entered on the spreadsheet: two for the parameters and a third 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 two independent distributions as follows:

$$f(\delta,\sigma) = f_1(\delta)f_2(\sigma)$$

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

$$Assurance = E_{\delta,\sigma}\big(P_1(H|\delta,\sigma)\big) = \iint P_1(H|\delta,\sigma)f_1(\delta)f_2(\sigma)d\delta \, d\sigma$$

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 $1 - \text{Prob}(Min \le X \le Max)$ 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

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

A truncated version of the distribution is constructed by dividing the density by $1 - \text{Prob}(Min \le X \le Max)$ 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 $1 - \text{Prob}(Min \le X \le Max)$ 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 ~ standard normal, then $X = e^{\mu + \sigma Z}$ ~ 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 $1 - \text{Prob}(Min \le X \le Max)$ 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 test is to be conducted to determine if a new cancer treatment improves bone density. The adjusted mean bone density (AMBD) in the population of interest is 0.002300 gm/cm with a standard deviation of 0.000300 gm/cm. Clinicians decide that if the treatment increases AMBD by more than 5% (0.000115 gm/cm), it generates a significant health benefit.

The analysis will be a superiority test using the *t*-test at the 0.025 significance level. Power is to be calculated assuming that the new treatment shows at least 7.5% improvement on AMBD. 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. The required sample size is 573 per group (see Example 2 of the *Two-Sample T-Tests for Superiority by a Margin Assuming Equal Variance* procedure).

To complete their sample size study, the researchers want to run an assurance analysis for a range of group sample sizes from 100 to 800. An elicitation exercise determined that the prior distribution of the mean difference should be normal with mean 1.725 and standard deviation 0.5. The elicitation also concluded that prior distribution of the common group standard deviation should be a truncated-normal with mean 3, standard deviation 0.5, and left boundary 0.0001.

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)**
Higher Means Are...**Better (H1: δ > SM)**
Alpha...**0.025**
Group Allocation ....**Equal (N1 = N2)**
Sample Size Per Group **100 300 500 573 800**
SM (Superiority Margin) **1.15**
Prior Distribution of δ ....**Normal (Mean, SD)**
Mean...**1.725**
SD..**0.5**
Truncation Boundaries..................................**None**
Prior Distribution of σ ....**Normal (Mean, SD)**
Mean...**3**
SD..**0.5**
Truncation Boundaries..................................**Left**
Left Boundary **0.0001**

Options Tab

Number of Computation Points for each........**30**
  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:	Assurance
Higher Means Are:	Better
Hypotheses:	H0: δ ≤ SM vs. H1: δ > SM
Prior Type:	Independent Univariate Distributions

Prior Distributions
δ: Normal (Mean = 1.725, SD = 0.5).
σ: Normal (Mean = 3, SD = 0.5), Left Boundary = 0.0001.

		Sample Size			Superiority Margin	Expected Mean Difference	Expected Standard Deviation	
Assurance*	Power‡	N1	N2	N	SM	E(δ)	E(σ)	Alpha
0.35300	0.27052	100	100	200	1.15	1.725	3	0.025
0.56814	0.64940	300	300	600	1.15	1.725	3	0.025
0.64788	0.85769	500	500	1000	1.15	1.725	3	0.025
0.66584	0.90036	573	573	1146	1.15	1.725	3	0.025
0.70447	0.96943	800	800	1600	1.15	1.725	3	0.025

* The number of points used for computation of the prior(s) was 30.
‡ Power was calculated using δ = E(δ) = 1.725 and σ = E(σ) = 3.

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.
SM	The magnitude and direction of the superiority margin. Since higher means are better, this value is positive and is the distance above the reference mean that is considered superior.
E(δ)	The expected value over its prior distribution of the difference in the group means assumed by the alternative hypothesis. Note that δ = μ1 - μ2.
E(σ)	The expected value over its prior distribution of the standard deviation used for both groups.
Alpha	The probability of rejecting a true null hypothesis.

Summary Statements

A parallel two-group design will be used to test whether the Group 1 (treatment) mean (μ1) is superior to the Group 2 (control) mean (μ2) by a margin, with a superiority margin of 1.15 (H0: δ ≤ 1.15 versus H1: δ > 1.15, δ = μ1 - μ2). The comparison will be made using a one-sided, two-sample, equal-variance t-test, with a Type I error rate (α) of 0.025. The prior distribution used for the mean difference is Normal (Mean = 1.725, SD = 0.5). The prior distribution used for the standard deviation is Normal (Mean = 3, SD = 0.5), Left Boundary = 0.0001. With sample sizes of 100 for Group 1 (treatment) and 100 for Group 2 (control), the assurance (average power) is 0.353.

Dropout-Inflated Sample Size

Dropout Rate	Sample Size			Dropout-Inflated Enrollment Sample Size			Expected Number of Dropouts		
	N1	N2	N	N1'	N2'	N'	D1	D2	D
20%	100	100	200	125	125	250	25	25	50
20%	300	300	600	375	375	750	75	75	150
20%	500	500	1000	625	625	1250	125	125	250
20%	573	573	1146	717	717	1434	144	144	288
20%	800	800	1600	1000	1000	2000	200	200	400

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

Anticipating a 20% dropout rate, 125 subjects should be enrolled in Group 1, and 125 in Group 2, to obtain final group sample sizes of 100 and 100, respectively.

References

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.

This report shows the assurance values obtained by each sample size. Note that the assurance value at a sample size of 573, the size chosen in the power analysis, is 0.67.

Plots Section

Plots
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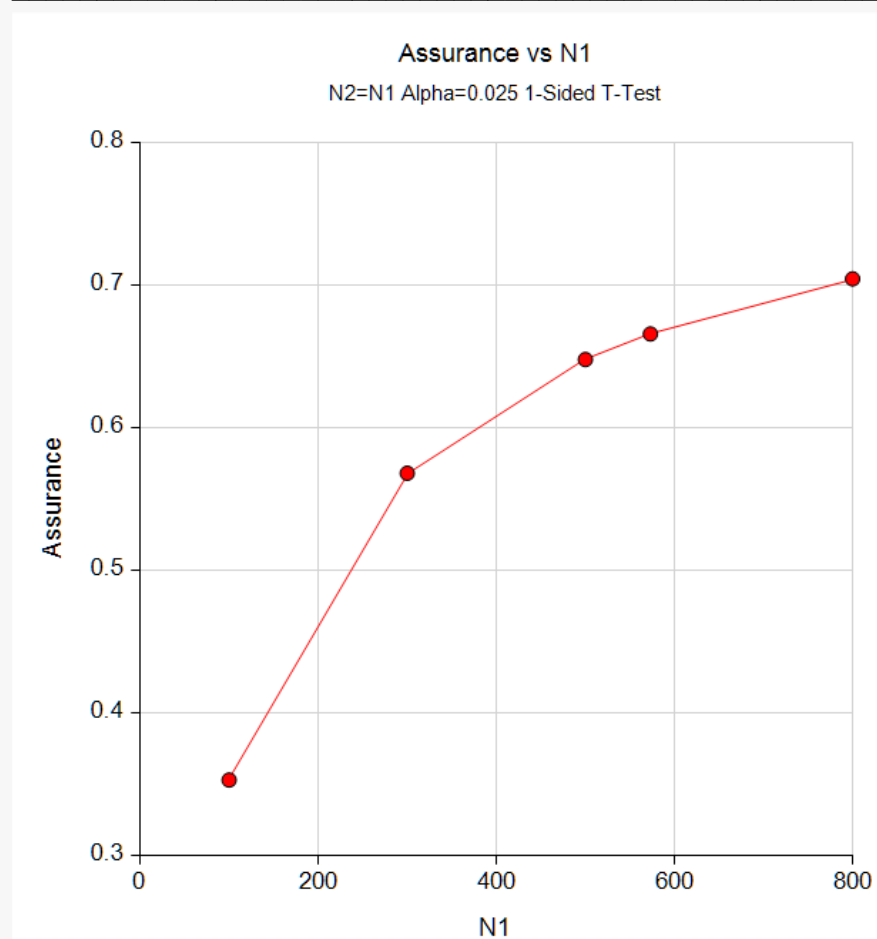
This plot shows the relationship between the assurance and sample size. Note the diminishing impact on assurance of each increase in the number of subjects.

Comparison Plots Section

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

Example 2 – Validation using Hand Computation

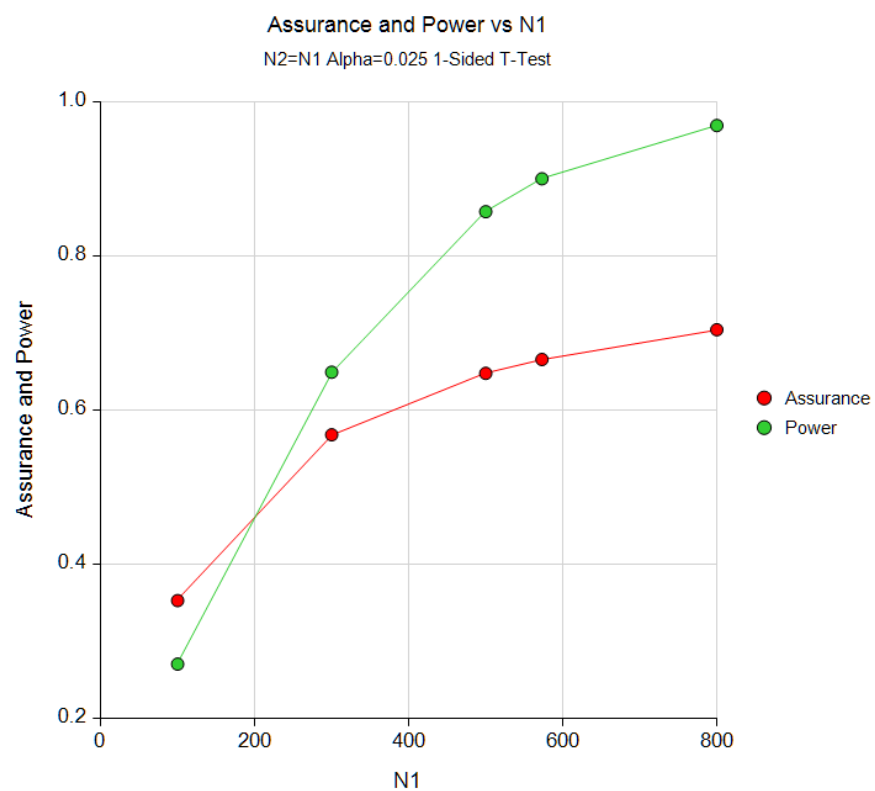We could not find a validation example in the literature, so we have developed a validation example of our own. Suppose a superiority by a margin, two-sample t-test will be used in which N1 = N2 = 150 and the significance level is 0.025. The superiority margin was set to 1.0. Higher means are better.

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

δ	Prob
5	0.3
6	0.4
7	0.3

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

σ	Prob
12	0.2
16	0.6
20	0.2

Note that in both 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 Superiority by a Margin Assuming Equal Variance* procedure is used to compute the power for each of the nine combinations of δ and σ. The results of these calculations were as follows.

Numeric Results

Solve For: Power
Test Type: Two-Sample Equal-Variance T-Test
Difference: $\delta = \mu1 - \mu2 = \mu T - \mu R$
Higher Means Are: Better
Hypotheses: H0: $\delta \le$ SM   vs.   H1: $\delta >$ SM

	Sample Size			Superiority Margin	Mean Difference	Standard Deviation	
Power	N1	N2	N	SM	δ	σ	Alpha
0.82055	150	150	300	1	5	12	0.025
0.57852	150	150	300	1	5	16	0.025
0.40769	150	150	300	1	5	20	0.025
0.94917	150	150	300	1	6	12	0.025
0.76963	150	150	300	1	6	16	0.025
0.57852	150	150	300	1	6	20	0.025
0.99077	150	150	300	1	7	12	0.025
0.89922	150	150	300	1	7	16	0.025
0.73556	150	150	300	1	7	20	0.025

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

$$Assurance = (0.82055 \times 0.3 \times 0.2) + (0.57852 \times 0.3 \times 0.6) + \cdots + (0.73556 \times 0.3 \times 0.2) = 0.750194.$$

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
5	0.3	12	0.2
6	0.4	16	0.6
7	0.3	20	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)**
Higher Means Are...**Better (H1: δ > SM)**
Alpha..**0.025**
Group Allocation ....**Equal (N1 = N2)**
Sample Size Per Group **150**
SM (Superiority Margin) **1**
Prior Distribution of δ ....**Custom (Values and Probabilities in Spreadsheet)**
Column of Values **C1**
Column of Pr(Values)....................................**C2**
Prior Distribution of σ ....**Custom (Values and Probabilities in Spreadsheet)**
Column of Values **C3**
Column of Pr(Values)....................................**C4**

Options Tab

Number of Computation Points for each........**50**
  Prior Distribution
Maximum N1 in Sample Size Search **5000**

Input Spreadsheet Data
―――

Row	C1	C2	C3	C4
1	5	0.3	12	0.2
2	6	0.4	16	0.6
3	7	0.3	20	0.2
―――

Output

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

Numeric Results

Solve For: Assurance
Higher Means Are: Better
Hypotheses: H0: δ ≤ SM   vs.   H1: δ > SM
Prior Type: Independent Univariate Distributions

Prior Distributions
δ: Point List (Values = C1, Probs = C2).
  C1: 5 6 7
  C2: 0.3 0.4 0.3
σ: Point List (Values = C3, Probs = C4).
  C3: 12 16 20
  C4: 0.2 0.6 0.2

		Sample Size			Superiority Margin	Expected Mean Difference	Expected Standard Deviation	
Assurance	Power‡	N1	N2	N	SM	E(δ)	E(σ)	Alpha
0.7502	0.76963	150	150	300	1	6	16	0.025

‡ Power was calculated using δ = E(δ) = 6 and σ = E(σ) = 16.

PASS has also calculated the assurance as 0.7502 which validates the procedure. Note that the slight difference between 0.7502 and the hand-calculated 0.750124 is because of rounding in the hand calculations.

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 0.4, 0.5, 0.6, 0.7, and 0.8.

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)
Higher Means Are...**Better (H1: δ > SM)**
Assurance..**0.4 0.5 0.6 0.7 0.8**
Alpha..**0.025**
Group Allocation ....**Equal (N1 = N2)**
SM (Superiority Margin) **1.15**
Prior Distribution of δ ....**Normal (Mean, SD)**
Mean..**1.725**
SD...**0.5**
Truncation Boundaries.................................**None**
Prior Distribution of σ ....**Normal (Mean, SD)**
Mean..**3**
SD...**0.5**
Truncation Boundaries.................................**Left**
Left Boundary **0.0001**

Options Tab

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: Sample Size
Higher Means Are: Better
Hypotheses: H0: δ ≤ SM   vs.   H1: δ > SM
Prior Type: Independent Univariate Distributions

Prior Distributions
δ: Normal (Mean = 1.725, SD = 0.5).
σ: Normal (Mean = 3, SD = 0.5), Left Boundary = 0.0001.
───

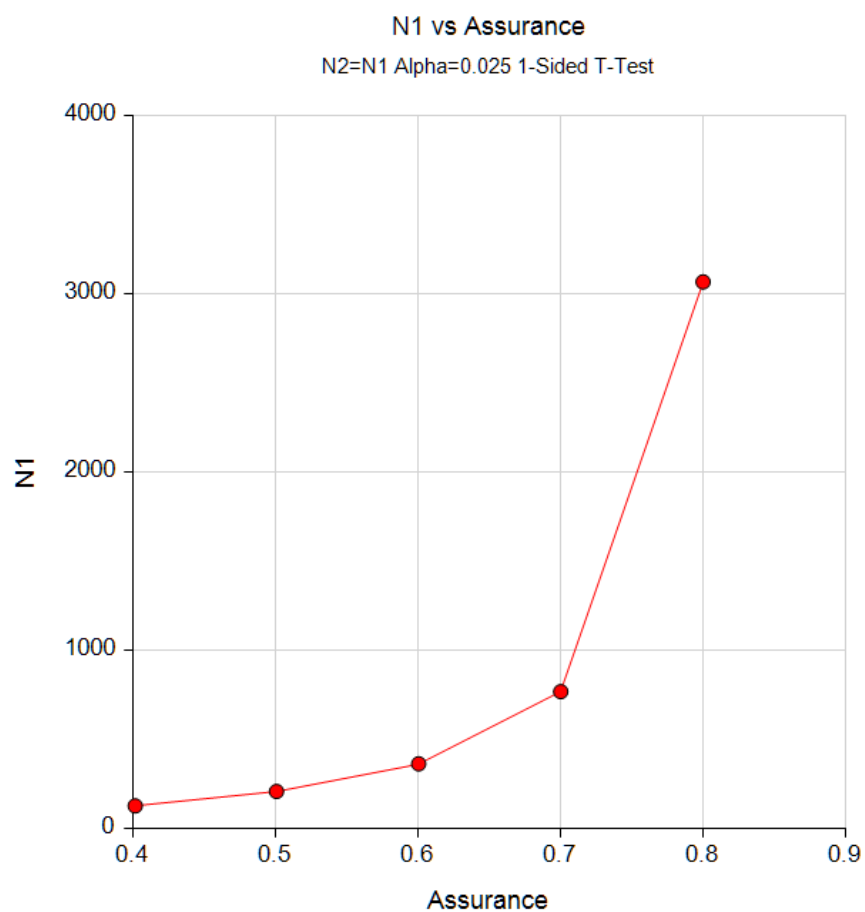| Assurance*			Sample Size			Superiority Margin	Expected Mean Difference	Expected Standard Deviation	
Actual	Target	Power‡	N1	N2	N	SM	E(δ)	E(σ)	Alpha
0.40151	0.4	0.33053	127	127	254	1.15	1.725	3	0.025
0.50069	0.5	0.49606	208	208	416	1.15	1.725	3	0.025
0.60042	0.6	0.73305	363	363	726	1.15	1.725	3	0.025
0.70008	0.7	0.96368	768	768	1536	1.15	1.725	3	0.025
0.80000	0.8	1.00000	3067	3067	6134	1.15	1.725	3	0.025

* The number of points used for computation of the prior(s) was 20.
‡ Power was calculated using δ = E(δ) = 1.725 and σ = E(σ) = 3.

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

Suppose a superiority by a margin, two-sample t-test will be used in which N1 = N2 = 100 and the significance level is 0.025. The superiority margin is set to 1.0. Higher means are better.

The joint prior distribution of the difference and standard deviation is approximated by the following table. Note the relationship between the difference and the standard deviation.

δ	σ	Prob
4	11	0.1
5	12	0.2
6	13	0.1
6	15	0.3
7	16	0.4
8	17	0.3
11	19	0.1
13	20	0.2
15	21	0.1

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

C1	C2	C3
4	11	0.1
5	12	0.2
6	13	0.1
6	15	0.3
7	16	0.4
8	17	0.3
11	19	0.1
13	20	0.2
15	21	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)**

Higher Means Are..**Better (H1: δ > SM)**

Alpha...**0.025**

Group Allocation ....**Equal (N1 = N2)**

Sample Size Per Group **100**

SM (Superiority Margin) **1**

Column of δ Values **C1**
Column of σ Values **C2**
Column of Probabilities.................................**C3**

Options Tab

Number of Computation Points for each........**50**
  Prior Distribution
Maximum N1 in Sample Size Search **5000**

Input Spreadsheet Data

Row	C1	C2	C3
1	4	11	0.1
2	5	12	0.2
3	6	13	0.1
4	6	15	0.3
5	7	16	0.4
6	8	17	0.3
7	11	19	0.1
8	13	20	0.2
9	15	21	0.1

Output

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

Numeric Results

Solve For:	Assurance
Higher Means Are:	Better
Hypotheses:	H0: δ ≤ SM vs. H1: δ > SM
Prior Type:	Joint Multivariate Distribution

Prior Distribution
Point Lists
δ: C1:   4 5 6 6 7 8 11 13 15
σ: C2:   11 12 13 15 16 17 19 20 21
Prob: C3:   0.1 0.2 0.1 0.3 0.4 0.3 0.1 0.2 0.1

		Sample Size			Superiority Margin	Expected Mean Difference	Expected Standard Deviation	
Assurance	Power‡	N1	N2	N	SM	E(δ)	E(σ)	Alpha
0.77343	0.85763	100	100	200	1	7.88889	16	0.025

‡ Power was calculated using δ = E(δ) = 7.88889 and σ = E(σ) = 16.

PASS has calculated the assurance as 0.77343.

Example 5 – Joint Prior Distribution 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 distribution of the difference is given as follows.

δ	Prob
5	0.3
6	0.4
7	0.3

Similarly, the prior distribution of the standard deviation is given as follows.

σ	Prob
12	0.2
16	0.6
20	0.2

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

δ	σ	P(δ)	P(σ)	P(δ)P(σ)
5	12	0.3	0.2	0.06
5	16	0.3	0.6	0.18
5	20	0.3	0.2	0.06
6	12	0.4	0.2	0.08
6	16	0.4	0.6	0.24
6	20	0.4	0.2	0.08
7	12	0.3	0.2	0.06
7	16	0.3	0.6	0.18
7	20	0.3	0.2	0.06

To run this example, the spreadsheet is loaded with the following three columns. (Note that columns C3 and C4 are used to hold intermediate values which are not referenced in this example. C3 holds P(δ) and C4 holds P(σ).)

C1	C2	C5
5	12	0.06
5	16	0.18
5	20	0.06
6	12	0.08
6	16	0.24
6	20	0.08
7	12	0.06
7	16	0.18
7	20	0.06

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)**
Higher Means Are..**Better (H1: δ > SM)**
Alpha..**0.025**
Group Allocation ....**Equal (N1 = N2)**
Sample Size Per Group **150**
SM (Superiority Margin)................................**1**
Column of δ Values **C1**
Column of σ Values **C2**
Column of Probabilities.................................**C5**

Options Tab

Number of Computation Points for each........**50**
  Prior Distribution
Maximum N1 in Sample Size Search **5000**

Input Spreadsheet Data

Row	C1	C2	C3	C4	C5
1	5	12	0.3	0.2	0.06
2	5	16	0.3	0.6	0.18
3	5	20	0.3	0.2	0.06
4	6	12	0.4	0.2	0.08
5	6	16	0.4	0.6	0.24
6	6	20	0.4	0.2	0.08
7	7	12	0.3	0.2	0.06
8	7	16	0.3	0.6	0.18
9	7	20	0.3	0.2	0.06

Output

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

Numeric Results
___

Solve For: Assurance
Higher Means Are: Better
Hypotheses: H0: δ ≤ SM   vs.   H1: δ > SM
Prior Type: Joint Multivariate Distribution

Prior Distribution
Point Lists
δ: C1:   5 5 5 6 6 6 7 7 7
σ: C2:   12 16 20 12 16 20 12 16 20
Prob: C5:   0.06 0.18 0.06 0.08 0.24 0.08 0.06 0.18 0.06
___

		Sample Size			Superiority Margin	Expected Mean Difference	Expected Standard Deviation	
Assurance	**Power‡**	**N1**	**N2**	**N**	**SM**	**E(δ)**	**E(σ)**	**Alpha**
0.7502	0.76963	150	150	300	1	6	16	0.025

‡ Power was calculated using δ = E(δ) = 6 and σ = E(σ) = 16.

PASS has calculated the assurance as 0.7502 which matches the result in Example 2. This validates the joint prior method.