Chapter 320

Equivalence Tests for the Mean Ratio in a Three-Arm Trial (Normal Data) (Simulation)

Introduction

This procedure computes power and sample size of an equivalence test procedure that compares three means from independent groups using various mean ratios. Schuirmann's (1987) two one-sided tests (TOST) approach is used to test equivalence. The t-test is commonly used in this situation, but Welch's unequal variance test is also available.

Measurements are made on individuals that have been randomly assigned to one of three groups: treatment group, reference group, or placebo group. This *three-arm* design may be analyzed by an initial test of treatment superiority over the placebo followed by a two-arm equivalence test of the ratio of the treatment and reference means or of the ratio of the treatment – placebo means and the reference – placebo means. The details are found in Chang *et al.* (2014).

Because of the complicated analysis procedure (two tests), the power and sample size results are based on simulation. Chang et al. (2014) gives analytic results for the case of equal sample sizes, but a more flexible algorithm was needed for the case of unequal sample sizes and variances.

Technical Details

Computer simulation allows us to estimate the power and significance level that is actually achieved by a test procedure in situations that are not mathematically tractable.

The steps to a simulation study are as follows.

1. Specify how the tests are carried out. This includes indicating how the test statistics are calculated and how the significance levels are specified.
2. Generate random samples from the distributions specified by the alternative hypothesis. Calculate the test statistics from the simulated data and determine if the null hypothesis is accepted or rejected. Tabulate the number of rejections and use this to calculate the test's power.
3. Repeat step 2 several thousand times, tabulating the number of times the simulated data leads to a rejection of the null hypothesis. The power is the proportion of simulated samples in step 2 that lead to rejection.

Equivalence Assessment Methods

This section describes the analysis methods that can be used to assess equivalence that are available in this procedure. We begin with the design setting.

Suppose a pool of subjects is randomly assigned to one of three groups: treatment, reference, or placebo. The subject responses from each group are assumed to be normally distributed with $X_T \sim N(\mu_T, \sigma_T^2)$, $X_R \sim N(\mu_R, \sigma_R^2)$, and $X_P \sim N(\mu_P, \sigma_P^2)$. Samples of size $n_T, n_R,$ and n_P are thus obtained from the three arms.

Chang *et al.* (2014) present three methods for conducting an analysis of various ratios of the means. Each results in different sample size requirements. Each of these methods is based on the following summary statistics:

$$\bar{X}_i = \frac{\sum_{k=1}^{n_i} X_{ik}}{n_i}$$

$$s_i^2 = \frac{\sum_{k=1}^{n_i} (X_{ik} - \bar{X}_i)^2}{n_i - 1}$$

where *i =T, R, P.*

(B) Treatment Efficacy Test followed by Treatment vs Reference Equivalence Test

This method first tests whether the treatment is better than the placebo. This is a one-sided test, so the significance level is set at 0.025. If this hypothesis is rejected, then a second equivalence test is run. This second test is based on the ratio of the treatment and the reference means. It uses a significance level of 0.05 for both TOST tests.

Hypotheses

The treatment efficacy hypotheses are:

$$H_0: \mu_T - \mu_P \leq 0 \quad \text{versus} \quad H_1: \mu_T - \mu_P > 0.$$

The lower and upper equivalence hypotheses are

$$H_{0L}: \frac{\mu_T}{\mu_R} \leq E_L \quad \text{versus} \quad H_{1L}: \frac{\mu_T}{\mu_R} > E_L \quad \text{and} \quad H_{0U}: \frac{\mu_T}{\mu_R} \geq E_U \quad \text{versus} \quad H_{1U}: \frac{\mu_T}{\mu_R} < E_U \,.$$

Unequal Variance Test Statistics

The treatment efficacy test uses the one-sided test statistics t_S. This is given by

$$t_S = \frac{\bar{X}_T - \bar{X}_P}{\sqrt{\frac{s_T^2}{n_T} + \frac{s_P^2}{n_P}}}$$

The degrees of freedom are

$$\nu_S = \frac{\left(\frac{s_T^2}{n_T} + \frac{s_P^2}{n_P}\right)^2}{\frac{s_T^4/n_T^2}{n_T - 1} + \frac{s_P^4/n_P^2}{n_P - 1}}$$

The equivalence tests use the pair of TOST test statistics t_L and t_U. These are given by

$$t_L = \frac{\bar{X}_T - E_L\bar{X}_R}{\sqrt{\frac{s_T^2}{n_T} + E_L^2\frac{s_R^2}{n_R}}}$$

$$t_U = \frac{\bar{X}_T - E_U\bar{X}_R}{\sqrt{\frac{s_T^2}{n_T} + E_U^2\frac{s_R^2}{n_R}}}$$

The degrees of freedom of these t-tests are

$$\nu_L = \frac{\left(\frac{s_T^2}{n_T} + E_L^2\frac{s_R^2}{n_R}\right)^2}{\frac{s_T^4/n_T^2}{n_T - 1} + E_L^4\left(\frac{s_R^4/n_R^2}{n_R - 1}\right)}$$

$$\nu_U = \frac{\left(\frac{s_T^2}{n_T} + E_U^2\frac{s_R^2}{n_R}\right)^2}{\frac{s_T^4/n_T^2}{n_T - 1} + E_U^4\left(\frac{s_R^4/n_R^2}{n_R - 1}\right)}$$

Equal Variance Test Statistics

The treatment efficacy test uses the one-sided test statistics t_S. This test statistic is given by

$$t_S = \frac{\bar{X}_T - \bar{X}_R}{\sqrt{s_{pool}^2\left(\frac{1}{n_T} + \frac{1}{n_P}\right)}}$$

where

$$s_{pool}^2 = \frac{s_T^2(n_T - 1) + s_P^2(n_P - 1)}{n_T + n_P - 2}$$

The degrees of freedom of this test are $\nu_S = n_T + n_P - 2$.

The equivalence tests use the pair of TOST test statistics t_L and t_U. These are given by

$$t_L = \frac{\bar{X}_T - E_L\bar{X}_R}{\sqrt{s_{pool}^2\left(\frac{1}{n_T} + E_L^2\frac{1}{n_R}\right)}}$$

$$t_U = \frac{\bar{X}_T - E_U\bar{X}_R}{\sqrt{s_{pool}^2\left(\frac{1}{n_T} + E_U^2\frac{1}{n_R}\right)}}$$

$$s_{pool}^2 = \frac{s_T^2(n_T - 1) + s_R^2(n_R - 1)}{n_T + n_R - 2}$$

The degrees of freedom for both tests given by $\nu_L = \nu_U = n_T + n_R - 2$.

(C) Treatment Efficacy Test followed by Treatment vs Reference Equivalence Test of Mean Differences

This method first tests whether the treatment is better than the placebo. This is a one-sided test, so the significance level is set at 0.025.

If this hypothesis is rejected, then a second equivalence test is run. This second test is based on the ratio of the treatment mean minus the placebo mean and the reference mean minus the placebo mean. This equivalence test uses a significance level of 0.05 for both TOST tests.

Hypotheses

The treatment efficacy hypotheses are:

$$H_0: \mu_T - \mu_P \leq 0 \quad \text{versus} \quad H_1: \mu_T - \mu_P > 0.$$

The lower and upper equivalence hypotheses are

$$H_{0L}: \frac{\mu_T - \mu_P}{\mu_R - \mu_P} \leq E_L \quad \text{versus} \quad H_{1L}: \frac{\mu_T - \mu_P}{\mu_R - \mu_P} > E_L \quad \text{and} \quad H_{0U}: \frac{\mu_T - \mu_P}{\mu_R - \mu_P} \geq E_U \quad \text{versus} \quad H_{1U}: \frac{\mu_T - \mu_P}{\mu_R - \mu_P} < E_U\,.$$

Unequal Variance Test Statistics

The treatment efficacy test uses the one-sided test statistics t_S. This is given by

$$t_S = \frac{\bar{X}_T - \bar{X}_P}{\sqrt{\frac{s_T^2}{n_T} + \frac{s_P^2}{n_P}}}$$

The degrees of freedom are

$$\nu_S = \frac{\left(\frac{s_T^2}{n_T} + \frac{s_P^2}{n_P}\right)^2}{\frac{s_T^4/n_T^2}{n_T - 1} + \frac{s_P^4/n_P^2}{n_P - 1}}$$

The equivalence tests use the pair of TOST test statistics t_L and t_U. These are given by

$$t_L = \frac{\bar{X}_T - E_L\bar{X}_R - (1 - E_L)\bar{X}_P}{\sqrt{\frac{s_T^2}{n_T} + E_L^2\frac{s_R^2}{n_R} + (1 - E_L)^2\frac{s_P^2}{n_P}}}$$

$$t_U = \frac{\bar{X}_T - E_U\bar{X}_R - (1 - E_U)\bar{X}_P}{\sqrt{\frac{s_T^2}{n_T} + E_U^2\frac{s_R^2}{n_R} + (1 - E_U)^2\frac{s_P^2}{n_P}}}$$

The degrees of freedom of these t-tests are

$$\nu_L = \frac{\left(\frac{s_T^2}{n_T} + E_L^2\frac{s_R^2}{n_R} + (1 - E_L)^2\frac{s_P^2}{n_P}\right)^2}{\frac{s_T^4/n_T^2}{n_T - 1} + E_L^4\left(\frac{s_R^4/n_R^2}{n_R - 1}\right) + (1 - E_L)^4\left(\frac{s_P^4/n_P^2}{n_P - 1}\right)}$$

$$\nu_U = \frac{\left(\frac{s_T^2}{n_T} + E_U^2\frac{s_R^2}{n_R} + (1 - E_U)^2\frac{s_P^2}{n_P}\right)^2}{\frac{s_T^4/n_T^2}{n_T - 1} + E_U^4\left(\frac{s_R^4/n_R^2}{n_R - 1}\right) + (1 - E_U)^4\left(\frac{s_P^4/n_P^2}{n_P - 1}\right)}$$

Equal Variance Test Statistics

The treatment efficacy test uses the one-sided test statistics t_S. This test statistic is given by

$$t_S = \frac{\bar{X}_T - \bar{X}_R}{\sqrt{s_{pool}^2\left(\frac{1}{n_T} + \frac{1}{n_P}\right)}}$$

where

$$s_{pool}^2 = \frac{s_T^2(n_T - 1) + s_P^2(n_P - 1)}{n_T + n_P - 2}$$

The degrees of freedom of this test are $\nu_S = n_T + n_P - 2$.

The equivalence tests use the pair of TOST test statistics t_L and t_U. These are given by

$$t_L = \frac{\bar{X}_T - E_L\bar{X}_R - (1 - E_L)\bar{X}_P}{\sqrt{s_{pool}^2\left(\frac{1}{n_T} + \frac{E_L^2}{n_R} + \frac{(1 - E_L)^2}{n_P}\right)}}$$

$$t_U = \frac{\bar{X}_T - E_U\bar{X}_R - (1 - E_U)\bar{X}_P}{\sqrt{s_{pool}^2\left(\frac{1}{n_T} + \frac{E_U^2}{n_R} + \frac{(1 - E_U)^2}{n_P}\right)}}$$

$$s_{pool}^2 = \frac{s_T^2(n_T - 1) + s_R^2(n_R - 1) + s_P^2(n_P - 1)}{n_T + n_R + n_P - 3}$$

The degrees of freedom for both tests given by $\nu_L = \nu_U = n_T + n_R + n_P - 3$.

(D) Treatment vs Reference Equivalence Test of Mean Differences

This method skips the treatment versus placebo test that was used in methods (B) and (C). This is replaced by the lower TOST test which is now conducted at a significance level of 0.025.

The equivalence test is run. This test is based on the ratio of the treatment mean minus the placebo mean and the reference mean minus the placebo mean. This equivalence test uses a significance level of 0.025 for t_L and 0.05 for t_U.

Hypotheses

The lower and upper equivalence hypotheses are

$$H_{0L}: \frac{\mu_T - \mu_P}{\mu_R - \mu_P} \leq E_L \quad \text{versus} \quad H_{1L}: \frac{\mu_T - \mu_P}{\mu_R - \mu_P} > E_L \quad \text{and} \quad H_{0U}: \frac{\mu_T - \mu_P}{\mu_R - \mu_P} \geq E_U \quad \text{versus} \quad H_{1U}: \frac{\mu_T - \mu_P}{\mu_R - \mu_P} < E_U\,.$$

Unequal Variance Test Statistics

The equivalence tests use the pair of TOST test statistics t_L and t_U. These are given by

$$t_L = \frac{\bar{X}_T - E_L\bar{X}_R - (1-E_L)\bar{X}_P}{\sqrt{\frac{s_T^2}{n_T} + E_L^2\frac{s_R^2}{n_R} + (1-E_L)^2\frac{s_P^2}{n_P}}}$$

$$t_U = \frac{\bar{X}_T - E_U\bar{X}_R - (1-E_U)\bar{X}_P}{\sqrt{\frac{s_T^2}{n_T} + E_U^2\frac{s_R^2}{n_R} + (1-E_U)^2\frac{s_P^2}{n_P}}}$$

The degrees of freedom of these t-tests are

$$\nu_L = \frac{\left(\frac{s_T^2}{n_T} + E_L^2\frac{s_R^2}{n_R} + (1-E_L)^2\frac{s_P^2}{n_P}\right)^2}{\frac{s_T^4/n_T^2}{n_T-1} + E_L^4\left(\frac{s_R^4/n_R^2}{n_R-1}\right) + (1-E_L)^4\left(\frac{s_P^4/n_P^2}{n_P-1}\right)}$$

$$\nu_U = \frac{\left(\frac{s_T^2}{n_T} + E_U^2\frac{s_R^2}{n_R} + (1-E_U)^2\frac{s_P^2}{n_P}\right)^2}{\frac{s_T^4/n_T^2}{n_T-1} + E_U^4\left(\frac{s_R^4/n_R^2}{n_R-1}\right) + (1-E_U)^4\left(\frac{s_P^4/n_P^2}{n_P-1}\right)}$$

Equal Variance Test Statistics

The equivalence tests use the pair of TOST test statistics t_L and t_U. These are given by

$$t_L = \frac{\bar{X}_T - E_L\bar{X}_R - (1-E_L)\bar{X}_P}{\sqrt{s_{pool}^2\left(\frac{1}{n_T} + \frac{E_L^2}{n_R} + \frac{(1-E_L)^2}{n_P}\right)}}$$

$$t_U = \frac{\bar{X}_T - E_U\bar{X}_R - (1-E_U)\bar{X}_P}{\sqrt{s_{pool}^2\left(\frac{1}{n_T} + \frac{E_U^2}{n_R} + \frac{(1-E_U)^2}{n_P}\right)}}$$

$$s_{pool}^2 = \frac{s_T^2(n_T-1) + s_R^2(n_R-1) + s_P^2(n_P-1)}{n_T+n_R+n_P-3}$$

The degrees of freedom for both tests given by $\nu_L = \nu_U = n_T + n_R + n_P - 3$.

Solution by Simulation

Because of the complexity of the experimental procedure, power and sample size are solved for using simulation. The accuracy of the simulation depends heavily upon the number of simulations, M. Of course, as M is increased, the solution time also increases.

We have found the following strategy to be reasonable. Set M to 1000 (or even 500) while you are experimenting with various settings. Once you have a set of options that you like, set M to 5000 (or higher).

Note that Chang *et al.* (2014) present closed form approximations. Unfortunately, their results are only given for equal group sample sizes. This is often not the case for three-arm designs such as this.

Example 1 – Power at Various Sample Sizes

Researchers are planning a three-arm trial to determine if the response to a new drug is equivalent to the response to a reference drug. The average response level to the reference drug is approximately 63 with a standard deviation of 5 in all groups. The response at the placebo is 43. They want to investigate the power when the treatment response is also 63.

The researchers decide to use the (C) method for the analysis of the results. This method considers the ratio of the treatment - placebo difference to the reference – placebo difference. They set the equivalence boundaries at 0.8 and 1.25. The significance levels are 0.025 for the first test and 0.05 for the equivalence test.

An initial run of the procedure with only 500 simulations yielded a sample size of 25 per group, so they want to investigate the group sizes of 20, 25, and 30 when the number of simulations is 5000.

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**
Testing Procedure	**Chang (C): Equivalence of Mean Difference Ratio after Treatment Efficacy**
Test Type	**T-Test Assuming Equal Variances**
Simulations	**5000**
Random Seed	**5567949** (for reproducibility)
α1 (One-Sided Alpha)	**0.025**
α2 (Equivalence Alpha)	**0.05**
Group Allocation Input Type	**Equal to ni (Sample Size Per Group)**
ni (Sample Size Per Group)	**20 25 30**
μ_T (Treatment Group Mean)	**63**
μ_R (Reference Group Mean)	**63**
μ_P (Placebo Group Mean)	**43**
σ Input Type	**Equal ($\sigma_T = \sigma_R = \sigma_P = \sigma$)**
σ (Group Standard Deviation)	**5**
E_L (Lower Equiv Limit)	**0.8**
E_U (Upper Equiv Limit)	**1.25**

Options Tab	
Random Normal Method	**Box - Muller**
Maximum N Before Search Termination	**5000**

Output

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

Numeric Reports

Numeric Results

Solve For:	Power
Groups:	T = Treatment, R = Reference, P = Placebo
Testing Procedure:	Chang Test (C): Equivalence of Mean Difference Ratio after Treatment Efficacy
Test Type:	T-Test Assuming Equal Variances
Treatment Efficacy Hypotheses:	H0s: $\mu_T - \mu_P \le 0$ vs. H1s: $\mu_T - \mu_P > 0$, Alpha = α1
Lower Equivalence Hypotheses:	H0L: $(\mu_T - \mu_P) / (\mu_R - \mu_P) \le E_L$ vs. H1L: $(\mu_T - \mu_P) / (\mu_R - \mu_P) > E_L$, Alpha = α2
Upper Equivalence Hypotheses:	H0U: $(\mu_T - \mu_P) / (\mu_R - \mu_P) \ge E_U$ vs. H1U: $(\mu_T - \mu_P) / (\mu_R - \mu_P) < E_U$, Alpha = α2

	Sample Size				Means	Ratio of Mean Differences: Equivalence Limits				Alpha	
Power	n_T	n_R	n_P	N	$\mu_T \mid \mu_R \mid \mu_P$	Lower E_L	Upper E_U	Actual E_A	Standard Deviation σ	One-Sided α1	Equivalence α2
0.728	20	20	20	60	63 | 63 | 43	0.8	1.25	1	5	0.025	0.05
0.848	25	25	25	75	63 | 63 | 43	0.8	1.25	1	5	0.025	0.05
0.915	30	30	30	90	63 | 63 | 43	0.8	1.25	1	5	0.025	0.05

Simulations: 5000. Run Time: 14.62 seconds. Random Normal Method: Box - Muller.
User-Entered Random Seed: 5567949

Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
n_T	The sample size of the treatment group.
n_R	The sample size of the reference (control) group.
n_P	The sample size of the placebo group.
N	The total sample size of the trial.
$\mu_T \mid \mu_R \mid \mu_P$	The means of the treatment, reference, and control groups, respectively. The power is calculated assuming these values.
E_L	The lower equivalence boundary of the ratio of mean differences, $(\mu_T - \mu_P) / (\mu_R - \mu_P)$.
E_U	The upper equivalence boundary of the ratio of mean differences, $(\mu_T - \mu_P) / (\mu_R - \mu_P)$.
E_A	The ratio of the mean differences assumed by the alternative hypothesis. That is, $E_A = (\mu_T - \mu_P) / (\mu_R - \mu_P)$.
σ	The common standard deviation of all the groups.
α1	The probability of rejecting a one-sided test.
α2	The probability of rejecting the equivalence test.

Summary Statements

A parallel three-group (treatment, reference, placebo) design will be used to test whether the treatment mean is superior to the placebo mean and equivalent to the reference mean using Chang, Tsong, Dong, and Zhao (2014) method C. In this method, the treatment is first compared to the placebo using a one-sided t-test (H0s: $\mu_T - \mu_P \le 0$ versus H1s: $\mu_T - \mu_P > 0$), with a Type I error rate (α) of 0.025. If this hypothesis is rejected, a second (equivalence) test is run using two one-sided t-tests of the ratio of the mean differences, involving all 3 means (H0: $(\mu_T - \mu_P) / (\mu_R - \mu_P) \le 0.8$ or $(\mu_T - \mu_P) / (\mu_R - \mu_P) \ge 1.25$ versus H1: $0.8 < (\mu_T - \mu_P) / (\mu_R - \mu_P) < 1.25$), with each one-sided test having a Type I error rate (α) of 0.05 (corresponding to an overall equivalence test Type I error rate (α) of 0.05). The group means are assumed to be 63 (treatment), 63 (reference), and 43 (placebo). The standard deviation for each of the three groups is assumed to be 5. To detect a mean difference ratio, $(\mu_T - \mu_P) / (\mu_R - \mu_P)$, of 1, with sample sizes of 20 for Group 1 (treatment), 20 for Group 2 (reference), and 20 for Group 3 (placebo), the power is 0.728. These results are based on 5000 simulations (Monte Carlo samples).

Dropout-Inflated Sample Size

Group	Dropout Rate	Sample Size ni	Dropout-Inflated Enrollment Sample Size ni'	Expected Number of Dropouts Di
1 - 3	20%	20	25	5
Total		60	75	15
1 - 3	20%	25	32	7
Total		75	96	21
1 - 3	20%	30	38	8
Total		90	114	24

Group	Lists the group numbers.
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.
ni	The evaluable sample size for each group at which power is computed (as entered by the user). If ni subjects are evaluated out of the ni' subjects that are enrolled in the study, the design will achieve the stated power.
ni'	The number of subjects that should be enrolled in each group in order to obtain ni evaluable subjects, based on the assumed dropout rate. ni' is calculated by inflating ni using the formula ni' = ni / (1 - DR), with ni' 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.)
Di	The expected number of dropouts in each group. Di = ni' - ni.

Dropout Summary Statements

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

References

Chang,Y.W., Tsong, Y., Dong, X., Zhao, Z. 2014. 'Sample size determination for a three-arm equivalence trial of normally distributed responses.' Journal of Biopharmaceutical Statistics. Volume 24, Pages 1190-1202.

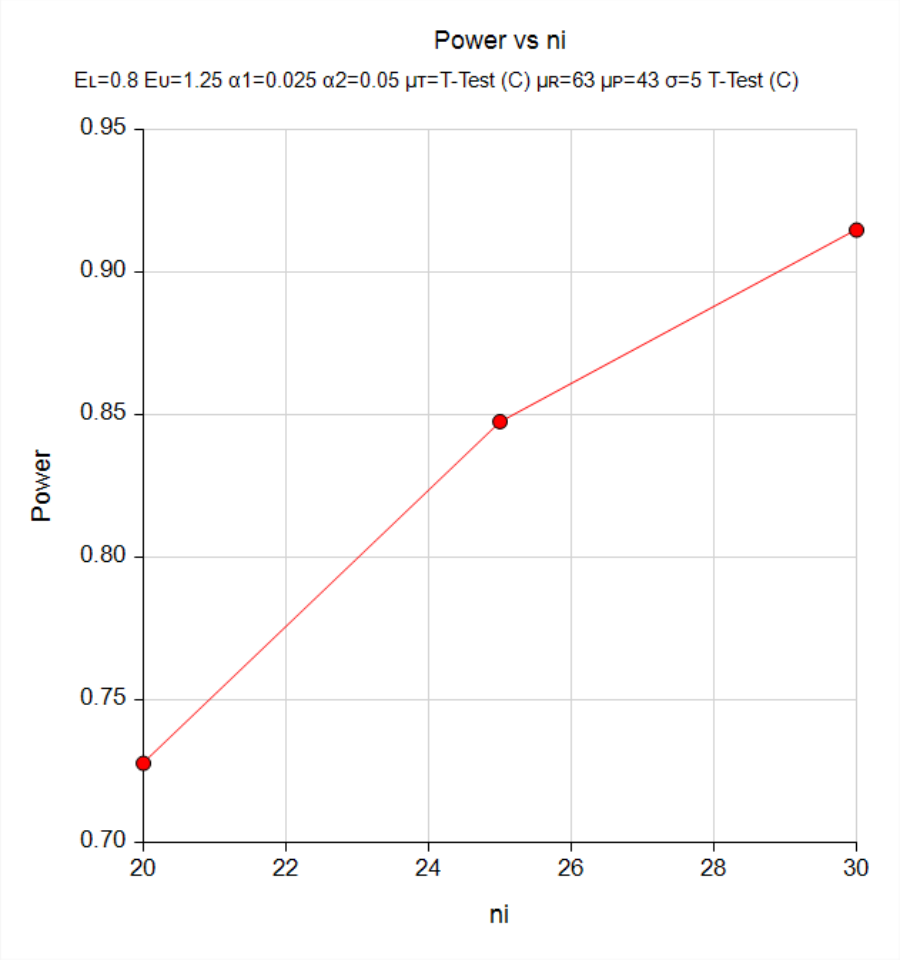
Blackwelder, W.C. 1998. 'Equivalence Trials.' In Encyclopedia of Biostatistics, John Wiley and Sons. New York. Volume 2, 1367-1372.

Devroye, Luc. 1986. Non-Uniform Random Variate Generation. Springer-Verlag. New York.

This report shows the estimated power for each group sample size.

Plots Section

Plots



This plot presents the power for the various sample sizes.

Example 2 – Validation using Chang et al. (2014)

Chang *et al.* (2014) presents several tables of results for power and sample size procedures. We will use the second row of Table 4, page 1200, as the validation result for this procedure.

In this table, the average response level to the reference drug is approximately 10 with a standard deviation of 3 in all groups. The response at the placebo is 0. They want to investigate the power when the treatment response is also 10.

The (C) method is used for the analysis of the results. The equivalence boundaries are 0.8 and 1.25. The significance levels are 0.025 for the first test and 0.05 for the equivalence test. The power is to be 80%. The number of simulations is 5000.

The resulting group sample size is 33.

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**
Testing Procedure	**Chang (C): Equivalence of Mean Difference Ratio after Treatment Efficacy**
Test Type	**T-Test Assuming Equal Variances**
Simulations	**5000**
Random Seed	**4638088 (for reproducibility)**
Power	**0.8**
α1 (One-Sided Alpha)	**0.025**
α2 (Equivalence Alpha)	**0.05**
Group Allocation Input Type	**Equal Allocation ($A_T = A_R = A_P$)**
μ_T (Treatment Group Mean)	**10**
μ_R (Reference Group Mean)	**10**
μ_P (Placebo Group Mean)	**0**
σ Input Type	**Equal ($\sigma_T = \sigma_R = \sigma_P = \sigma$)**
σ (Group Standard Deviation)	**3**
E_L (Lower Equiv Limit)	**0.8**
E_U (Upper Equiv Limit)	**1.25**

Options Tab	
Random Normal Method	**Box - Muller**
Maximum N Before Search Termination	**5000**

Output

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

Numeric Results

Solve For:	Sample Size
Groups:	T = Treatment, R = Reference, P = Placebo
Testing Procedure:	Chang Test (C): Equivalence of Mean Difference Ratio after Treatment Efficacy
Test Type:	T-Test Assuming Equal Variances
Treatment Efficacy Hypotheses:	H0s: $\mu_T - \mu_P \le 0$ vs. H1s: $\mu_T - \mu_P > 0$, Alpha = α1
Lower Equivalence Hypotheses:	H0L: $(\mu_T - \mu_P) / (\mu_R - \mu_P) \le E_L$ vs. H1L: $(\mu_T - \mu_P) / (\mu_R - \mu_P) > E_L$, Alpha = α2
Upper Equivalence Hypotheses:	H0U: $(\mu_T - \mu_P) / (\mu_R - \mu_P) \ge E_U$ vs. H1U: $(\mu_T - \mu_P) / (\mu_R - \mu_P) < E_U$, Alpha = α2

					Ratio of Mean Differences					
	Sample Size				Means	Equivalence Limits				Alpha	
Power	n_T	n_R	n_P	N	μ_T | μ_R | μ_P	Lower E_L	Upper E_U	Actual E_A	Standard Deviation σ	One-Sided α1	Equivalence α2
0.804	33	33	33	99	10 | 10 | 0	0.8	1.25	1	3	0.025	0.05

Simulations: 5000. Run Time: 72.84 seconds. Random Normal Method: Box - Muller.
User-Entered Random Seed: 4638088

PASS also finds the sample size to be 33 per group.