

## Chapter 682

# Sample Size of a Pilot Study using the Non-Central t to Allow for Uncertainty in the SD

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## Introduction

This routine obtains the sample size of an external pilot study by minimizing the combined sample size of both the pilot study and the main study. The sample size of the main study is estimated using a formula, based on the non-central t-distribution (NCT), that allows for imprecision in the estimated variance.

There is a trade-off. As the pilot study size is increased, the main study size based on the NCT is decreased. There is usually a pilot size that minimizes the total sample size.

Julious and Owen (2006) presented the original work on this technique. Whitehead *et al.* (2016) present further details. Note that this paper also presents an alternative algorithm based on the upper confidence limit of the standard deviation that is much more conservative than this method. This alternative method is also available in PASS. Machin *et al.* (2018) present additional details and sample size tables.

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## Technical Details

### NCT Approach to Allow for Imprecision in $\sigma$

Suppose a pilot study results in an estimate  $s_{Pilot}$  of  $\sigma$  that is based on  $df$  degree of freedom. In a two-group trial,  $df = N1 + N2 - 2 = N_{PILOT} - 2$ . This routine calculates the main trial size using

$$N_{MAIN} = \frac{(R + 1)^2}{R} \frac{\theta^2}{\left(\frac{\delta}{s_{Pilot}}\right)^2}$$

where  $\theta = \text{NCT}\left(1 - \beta, df, t_{1-\frac{\alpha}{2}, N_{MAIN}-2}\right)$  and  $\text{NCT}(x, f, nc)$  is a cumulative non-central t-distribution with  $f$  degrees of freedom and noncentrality  $nc$ . Since  $N_{MAIN}$  occurs on both sides of the above equation, it must be solved for by iteration. The algorithm begins with  $\theta_0 = \text{NCT}\left(1 - \beta, df, z_{1-\frac{\alpha}{2}}\right)$  and iterates until there is little change in  $N_{MAIN}$ .

## Sample Size of a Pilot Study using the Non-Central t to Allow for Uncertainty in the SD

The overall trial size is given by  $N_{TOTAL} = N_{PILOT} + N_{MAIN}$ .  $N_{TOTAL}$  can be minimized by a brute-force search of values of  $N_{PILOT}$ , beginning at 3. This gives an optimum value of the sample size of the pilot study.

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## Procedure Options

This section describes the options that are specific to this procedure. These are located on the Design tab. For more information about the options of other tabs, go to the Procedure Window chapter.

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## Design Tab

The Design tab contains most of the parameters and options that you will be concerned with.

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### Solve For

#### Solve For

This option specifies the parameter to be solved for from the other parameters.

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### Pilot Study

#### **$N_{PILOT}$ (Pilot Sample Size)**

Enter one or more values of the confidence level percentage. Usually, this value is set at 80, 90, or 95. Enter one or more values for the sample size of the pilot study ( $N_{PILOT}$ ). This is the total number of subjects in the two groups of the pilot study. This value will be used to estimate the combined sample size of the pilot study and the main study. That is, to calculate  $N_{TOTAL} = N_{PILOT} + N_{MAIN}$ .

You can enter any value  $> 2$ . Usually, a value between 10 and 300 is used. One study of clinical trials using means found the median pilot study size to be 30.

You may enter a single value such as '24', a range of values such as '20 to 60 by 2', or a list of values such as '10 30 80 90'.

#### **s (SD Anticipated from Pilot Study)**

Enter an estimate of the standard deviation to be obtained in the pilot study. Use the best estimate of  $\sigma$  that you have available before the pilot study is conducted.

The range is any value greater than zero. If you want to use standardized values for the effect size, enter a '1' here and use a standardized effect size (less than one) for  $\delta$ .

You can enter a single value such as '2' or a series of values such as '1 2 3' or '1 to 10 by 1'.

Press the  $\sigma$  button to load the Standard Deviation Estimator window.

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### Main Study

#### **Power of Main Study**

This is the power of the test used in the main study. It does not apply to the pilot study.

Power is the probability of rejecting the null hypothesis when it is false. Power is equal to  $1 - \text{Beta}$ , so specifying power implicitly specifies beta.

Beta is the probability of obtaining a false negative with the statistical test. That is, it is the probability of accepting a false null hypothesis.

The valid range is 0 to 1. Usually, the chosen power is between 0.8 and 0.99.

## Sample Size of a Pilot Study using the Non-Central t to Allow for Uncertainty in the SD

Different disciplines have different standards for setting power. The most common choice is 0.90, but 0.80 is also popular.

You can enter a single value such as 0.90 or a series of values such as 0.70 0.80 0.90 or 0.70 to 0.90 by 0.05.

When a series of values is entered, PASS will generate a separate calculation result for each value of the series.

### Alpha of Main Study

This is the alpha (significance level) of the test used in the main study. It does not apply to the pilot study.

Alpha is the probability of obtaining a false positive with the statistical test. That is, it is the probability of rejecting a true null hypothesis.

The null hypothesis is usually that the parameters of interest (means, proportions, etc.) are equal.

Since Alpha is a probability, it is bounded by 0 and 1. Commonly, it is between 0.001 and 0.10. Alpha is often set to 0.05 for two-sided tests and to 0.025 for one-sided tests.

You can enter a single value such as 0.05 or a series of values such as 0.05 0.10 0.15 or 0.05 to 0.15 by 0.01.

When a series of values is entered, PASS will generate a separate calculation result for each value of the series.

### R (Allocation Ratio in Main Study)

Enter one or more values of the allocation ratio ( $N1 / N2$ ) of the sample sizes of the groups in the main study. The pilot study is assumed to have equal group sizes.

R must be positive. Usually, R is between 0.2 and 5 with '1' being by far the most frequently used value.

An R of one (equal group sizes) will result in the smallest sample sizes.

### $\delta$ (Mean Difference in Main Study)

Enter the detectable difference ( $\delta = \mu1 - \mu2$ ) to be used in the main study. This parameter is not used in the pilot study. Note that the scale of this value must match the scale of the standard deviation.

The range of this parameter is any value other than 0.

If you want to use standardized values for the effect size, enter a '1' for s and use a standardized effect size (less than one) for  $\delta$ .

Cohen (1988) gave the following interpretation of  $d = \delta/\sigma$  values that is still common: small 0.2, medium 0.5, and large 0.8.

You can enter a single value such as 0.5 or a series of values such as 0.2 0.5 0.8 or 0.2 to 1 by 0.1.

## Sample Size of a Pilot Study using the Non-Central t to Allow for Uncertainty in the SD

**Example 1 – Calculating the pilot study sample size**

Suppose you want to find appropriate pilot study sample sizes when  $s = 1$ , power = 0.8, alpha = 0.05,  $R = 1$ , and  $\delta = 0.2$  to 1.0.

**Setup**

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Sample Size of a Pilot Study using the Non-Central t to Allow for Uncertainty in the SD** procedure. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu of the procedure window and choosing **Open Example Template**.

**Option****Value****Design Tab**

Solve For ..... **NPILOT (Pilot Sample Size)**  
 s (SD Anticipated from Pilot Study) ..... **1**  
 Power of Main Study..... **0.80**  
 Alpha of Main Study..... **0.05**  
 R (Allocation Ratio in Main Study)..... **1.0**  
 $\delta$  (Mean Difference in Main Study) ..... **0.2 to 1 by 0.2**

**Annotated Output**

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

**Numeric Results****Numeric Results**

	Pilot Study Sample Size	Main Study Sample Size	Total Sample Size	Alloc Ratio N1/N2	Power	Alpha	Pilot Standard Deviation
$\delta$	NPILOT	NMAIN	NTOTAL	R			s
0.20	39	821.5	860.5	1.000	0.800	0.050	1.00
0.40	21	216.3	237.3	1.000	0.800	0.050	1.00
0.60	15	101.2	116.2	1.000	0.800	0.050	1.00
0.80	12	60.1	72.1	1.000	0.800	0.050	1.00
1.00	10	40.8	50.8	1.000	0.800	0.050	1.00

**Report Definitions**

$\delta = \mu_1 - \mu_2$  is the difference between the means. It is used to calculate the effect size ( $\delta/\sigma$ ).

NPILOT is the total sample size of the pilot study. This is what is being determined by this procedure.

NMAIN is the estimated total sample size of the main study.

NTOTAL is the estimated combined sample size (NPILOT + NMAIN) of the both the pilot and the main study.

R is the allocation ratio of the two groups being compared by the study.  $R = N1/N2$ .

Power is the probability of rejecting a false null hypothesis planned to be used in the main study.

Alpha is the probability of rejecting a true null hypothesis planned to be used in the main study.

s is the standard deviation to be used for planning before the pilot study.

**References**

Julious, S.A. and Owen, R.J. 2006. 'Sample size calculations for clinical studies allowing for uncertainty about the variance'. Pharmaceutical Statistics. Vol 5. Pages 29-37.

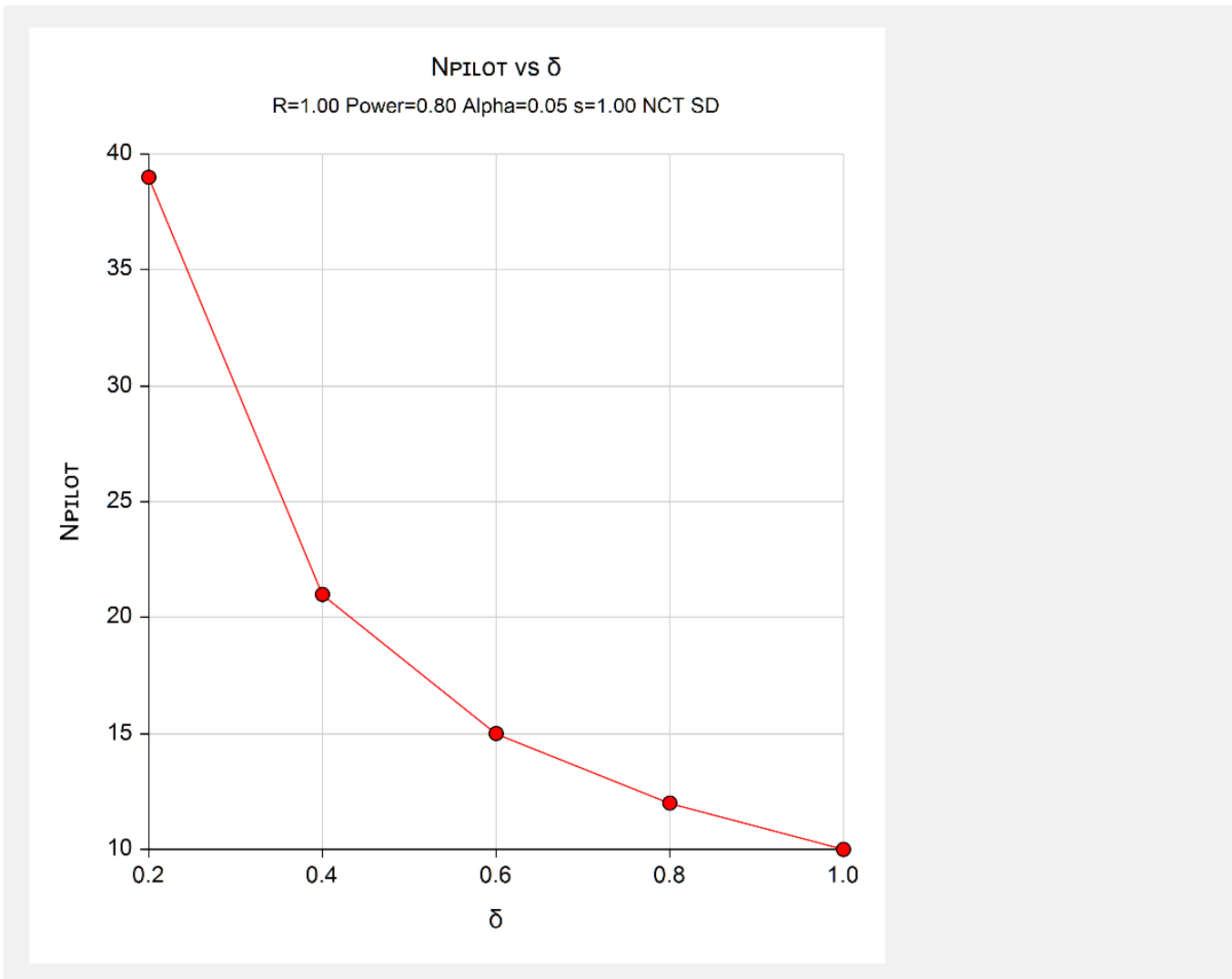
Whitehead, A.L., Julious, S, Cooper, C.L., Campbell, M.J. 2016. 'Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable'. Stat Meth Med Res. Vol 25(3). Pages 1057-1073.

Machin, D, Campbell, M.J., Tan, S.B, Tan, S.H. 2018. 'Sample Sizes for Clinical, Laboratory and Epidemiology Studies, Fourth Edition'. John Wiley and Sons. Hoboken, New Jersey.

**Sample Size of a Pilot Study using the Non-Central t to Allow for Uncertainty in the SD****Summary Statements**

The optimum pilot sample size is 39 is anticipated to result in a total combined sample size in both the pilot and the main studies of 860.5. This is based on an adjustment for the imprecision of the estimate of  $\sigma$  using the non-central t (NCT) distribution. The power set to 0.800, the significance level (alpha) set to 0.050, the allocation ratio set to 1.000, the pilot standard deviation set to 1.00, and the detectable mean difference,  $\delta$ , set to 0.20.

This report shows the calculated multiple for each of the scenarios.

**Plots Section**

This plot shows the various values of the pilot sample size for various values of the detectable difference.

## Example 2 – Validation using Machin *et al.* (2018)

Machin *et al.* (2018) page 267 give Table 16.5 which contains pilot sample sizes for various scenarios. We will duplicate the last section of this table as a validation example. In this example  $s = 1$ , power = 0.8, alpha = 0.05,  $R = 1$ , and  $\delta = 0.05, 0.1, 0.2, 0.3, 0.4, 0.5$ . The corresponding pilot study sample sizes are 148, 76, 40, 28, 22, 20. Note that the 148 is a correction of a typo in which the value is incorrectly given as 188. The typo can be seen by referring to Whitehead *et al.* (2016) page 1065 since Machin's Table 16.5 is a reproduction of Whitehead's Table 5.

### Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Sample Size of a Pilot Study using the Non-Central t to Allow for Uncertainty in the SD** procedure. You may then make the appropriate entries as listed below, or open **Example 2** by going to the **File** menu of the procedure window and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
<b>Design Tab</b>	
Solve For .....	<b>NPILOT (Pilot Sample Size)</b>
s (SD Anticipated from Pilot Study) .....	<b>1</b>
Power of Main Study.....	<b>0.80</b>
Alpha of Main Study.....	<b>0.05</b>
R (Allocation Ratio in Main Study).....	<b>1.0</b>
$\delta$ (Mean Difference in Main Study).....	<b>0.05 0.1 0.2 0.3 0.4 0.5</b>

### Output

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

#### Numeric Results

Numeric Results							
$\delta$	Pilot Study Sample Size NPILOT	Main Study Sample Size NMAIN	Total Sample Size NTOTAL	Alloc Ratio N1/N2 R	Power	Alpha	Pilot Standard Deviation s
0.05	148	12703.7	12851.7	1.000	0.800	0.050	1.00
0.10	76	3211.8	3287.8	1.000	0.800	0.050	1.00
0.20	39	821.5	860.5	1.000	0.800	0.050	1.00
0.30	27	375.0	402.0	1.000	0.800	0.050	1.00
0.40	21	216.3	237.3	1.000	0.800	0.050	1.00
0.50	18	141.5	159.5	1.000	0.800	0.050	1.00

PASS matches the pilot sample sizes to within rounding.

## Example 3 – Calculating the total sample size for various pilot study sample sizes

Suppose you want to see the total sample sizes for various pilot study sample sizes when  $s = 1$ , power = 0.8, alpha = 0.05,  $R = 1$ ,  $\delta = 0.5$ , and  $N_{\text{PILOT}} = 6$  to 40. Since we are interested in equal-group sizes, we will only consider even pilot sizes.

### Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Sample Size of a Pilot Study using the Non-Central t to Allow for Uncertainty in the SD** procedure. You may then make the appropriate entries as listed below, or open **Example 3** by going to the **File** menu of the procedure window and choosing **Open Example Template**.

#### Design Tab

Solve For ..... **NTOTAL (NPILOT + NMAIN)**  
 $N_{\text{PILOT}}$  (Pilot Sample Size) ..... **6 to 40 by 2**  
 $s$  (SD Anticipated from Pilot Study) ..... **1**  
 Power of Main Study..... **0.80**  
 Alpha of Main Study..... **0.05**  
 $R$  (Allocation Ratio in Main Study)..... **1.0**  
 $\delta$  (Mean Difference in Main Study)..... **0.5**

### Output

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

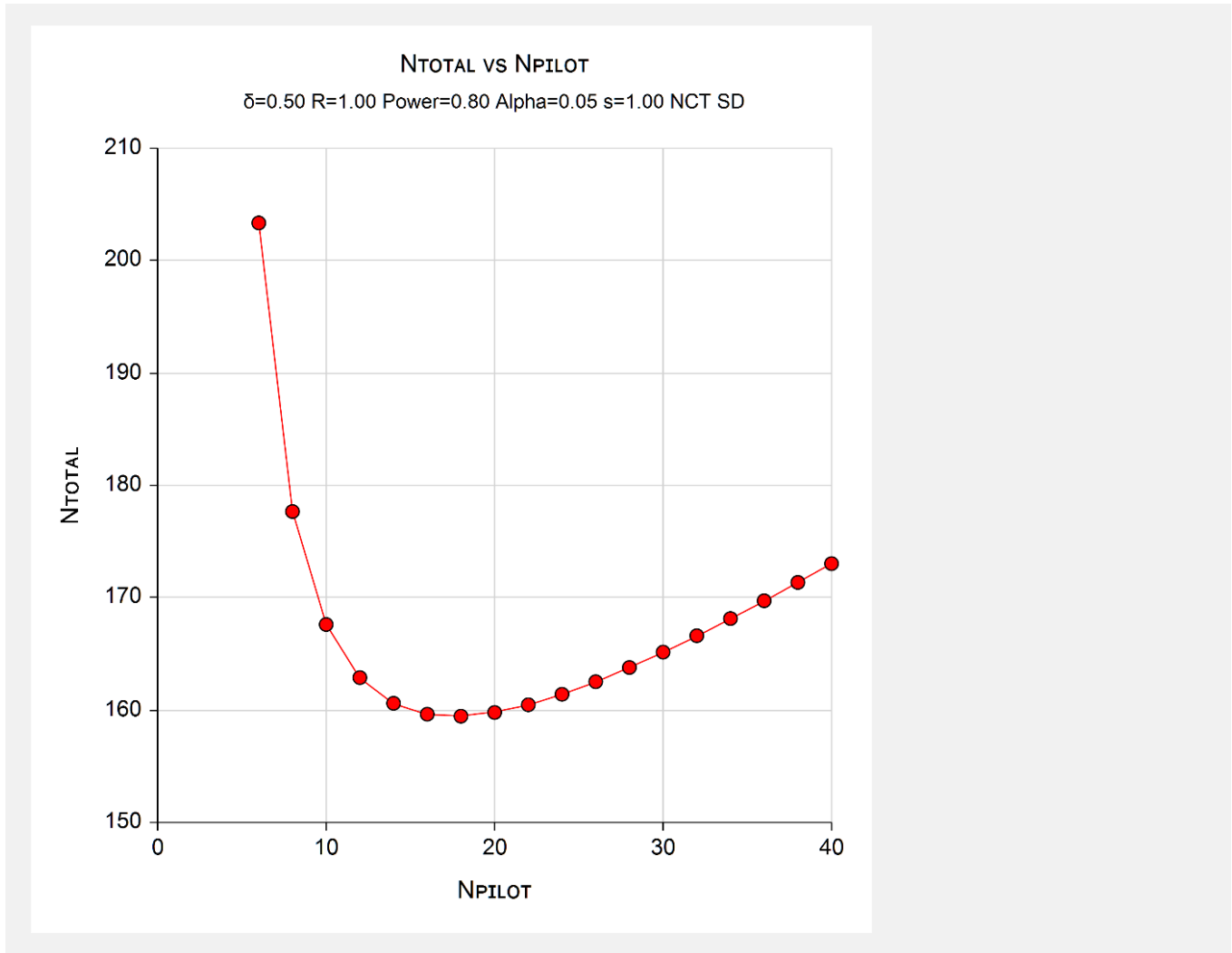
#### Numeric Results

Numeric Results							
$\delta$	Pilot Study Sample Size $N_{\text{PILOT}}$	Main Study Sample Size $N_{\text{MAIN}}$	Total Sample Size $N_{\text{TOTAL}}$	Alloc Ratio $N1/N2$ $R$	Power	Alpha	Pilot Standard Deviation $s$
0.50	6	197.4	203.4	1.000	0.800	0.050	1.00
0.50	8	169.7	177.7	1.000	0.800	0.050	1.00
0.50	10	157.6	167.6	1.000	0.800	0.050	1.00
0.50	12	150.9	162.9	1.000	0.800	0.050	1.00
0.50	14	146.6	160.6	1.000	0.800	0.050	1.00
0.50	16	143.6	159.6	1.000	0.800	0.050	1.00
<b>0.50</b>	<b>18</b>	<b>141.5</b>	<b>159.5</b>	<b>1.000</b>	<b>0.800</b>	<b>0.050</b>	<b>1.00</b>
0.50	20	139.8	159.8	1.000	0.800	0.050	1.00
0.50	22	138.5	160.5	1.000	0.800	0.050	1.00
0.50	24	137.4	161.4	1.000	0.800	0.050	1.00
0.50	26	136.5	162.5	1.000	0.800	0.050	1.00
0.50	28	135.8	163.8	1.000	0.800	0.050	1.00
0.50	30	135.2	165.2	1.000	0.800	0.050	1.00
0.50	32	134.6	166.6	1.000	0.800	0.050	1.00
0.50	34	134.1	168.1	1.000	0.800	0.050	1.00
0.50	36	133.7	169.7	1.000	0.800	0.050	1.00
0.50	38	133.4	171.4	1.000	0.800	0.050	1.00
0.50	40	133.0	173.0	1.000	0.800	0.050	1.00

This report shows the estimated total sample size for each value of the pilot sample size. Note that the total sample size is a minimum of 159.5 when the pilot sample size is 18. If you refer back to Example 2, you will see that the optimum pilot size for  $\delta = 0.5$  is indeed 18.

Sample Size of a Pilot Study using the Non-Central t to Allow for Uncertainty in the SD

Plots Section



This plot shows the various values of the sample sizes.