

Chapter 681

Sample Size of a Pilot Study using the Upper Confidence Limit of the SD

Introduction

This routine obtains the sample size of an external pilot study by trying to minimize the combined sample size of both the pilot study and the main study. The sample size of the main study is estimated using an upper confidence limit (UCL) of σ calculated from the pilot data.

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

Browne (1995), Kieser and Wassmer (1996), and Machin *et al.* (2018) point out that using the standard deviation from a small pilot study directly in sample size calculations tends to result in under-powered studies. They indicate that if s is replaced by s_{UCL} , where s_{UCL} is the 100 γ % upper confidence limit of s , before the sample size calculations are made, the probability that the planned power of the main trial is achieved is about γ . Whitehead *et al.* (2016) outlines an algorithm to determine the optimum value of the pilot study. Note that this paper also presents an alternative algorithm based on the non-central t distribution that results in much smaller sample sizes. This other algorithm is also available in **PASS**.

Technical Details

Upper Confidence Limit (UCL) of σ

Suppose a pilot study results in an estimate s_{Pilot} of σ . The 100 γ % UCL is given by

$$UCL(\gamma, df) = \sqrt{\frac{df}{\chi^2(1 - \gamma, df)}} s_{Pilot} = M s_{Pilot}$$

where df is the degrees of freedom of s_{Pilot} and $\chi^2(1 - \gamma, df)$ is the $1 - \gamma$ percentile of the Chi-squared distribution with df degrees of freedom. In a two-group trial, $df = N1 + N2 - 2 = N_{PILOT} - 2$.

Thus, the estimate of σ that is used in the sample size calculation of the main trial is given by inflating the standard deviation obtained from the pilot study by the inflation factor M .

Machin *et al.* (2016) provide a common approximation for the determining the sample size of the main trial.

$$N_{MAIN} = \frac{(R + 1)^2 \left(z_{1-\beta} + z_{1-\frac{\alpha}{2}} \right)^2}{R \left(\frac{\delta}{M s_{Pilot}} \right)^2} + \left\lceil \frac{z_{1-\frac{\alpha}{2}}^2}{2} \right\rceil$$

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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.

Example 1 – Calculating the Pilot Study Sample Size

Suppose you want to find appropriate pilot study sample sizes when $s = 1$, $CL = 80$, power = 0.8, $\alpha = 0.05$, $R = 1$, and $\delta = 0.2$ to 1.0.

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 **NPILOT (Pilot Sample Size)**
 s (SD Anticipated from Pilot Study)..... **1**
 CL (Confidence Level of UCL of σ)..... **80**
 Power of Main Study..... **0.80**
 Alpha of Main Study..... **0.05**
 R (Allocation Ratio in Main Study) **1.0**
 δ (Mean Difference in Main Study) **0.2 to 1 by 0.2**

Output

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

Numeric Reports

Numeric Results

Solve For: **NPILOT (Pilot Sample Size)**

Pilot Study

Confidence Level of UCL of σ CL	Sample Size NPILOT	Standard Deviation		Power	Main Study			Total Combined Sample Size NTOTAL	
		Anticipated s	Inflation Factor M		Sample Size NMAIN	Allocation Ratio R	Mean Difference δ		Alpha
80	77	1	1.078	0.8	912.0	1	0.2	0.05	989.0
80	35	1	1.126	0.8	248.6	1	0.4	0.05	283.6
80	23	1	1.166	0.8	118.6	1	0.6	0.05	141.6
80	18	1	1.198	0.8	70.4	1	0.8	0.05	88.4
80	14	1	1.240	0.8	48.3	1	1.0	0.05	62.3

CL The confidence level (percentage) of the one-sided confidence interval for the standard deviation from the pilot study.
 NPILOT The total sample size of the pilot study. This is what is being determined by this procedure.
 s The standard deviation to be used for planning before the pilot study.
 M The multiplier to inflate s to its UCL for use as an estimate of σ in the main trial planning.
 Power The probability of rejecting a false null hypothesis planned to be used in the main study.
 NMAIN The estimated total sample size of the main study. $N_{MAIN} = N_1 + N_2$.
 R The allocation ratio of the two groups being compared by the study. $R = N_1 / N_2$.
 δ The difference between the means. It is used to calculate the effect size (δ / σ). $\delta = \mu_1 - \mu_2$.
 Alpha The probability of rejecting a true null hypothesis planned to be used in the main study.
 NTOTAL The estimated combined sample size of the both the pilot and the main study. $N_{TOTAL} = N_{PILOT} + N_{MAIN}$.

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Summary Statements

A pilot study will be used in conjunction with a main study for the purpose of comparing the means of two groups. In part, the pilot study will be used to identify an appropriate upper limit standard deviation estimate to avoid under-powering the main study. The Type I error rate (α) of the main study will be 0.05. The anticipated standard deviation estimate from the pilot study is 1, and the confidence level for the upper confidence limit of the standard deviation will be 80%. To detect a mean difference of 0.2 in the main study with 80% power, the optimum pilot study sample size is 77 and the total combined sample size in both the pilot and the main studies is 989 (with 912 total subjects in the main study, with an assumed allocation ratio in the main study, $R = N1 / N2$, of 1).

Dropout-Inflated Sample Size

Dropout Rate	Sample Size N _{PILOT}	Dropout- Inflated Enrollment Sample Size N _{PILOT} '	Expected Number of Dropouts D
20%	77	97	20
20%	35	44	9
20%	23	29	6
20%	18	23	5
20%	14	18	4

Dropout Rate	The percentage of subjects (or items) that are expected to be lost at random during the course of the study and for whom no response data will be collected (i.e., will be treated as "missing"). Abbreviated as DR.
N _{PILOT}	The evaluable sample size at which power is computed. If N _{PILOT} subjects are evaluated out of the N _{PILOT} ' subjects that are enrolled in the study, the design will achieve the stated power.
N _{PILOT} '	The total number of subjects that should be enrolled in the study in order to obtain N _{PILOT} evaluable subjects, based on the assumed dropout rate. After solving for N _{PILOT} , N _{PILOT} ' is calculated by inflating N _{PILOT} using the formula $N_{PILOT}' = N_{PILOT} / (1 - DR)$, with N _{PILOT} ' always rounded up. (See Julious, S.A. (2010) pages 52-53, or Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. (2018) pages 32-33.)
D	The expected number of dropouts. $D = N_{PILOT}' - N_{PILOT}$.

Dropout Summary Statements

Anticipating a 20% dropout rate, 97 subjects should be enrolled to obtain a final sample size of 77 subjects.

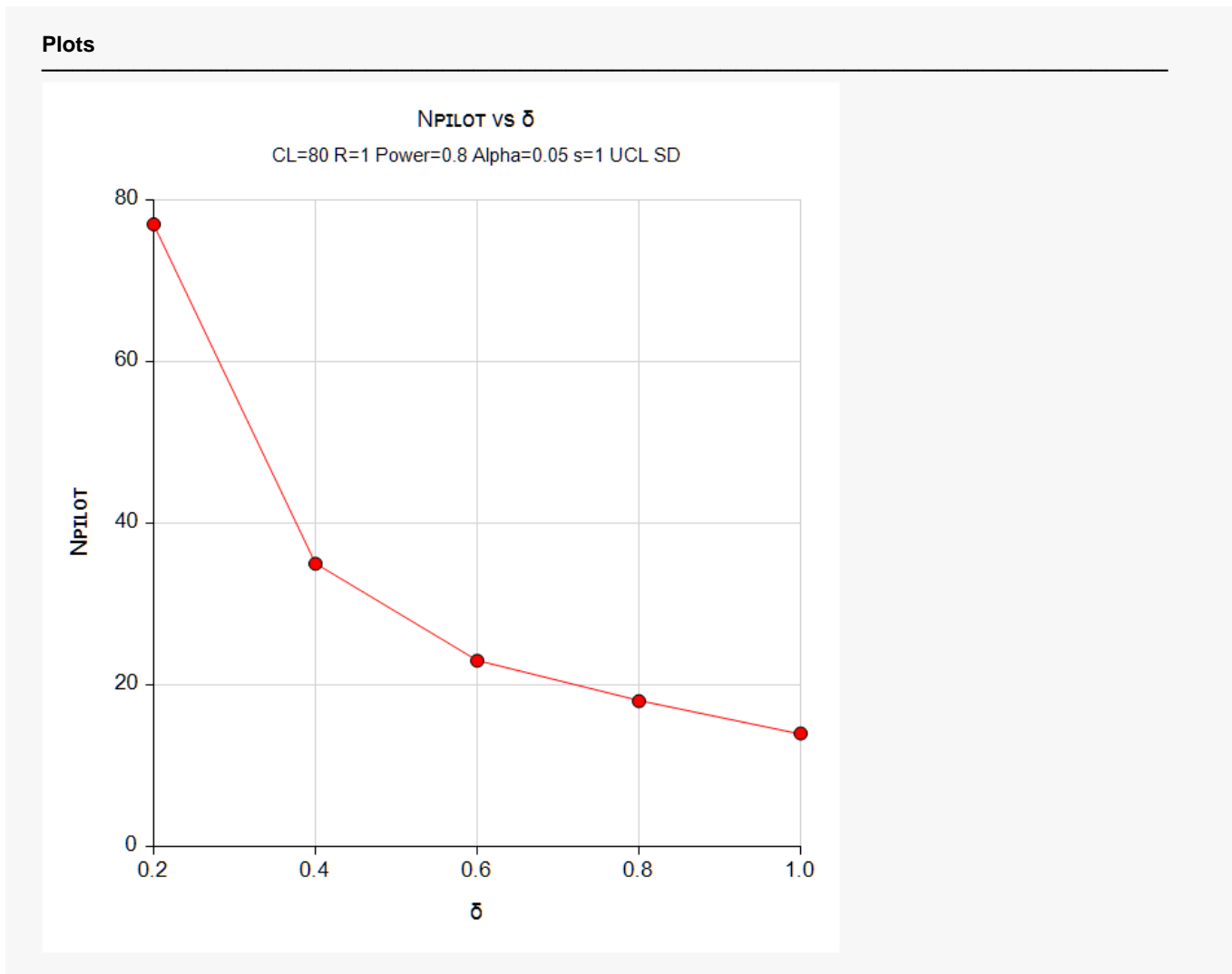
References

- Browne, R.H. 1995. 'On the use of a pilot sample for sample size determination'. Stat Med. Vol 14. Pages 1933-1940.
- 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.

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

Sample Size of a Pilot Study using the Upper Confidence Limit of the SD

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 first column of this table as a validation example. In this example $s = 1$, $CL = 80$, power = 0.8, $\alpha = 0.05$, $R = 1$, and $\delta = 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.00$. The corresponding pilot study sample sizes are 420, 176, 78, 48, 36, 28, 24, 20, 18, 16, 14. Note that the last three values are from Whitehead *et al.* (2016) page 1065 since Table 16.5 is reset 20 for sample sizes less than 20.

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 **N_{PILOT} (Pilot Sample Size)**
 s (SD Anticipated from Pilot Study)..... **1**
 CL (Confidence Level of UCL of σ)..... **80**
 Power of Main Study..... **0.80**
 Alpha of Main Study..... **0.05**
 R (Allocation Ratio in Main Study) **1.0**
 δ (Mean Difference in Main Study) **0.05 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1**

Output

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

Numeric Results

Solve For: **N_{PILOT} (Pilot Sample Size)**

Pilot Study

Confidence Level of UCL of σ CL	Sample Size N _{PILOT}	Standard Deviation		Power	Main Study			Alpha	Total Combined Sample Size N _{TOTAL}
		Anticipated s	Inflation Factor M		Sample Size N _{MAIN}	Allocation Ratio R	Mean Difference δ		
80	420	1	1.031	0.8	13340.4	1	0.05	0.05	13760.4
80	176	1	1.049	0.8	3454.5	1	0.10	0.05	3630.5
80	77	1	1.078	0.8	912.0	1	0.20	0.05	989.0
80	48	1	1.103	0.8	424.6	1	0.30	0.05	472.6
80	35	1	1.126	0.8	248.6	1	0.40	0.05	283.6
80	28	1	1.145	0.8	164.7	1	0.50	0.05	192.7
80	23	1	1.166	0.8	118.6	1	0.60	0.05	141.6
80	20	1	1.183	0.8	89.7	1	0.70	0.05	109.7
80	18	1	1.198	0.8	70.4	1	0.80	0.05	88.4
80	16	1	1.216	0.8	57.3	1	0.90	0.05	73.3
80	14	1	1.240	0.8	48.3	1	1.00	0.05	62.3

PASS matches the first column 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 $s = 1$, $CL = 80$, $\text{power} = 0.8$, $\alpha = 0.05$, $R = 1$, $\delta = 0.5$, and $N_{\text{PILOT}} = 6$ to 50 .

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	NTOTAL (NPILOT + NMAIN)
NPILOT (Pilot Sample Size).....	6 to 50 by 2
s (SD Anticipated from Pilot Study).....	1
CL (Confidence Level of UCL of σ).....	80
Power of Main Study.....	0.80
Alpha of Main Study.....	0.05
R (Allocation Ratio in Main Study)	1.0
δ (Mean Difference in Main Study)	0.5

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Output

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

Numeric Reports

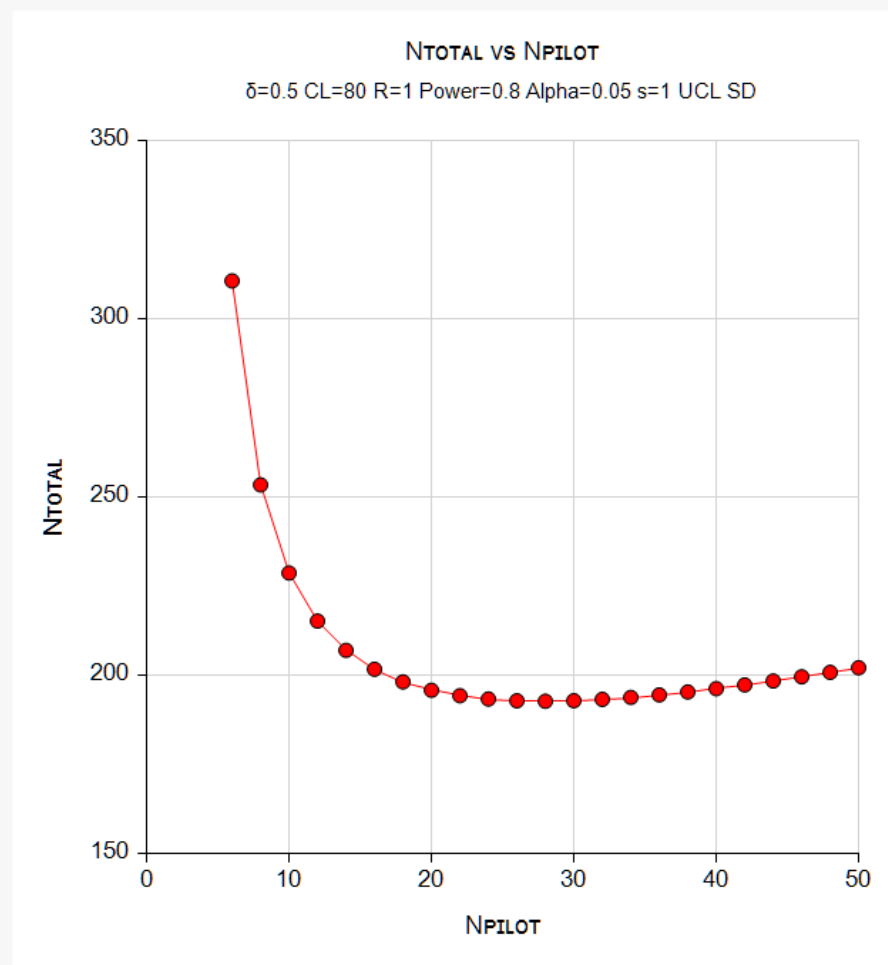
Numeric Results										
Solve For: $N_{TOTAL} (N_{PILOT} + N_{MAIN})$										
Pilot Study				Main Study					Total Combined Sample Size	
Confidence Level of UCL of σ CL	Sample Size N_{PILOT}	Standard Deviation		Power	Sample Size N_{MAIN}	Allocation Ratio R	Mean Difference δ	Alpha	Total Combined Sample Size N_{TOTAL}	
		Anticipated s	Inflation Factor M							
80	6	1	1.558	0.8	304.7	1	0.5	0.05	310.7	
80	8	1	1.398	0.8	245.4	1	0.5	0.05	253.4	
80	10	1	1.320	0.8	218.7	1	0.5	0.05	228.7	
80	12	1	1.272	0.8	203.2	1	0.5	0.05	215.2	
80	14	1	1.240	0.8	193.0	1	0.5	0.05	207.0	
80	16	1	1.216	0.8	185.7	1	0.5	0.05	201.7	
80	18	1	1.198	0.8	180.2	1	0.5	0.05	198.2	
80	20	1	1.183	0.8	175.8	1	0.5	0.05	195.8	
80	22	1	1.171	0.8	172.3	1	0.5	0.05	194.3	
80	24	1	1.161	0.8	169.4	1	0.5	0.05	193.4	
80	26	1	1.153	0.8	166.9	1	0.5	0.05	192.9	
80	28	1	1.145	0.8	164.7	1	0.5	0.05	192.7	
80	30	1	1.139	0.8	162.9	1	0.5	0.05	192.9	
80	32	1	1.133	0.8	161.3	1	0.5	0.05	193.3	
80	34	1	1.128	0.8	159.8	1	0.5	0.05	193.8	
80	36	1	1.123	0.8	158.5	1	0.5	0.05	194.5	
80	38	1	1.119	0.8	157.3	1	0.5	0.05	195.3	
80	40	1	1.116	0.8	156.3	1	0.5	0.05	196.3	
80	42	1	1.112	0.8	155.3	1	0.5	0.05	197.3	
80	44	1	1.109	0.8	154.4	1	0.5	0.05	198.4	
80	46	1	1.106	0.8	153.6	1	0.5	0.05	199.6	
80	48	1	1.103	0.8	152.8	1	0.5	0.05	200.8	
80	50	1	1.101	0.8	152.1	1	0.5	0.05	202.1	

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 192.7 when the pilot sample size is 28. If you refer back to Example 2, you will see that the optimum pilot size for $\delta = 0.5$ is indeed 28.

Sample Size of a Pilot Study using the Upper Confidence Limit of the SD

Plots Section

Plots



This plot shows the various values of the sample sizes.