Chapter 682

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

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.

Technical Details

NCT Approach to Allow for Imprecision in σ

Suppose a pilot study results in an estimate s_{Pilot} of σ 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 $\theta = \mathrm{NCT}\left(1-\beta, df, t_{1-\frac{\alpha}{2}, N_{MAIN}-2}\right)$ and 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 $\theta_0 = \mathrm{NCT}\left(1-\beta, df, z_{1-\frac{\alpha}{2}}\right)$ and iterates until there is little change in N_{MAIN}.

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, power = 0.8, alpha = 0.05, R = 1, and δ = 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**
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		Main Study					Total
Sample Size NPILOT	Anticipated Standard Deviation s	Power	Sample Size NMAIN	Allocation Ratio R	Mean Difference δ	Alpha	Combined Sample Size NTOTAL
39	1	0.8	821.5	1	0.2	0.05	860.5
21	1	0.8	216.3	1	0.4	0.05	237.3
15	1	0.8	101.2	1	0.6	0.05	116.2
12	1	0.8	60.1	1	0.8	0.05	72.1
10	1	0.8	40.8	1	1.0	0.05	50.8

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.
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. NMAIN = N1 + N2.
R The allocation ratio of the two groups being compared by the study. R = N1 / N2.
δ The difference between the means. It is used to calculate the effect size (δ / σ). δ = μ1 - μ2.
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. NTOTAL = NPILOT + NMAIN.

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 adjustment for the imprecision of the estimate of σ, using the non-central t (NCT) distribution, 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. To detect a mean difference of 0.2 in the main study with 80% power, the optimum pilot study sample size is 39 and the total combined sample size in both the pilot and the main studies is 860.5 (with 821.5 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 NPILOT	Dropout-Inflated Enrollment Sample Size NPILOT'	Expected Number of Dropouts D
20%	39	49	10
20%	21	27	6
20%	15	19	4
20%	12	15	3
20%	10	13	3

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.
NPILOT The evaluable sample size at which power is computed. If NPILOT subjects are evaluated out of the NPILOT' subjects that are enrolled in the study, the design will achieve the stated power.
NPILOT' The total number of subjects that should be enrolled in the study in order to obtain NPILOT evaluable subjects, based on the assumed dropout rate. After solving for NPILOT, NPILOT' is calculated by inflating NPILOT using the formula NPILOT' = NPILOT / (1 - DR), with NPILOT' 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 = NPILOT' - NPILOT.

Dropout Summary Statements

Anticipating a 20% dropout rate, 49 subjects should be enrolled to obtain a final sample size of 39 subjects.

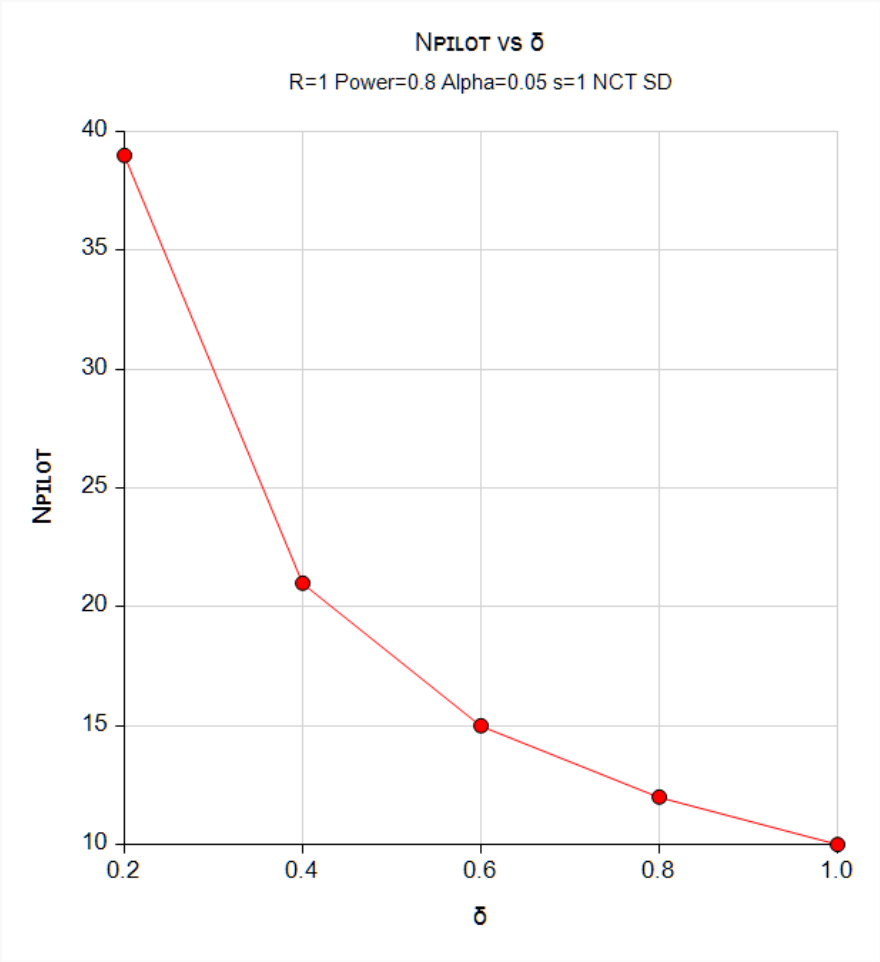
References

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.

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

Plots Section

Plots



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 δ = 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

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 ..... **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**
δ (Mean Difference in Main Study) **0.05 0.1 0.2 0.3 0.4 0.5**

Output

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

Numeric Results

Solve For: NPILOT (Pilot Sample Size)

Pilot Study		Main Study					Total
Sample Size NPILOT	Anticipated Standard Deviation s	Power	Sample Size NMAIN	Allocation Ratio R	Mean Difference δ	Alpha	Combined Sample Size NTOTAL
148	1	0.8	12703.7	1	0.05	0.05	12851.7
76	1	0.8	3211.8	1	0.10	0.05	3287.8
39	1	0.8	821.5	1	0.20	0.05	860.5
27	1	0.8	375.0	1	0.30	0.05	402.0
21	1	0.8	216.3	1	0.40	0.05	237.3
18	1	0.8	141.5	1	0.50	0.05	159.5

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, δ = 0.5, and N_{PILOT} = 6 to 40. Since we are interested in equal-group sizes, we will only consider even pilot sizes.

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 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**
δ (Mean Difference in Main Study) **0.5**

Output

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

Numeric Reports

Numeric Results

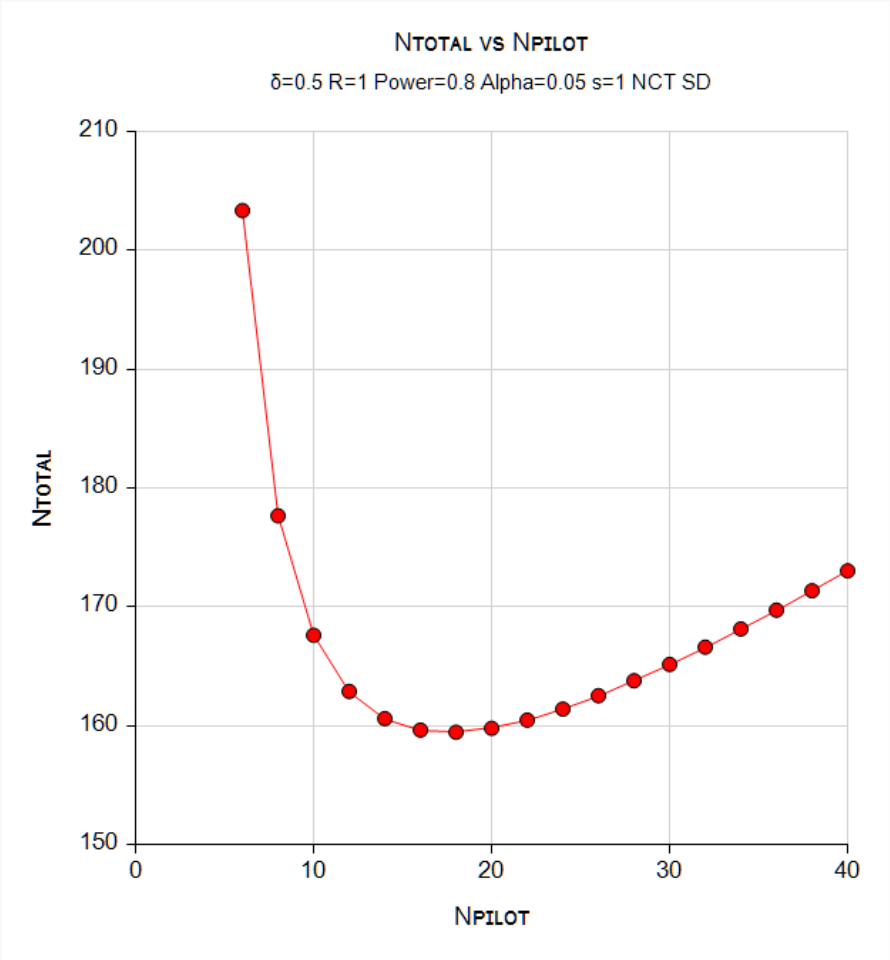
Solve For: NTOTAL (NPILOT + NMAIN)

Pilot Study		Main Study					Total
Sample Size NPILOT	Anticipated Standard Deviation s	Power	Sample Size NMAIN	Allocation Ratio R	Mean Difference δ	Alpha	Combined Sample Size NTOTAL
6	1	0.8	197.4	1	0.5	0.05	203.4
8	1	0.8	169.7	1	0.5	0.05	177.7
10	1	0.8	157.6	1	0.5	0.05	167.6
12	1	0.8	150.9	1	0.5	0.05	162.9
14	1	0.8	146.6	1	0.5	0.05	160.6
16	1	0.8	143.6	1	0.5	0.05	159.6
18	1	0.8	141.5	1	0.5	0.05	159.5
20	1	0.8	139.8	1	0.5	0.05	159.8
22	1	0.8	138.5	1	0.5	0.05	160.5
24	1	0.8	137.4	1	0.5	0.05	161.4
26	1	0.8	136.5	1	0.5	0.05	162.5
28	1	0.8	135.8	1	0.5	0.05	163.8
30	1	0.8	135.2	1	0.5	0.05	165.2
32	1	0.8	134.6	1	0.5	0.05	166.6
34	1	0.8	134.1	1	0.5	0.05	168.1
36	1	0.8	133.7	1	0.5	0.05	169.7
38	1	0.8	133.4	1	0.5	0.05	171.4
40	1	0.8	133.0	1	0.5	0.05	173.0

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 δ = 0.5 is indeed 18.

Plots Section

Plots



This plot shows the various values of the sample sizes.