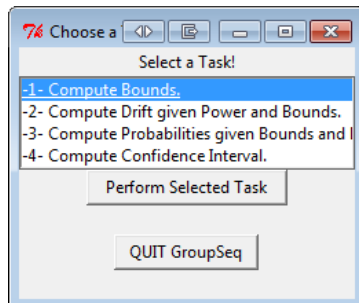


Install the GroupSeq package in R by typing in: `install.packages("GroupSeq")`

The GroupSeq package provides a GUI that can be used to perform the required calculations. It should start automatically when loading the library (either through the menu, or by typing: `library(GroupSeq)`, or can be started manually when the library is loaded by typing in `groupseq()`

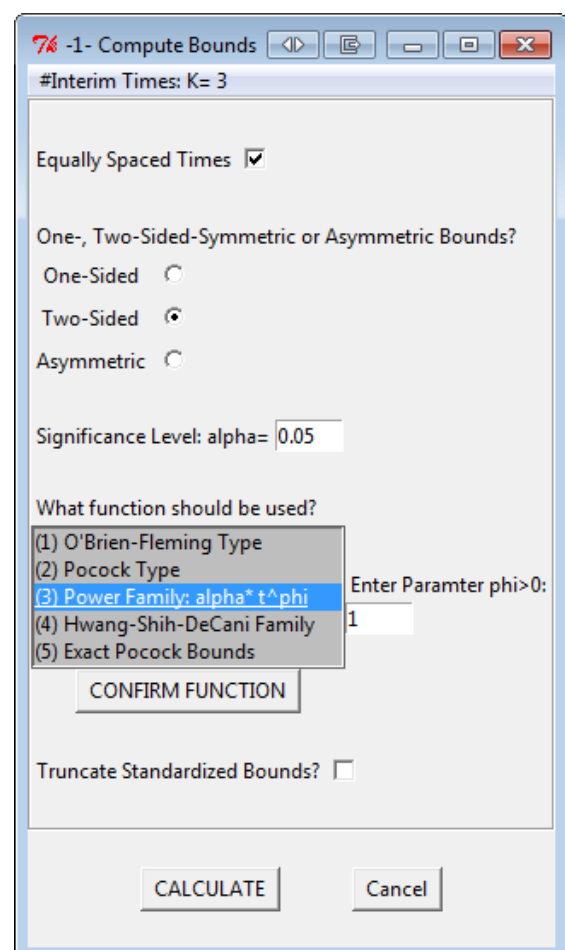
A menu appears in which four different tasks can be selected:



Computing bounds.

Suppose a researcher wants to compare two groups, collect a total of 180 participants, and perform 3 equally spaced analyses on the data. In the menu choose -1- Compute Bounds and click 'Perform Selected Task'. In the menu bar in the top, click on "#Interim Times: K = 1, and change it to 3. The default assumption is three equally spaced interim analyses (at 33%, 67% or 100% of the total sample size). Select 'Two-sided' bounds by clicking the corresponding radio button. In the 'What function should be used' menu select Power Family: $\alpha \cdot t^\phi$, click 'CONFIRM FUNCTION'. By default, a phi of 1 is entered, which is what we want. The menu should mirror the screenshot to the right. Click 'CALCULATE'.

The program provides the Lower Bounds and Upper bounds for the Z-scores, the incremental alpha, and the cumulative alpha. It does not provide the nominal alphas, which are the boundary alpha values at each interim analysis. However, the nominal alpha boundaries can be calculated from the Z-score using the Excel spreadsheet below (double-click to activate), giving two-tailed alpha boundaries of .017, .022, and .028 for times 1, 2, and 3.



| Calculate one- and two-tailed probability from Z | | |
|--|------------------------|------------------------|
| Z-score | two-tailed probability | one-tailed probability |
| 2.2937 | 0.0218 | 0.0109 |

The use of spending functions allows for more flexibility in the exact time the interim analyses are performed. For example, if a researcher wants to collect a total of 180 participants and perform 2 equally spaced interim analyses, but is only able to perform the first analysis when 70 participants are collected, she can remove the checkbox at “Equally Spaced Times” and type in $70/180 = 0.39$ in the first row, 0.66666 and 1 in the second and third rows, and click ‘Calculate’ to find a Z-boundary of 2.3358 for the first interim analysis, which equals a two-sided alpha boundary of 0.0195.

Computing the monitoring adjusted p -value.

After the data collection is terminated, the p -value adjusted for sequential testing must be calculated. Here, we continue the example discussed in the manuscript where the alpha boundary is crossed at the second analysis (see below for the data used in this example). In the menu choose -3- Compute Probabilities given Bounds and Drift. In the menu bar in the top, click on “#Interim Times: $K = 1$, and change it to 3. The default assumption is three equally spaced interim analyses (at 33%, 67% or 100% of the total sample size). Select the radio button next to ‘Two-Sided’. Check the “Enter Bounds Manually” checkbox. In the ‘Time 1’ row, type in 2.3940 (the boundary Z-score for the first interim analysis at time = 33% computed above). In the second row for Time 2, type in the Z-score associated with the observed p -value at the second interim analyses (in the example, $Z = 2.6050$). You can calculate the Z-score from the observed two-tailed p -value using the spreadsheet below:

| Calculate Z from two-tailed probability | | |
|---|--|---------|
| two-tailed probability | | Z-score |
| 0.0500 | | 1.9600 |

This spreadsheet is also available from: <http://osf.io/uygrs/files/>

In the third row, type in any number (e.g., 1). The p -value is only influenced by past interim analyses, not planned future analyses. The program should mirror the screenshot below. Click CALCULATE. The output (below, right) shows the cumulative exit probability at Time 2 is 0.0228, and thus the two-tailed p -value is approximately $p = .023$.

74 -3- Compute Probabilities given Boun...

#Interim Times: $K = 3$

Equally Spaced Times ☒

Enter Drift Parameter: 0

Drift is equal to the expectation of the Z statistic when time=1.

One-, Two-Sided-Symmetric or Asymmetric Bounds?

One-Sided ☐

Two-Sided ☒

Asymmetric ☐

Enter Bounds Manually ☒

Enter UPPER Bounds(standardized)

time 1 2.3940

time 2 2.6050

time 3 1

CALCULATE Cancel

74 -3- $K = 3$, drift parameter= 0

$K = 3$

manually entered Bounds

Drift = 0

Drift is equal to the expectation of the Z statistic when time=1.

| k | Times | Lower Bounds | Upper Bounds | Exit Probability | Cumulative Exit Prob. |
|---|-------|--------------|--------------|------------------|-----------------------|
| 1 | 0.333 | -2.394 | 2.394 | 0.0166657488 | 0.0166657488 |
| 2 | 0.667 | -2.605 | 2.605 | 0.0061456159 | 0.0228113647 |
| 3 | 1 | -1 | 1 | 0.2980825691 | 0.3208939338 |

Show Graph Save to File Cancel

Computing the monitoring adjusted difference and 95% CI

To compute the monitoring adjusted difference and 95% confidence interval we need to first calculate the drift parameter, θ , such that, as Proschan et al (2006) state ‘the one-tailed probability of results at least as extreme as those observed is 0.50.’ In the menu choose -2- Compute Drift Given Power and Bounds. In the menu bar in the top, click on “#Interim Times: K = 1”, and change it to 3. If the interim analyses were not equally spaced, uncheck the Equally Spaced Times checkbox and type in the times when the interim analyses were performed. Here, we continue to assume the first two interim analyses were equally spaced at 33% and 67% of the data collection. In the ‘Desired Power = it must be in (0,1)’ field fill in .50. Choose ‘One-Sided’ for the test. Check the checkbox “Enter Bounds Manually”. Type in 2.3940 in the first row (the boundary Z-score for the first interim analysis at time = 33% computed above). In the second row, type in the Z-score associated with the observed p -value when the interim analyses passed the boundary value (in the example, $Z = 2.6050$). In the last row, Type in a very high upper bound (i.e., 25). The program should mirror the screenshot to the right. Click ‘CALCULATE’. The Drift parameters is displayed as 3.05575.

-2- Compute Drift

#Interim Times: K= 3

Equally Spaced Times ☒

Desired Power - it must be in (0,1) : 0.5

One-, Two-sided-Symmetric or Asymmetric Bounds?

One-Sided ☒

Two-Sided ☐

Asymmetric ☐

Enter Bounds Manually ☒

Enter UPPER Bounds (standardized)

| | |
|--------|-------|
| time 1 | 2.394 |
| time 2 | 2.605 |
| time 3 | 25 |

CALCULATE Cancel

We can now calculate the mean difference adjusted for sequential analyses using: $M_{dif} \hat{\theta} \sqrt{2\sigma^2/N}$, where σ is the pooled sample variance, and N is the total number of participants that was planned for time = 100% (even when the study is stopped earlier!). The spreadsheet below can be used to perform these calculations, and the spreadsheet also provides Cohen’s d_s , a commonly used effect size in psychology (M_{dif}/SD_{pooled}). The data used in this example is provided at the end of this document.

To calculate the 95% confidence interval for this difference, choose -4- Compute Confidence Interval in the task menu. This is the only time that the number of *performed* instead of *planned* interim analyses is selected in the “#Interim Times” selection, and choose 2. Uncheck the equally spaced times checkbox, and type in 0.3333 as time 1 and 0.6666 as time 2. Enter the Z-value at the last analysis by typing in 2.605. Choose a two-sided test.

Select ‘Power Family α^*t^ϕ ’ in the Function menu, click CONFIRM FUNCTION and type in ‘1’ in the Phi field. The program should mirror the screenshot below.

76 -4- Compute Confidence Intervals

#Interim Times: K= 2

Equally Spaced Times ☐

time 1 0.3333

time 2 0.6666

Enter the standardized statistic (Z value) at the last analysis: 2.605

Enter Confidence Level - it must be in (0,1) : 0.95

One-, Two-sided symmetric or asymmetric bounds?

One-Sided ☐

Two-Sided ☒

Asymmetric ☐

Enter Bounds Manually ☐

Significance Level: alpha= 0.05

What function should be used?

(1) O'Brien-Fleming Type

(2) Pocock Type

(3) Power Family: $\alpha \cdot t^\phi$

(4) Hwang-Shih-DeCani Family

(5) Exact Pocock Bounds

Enter Parameter $\phi > 0$: 1

CONFIRM FUNCTION

Truncate standardized Bounds? ☐

CALCULATE Cancel

Click 'CALCULATE'. The Confidence Interval is displayed as 0.45546 – 5.51356. (Note these values differ slightly from Lan-DeMets' software where times are rounded to 2 digits).

By multiplying these values by $\sqrt{2\sigma^2/N}$ (which can be done with the spreadsheet below) we get the lower and upper 95% confidence intervals [1.4194, 17.1826].

| Calculate Differenc | | |
|---------------------|----------|--|
| | θ | |
| SD Group 1 | 21.2883 | |

This spreadsheet is also available from: <http://osf.io/uygrs/files/>

Data Used in Example:

Interim Analysis 1 after 60 participants.

Group Statistics^a

| | condition | N | Mean | Std. Deviation | Std. Error Mean |
|-------|-----------|----|---------|----------------|-----------------|
| value | 1,00 | 30 | 51,1840 | 22,59304 | 4,12491 |
| | 2,00 | 30 | 58,6043 | 23,08565 | 4,21484 |

a. interimanalysis = 1,00

Independent Samples Test^a

| | | Levene's Test for Equality of Variances | | t-test for Equality of Means | | | | | | |
|-------|-----------------------------|---|------|------------------------------|--------|-----------------|-----------------|-----------------------|---|---------|
| | | F | Sig. | t | df | Sig. (2-tailed) | Mean Difference | Std. Error Difference | 95% Confidence Interval of the Difference | |
| | | | | | | | | | Lower | Upper |
| value | Equal variances assumed | ,124 | ,726 | -1,258 | 58 | ,213 | -7,42033 | 5,89744 | -19,22534 | 4,38467 |
| | Equal variances not assumed | | | -1,258 | 57,973 | ,213 | -7,42033 | 5,89744 | -19,22545 | 4,38479 |

a. interimanalysis = 1,00

Interim Analyses 2 after 120 participants.

Group Statistics

| | condition | N | Mean | Std. Deviation | Std. Error Mean |
|-------|-----------|----|---------|----------------|-----------------|
| value | 1,00 | 60 | 49,4657 | 21,28825 | 2,74830 |
| | 2,00 | 60 | 59,5757 | 20,51583 | 2,64858 |

Independent Samples Test

| | | Levene's Test for Equality of Variances | | t-test for Equality of Means | | | | | | |
|-------|-----------------------------|---|------|------------------------------|---------|-----------------|-----------------|-----------------------|---|----------|
| | | F | Sig. | t | df | Sig. (2-tailed) | Mean Difference | Std. Error Difference | 95% Confidence Interval of the Difference | |
| | | | | | | | | | Lower | Upper |
| value | Equal variances assumed | ,052 | ,821 | -2,649 | 118 | ,009 | -10,11000 | 3,81682 | -17,66835 | -2,55165 |
| | Equal variances not assumed | | | -2,649 | 117,839 | ,009 | -10,11000 | 3,81682 | -17,66846 | -2,55154 |