Reproducing p-values for sequential designs using SAS

# Equal information stages

In the Wikipedia (<https://en.wikipedia.org/wiki/Pocock_boundary>) the following table for e.g. Pocock boundaries is mentioned:

|  |  |  |
| --- | --- | --- |
| List of *p*-values used at each interim analysis, assuming the overall *p*-value for the trial is 0.05 | | |
| **Number of planned analyses** | **Interim analysis** | ***p*-value threshold** |
| 2 | 1 | 0.0294 |
|  | 2 (final) | 0.0294 |
| 3 | 1 | 0.0221 |
|  | 2 | 0.0221 |
|  | 3 (final) | 0.0221 |
| 4 | 1 | 0.0182 |
|  | 2 | 0.0182 |
|  | 3 | 0.0182 |
|  | 4 (final) | 0.0182 |
| 5 | 1 | 0.0158 |
|  | 2 | 0.0158 |
|  | 3 | 0.0158 |
|  | 4 | 0.0158 |
|  | 5 (final) | 0.0158 |

These can be reproduced as follows:

First observe that the p-values above are for two-sided hypothesis and the p-values are two-sided:

Then in SAS

**proc** **seqdesign** altref=**10**

boundaryscale=pvalue

;

TwoSidedPocock: design method=poc

alt=twosided stop=reject

nstages=**5**

alpha=**0.05** beta=**0.10**

;

**run**;

give a table

| **Boundary Information (p-Value Scale) Null Reference = 0** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **\_Stage\_** |  | | **Alternative** | | **Boundary Values** | |
| **Information Level** | | **Reference** | | **Lower** | **Upper** |
| **Proportion** | **Actual** | **Lower** | **Upper** | **Alpha** | **Alpha** |
| **1** | 0.2000 | 0.025356 | -1.59237 | 1.59237 | 0.00791 | 0.99209 |
| **2** | 0.4000 | 0.050713 | -2.25195 | 2.25195 | 0.00791 | 0.99209 |
| **3** | 0.6000 | 0.076069 | -2.75807 | 2.75807 | 0.00791 | 0.99209 |
| **4** | 0.8000 | 0.101426 | -3.18474 | 3.18474 | 0.00791 | 0.99209 |
| **5** | 1.0000 | 0.126782 | -3.56065 | 3.56065 | 0.00791 | 0.99209 |

Note that this a one-sided p-value, so this has to be doubled:

2\*0.00791=0.01582

Also <https://online.stat.psu.edu/stat509/node/80/> gives:

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **R** | **Interim Analysis Number** | **O'Brien-Fleming** | | **Haybittle-Peto\*** | | **Pocock** | |
| **B** | **α** | **B** | **α** | **B** | **α** |
| **2** | 1 | 2.782 | 0.0054 | 3.0 | 0.002 | 2.178 | 0.0294 |
| 2 | 1.967 | 0.0492 | 1.960 | 0.0500 | 2.178 | 0.0294 |
| **3** | 1 | 3.438 | 0.0006 | 3.291 | 0.0010 | 2.289 | 0.0221 |
| 2 | 2.431 | 0.0151 | 3.291 | 0.0010 | 2.289 | 0.0221 |
| 3 | 1.985 | 0.0471 | 1.960 | 0.0500 | 2.289 | 0.0221 |
| **4** | 1 | 4.084 | 0.00005 | 3.291 | 0.00100 | 2.361 | 0.0182 |
| 2 | 2.888 | 0.0039 | 3.291 | 0.00100 | 2.361 | 0.0182 |
| 3 | 2.358 | 0.0184 | 3.291 | 0.00100 | 2.361 | 0.0182 |
| 4 | 2.042 | 0.0412 | 1.960 | 0.0500 | 2.361 | 0.0182 |
| **5** | 1 | 4.555 | 0.000005 | 3.291 | 0.00100 | 2.413 | 0.0158 |
| 2 | 3.221 | 0.0013 | 3.291 | 0.00100 | 2.413 | 0.0158 |
| 3 | 2.630 | 0.0085 | 3.291 | 0.00100 | 2.413 | 0.0158 |
| 4 | 2.277 | 0.0228 | 3.291 | 0.00100 | 2.413 | 0.0158 |
| 5 | 2.037 | 0.0417 | 1.960 | 0.0500 | 2.413 | 0.0158 |

And the O’Brien-Fleming boundaries can be calculated as:

**proc** **seqdesign** altref=**10**

boundaryscale=pvalue

;

TwoSidedOBrienFleming: design method=obf

alt=twosided stop=reject

nstages=**5**

alpha=**0.05** beta=**0.10**

;

**run**;

gives the one-sided p-values:

| **Boundary Information (p-Value Scale) Null Reference = 0** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **\_Stage\_** |  | | **Alternative** | | **Boundary Values** | |
| **Information Level** | | **Reference** | | **Lower** | **Upper** |
| **Proportion** | **Actual** | **Lower** | **Upper** | **Alpha** | **Alpha** |
| 1 | 0.2000 | 0.021571 | -1.46872 | 1.46872 | 2.53655E-6 | 1.00000 |
| 2 | 0.4000 | 0.043143 | -2.07709 | 2.07709 | 0.0006285 | 0.99937 |
| 3 | 0.6000 | 0.064714 | -2.54390 | 2.54390 | 0.00422 | 0.99578 |
| 4 | 0.8000 | 0.086286 | -2.93744 | 2.93744 | 0.01128 | 0.98872 |
| 5 | 1.0000 | 0.107857 | -3.28416 | 3.28416 | 0.02067 | 0.97933 |

So doubling gives

|  |  |
| --- | --- |
| 1 | 0.000005 |
| 2 | 0.0012 |
| 3 | 0.00844 |
| 4 | 0.02256 |
| 5 | 0.04134 |

# Unequal information levels

Often the futility boundary is nonbinding. And alpha levels are via Lan-DeMets with approximation to the O’Brien-Fleming or Pocock boundary:

title "60-100% at 199 or 331 patients";

**proc** **seqdesign** altref=**10**

boundaryscale=pvalue

;

TwoSidedOBrienFleming: design

method=errfuncOBF

alt=twosided stop=both (betaboundary=nonbinding)

nstages=**2**

info=cum(**199** **331**)

alpha=**0.05** beta=**0.10**

;

**run**;

| Boundary Information (p-Value Scale) Nonbinding Beta Boundary, Null Reference = 0 | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| \_Stage\_ |  | | Alternative | | Boundary Values | | | |
| Information Level | | Reference | | Lower | | Upper | |
| Proportion | Actual | Lower | Upper | Alpha | Beta | Beta | Alpha |
| 1 | 0.6012 | 0.066006 | -2.56916 | 2.56916 | 0.00384 | 0.22702 | 0.77298 | 0.99616 |
| 2 | 1.0000 | 0.109788 | -3.31343 | 3.31343 | 0.02379 | 0.02379 | 0.97621 | 0.97621 |

So the two-sided critical values at the 60% interim analysis are (agreeing with Cy proposal):

|  | Alpha |
| --- | --- |
| 1 | 0.00768 |
| 2 | 0.04758 |

Another scenario is with 265 of the 331 events :

title "80-100%";

**proc** **seqdesign** altref=**10**

boundaryscale=pvalue

;

TwoSidedOBrienFleming: design

method=errfuncOBF

alt=twosided stop=both (betaboundary=nonbinding)

nstages=**2**

info=cum(**265** **331**)

alpha=**0.05** beta=**0.10**

;

**run**;

Yielding:

| Boundary Information (p-Value Scale) Nonbinding Beta Boundary, Null Reference = 0 | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| \_Stage\_ |  | | Alternative | | Boundary Values | | | |
| Information Level | | Reference | | Lower | | Upper | |
| Proportion | Actual | Lower | Upper | Alpha | Beta | Beta | Alpha |
| 1 | 0.8006 | 0.091098 | -3.01824 | 3.01824 | 0.01224 | 0.06525 | 0.93475 | 0.98776 |
| 2 | 1.0000 | 0.113786 | -3.37322 | 3.37322 | 0.02143 | 0.02143 | 0.97857 | 0.97857 |

So two-sided:

|  | Alpha |
| --- | --- |
| 1 | 0.024448 |
| 2 | 0.04286 |

and with three interim analyses it becomes:

title "60-80-100%";

**proc** **seqdesign** altref=**10**

boundaryscale=pvalue

;

TwoSidedOBrienFleming: design

method=errfuncOBF

alt=twosided stop=both (betaboundary=nonbinding)

nstages=**3**

info=cum(**199** **265** **331**)

alpha=**0.05** beta=**0.10**

;

**run**;

with:

| Boundary Information (p-Value Scale) Nonbinding Beta Boundary, Null Reference = 0 | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| \_Stage\_ |  | | Alternative | | Boundary Values | | | |
| Information Level | | Reference | | Lower | | Upper | |
| Proportion | Actual | Lower | Upper | Alpha | Beta | Beta | Alpha |
| 1 | 0.6012 | 0.069341 | -2.63326 | 2.63326 | 0.00384 | 0.20880 | 0.79120 | 0.99616 |
| 2 | 0.8006 | 0.092338 | -3.03871 | 3.03871 | 0.01107 | 0.07339 | 0.92661 | 0.98893 |
| 3 | 1.0000 | 0.115335 | -3.39610 | 3.39610 | 0.02113 | 0.02113 | 0.97887 | 0.97887 |

So two-sided:

|  |  |
| --- | --- |
| 1 | 0.00768 |
| 2 | 0.02214 |
| 3 | 0.04226 |