Software Manual: Design and analysis of group sequential clinical trials with multiple primary endpoints

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Design and analysis of clinical trials with the software

Here we give an example of how to design and analyze a clinical trial with two primary endpoints. Consider a hypothetical SAMPLE clinical trial with two endpoints. The first endpoint has a normally distributed response, while the second endpoint has a time-to-event response. This design is inspired by clinical trials like COMPANION, which is a multicenter clinical study evaluating treatment of chronic heart failure. The primary endpoints of interests for the COMPANION trial are exercise performance and quality of life (normal type response) and all cause mortality (time-to-event type data). Details of the COMPANION trial can be found from Guidant Corporation’s webpage


and Bristow et al [7].

We plan 5 interim analyses for this SAMPLE trial. Our objective is to design a two-sided group sequential study with equally spaced information and global type I error 0.05 and type II error 0.1. We assume the response for the primary endpoint is distributed as $N(0,1)$ under $H_0$ and $N(0.33,1)$ under $H_1$. We assume that the true event time for the secondary endpoint has an

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exponential distribution with hazard rate $\lambda_0 = 0.1733$ and $\lambda_1 = 0.1118$ (hazard rates measured in months), under $H_0$ and $H_1$ respectively. The planned recruiting time is $T_0 = 28$ months with a $\tau = 6$ months follow-up time. Detailed information of the design can be found in Table 1.

**Design of SAMPLE trial**

We illustrate how to input information to compute the minimal sample size and corresponding critical boundaries with our software. In the design phase, we assume the two endpoints are independent. Under this assumption, both the sample size and the global alpha spending function are conservative. Since the $\alpha$ spending at the first look (interim analysis) is generally small, to avoid the possible loss of accuracy due to extreme values in simulations, the critical boundaries for the first look are calculated exactly by Algorithm AS 241 [8]. We assume equal sample sizes in the control and treatment groups. User inputs are marked by "[ ]".

**Example 1: Design of SAMPLE trial**

Page 1:
Design of Group Sequential Clinical Trials with Multiple Endpoints
Version 1.0
Section I: Calculations of Sample Size and Critical Boundaries
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University of Wisconsin-Madison

Page 2:
Section I -- Design of Group Sequential Clinical Trials
Minimal Sample Size and Corresponding Critical Boundaries Calculation:
Core Steps:
1. Sample size and Critical boundary calculation for each endpoint.
2. Multiple decision rules are used to control overall alpha and beta spending.
3. Key assumptions: independent endpoints; equal sample sizes in control and treatment groups.

Page 3:
Step 1 -- Calculation of each endpoint.
How many endpoints do you have (1 or 2)?
Please input the number of endpoints: [2]

Page 4:
Step 1 -- Calculation of each endpoint
Number of endpoints: 2
----------------------
Case Selection:
   Case 1. Two Normal Endpoints.
   Case 2. Two Survival Endpoints.
   Case 3. A Normal Endpoint(1st) and a Survival Endpoint(2nd).
   Case 4. A Survival Endpoint(1st) and a Normal Endpoint(2nd).
Please Select (1, 2, 3 or 4): [3]

Page 5:
Step 1 -- Calculation of each endpoint
Number of endpoints: 2
----------------------
What's the decision rule, hard or soft?
Choose either "h" or "s": [h]

Page 6:
Select the hard alternatives you want to control for type II error:
(1) H-0, (2) H+0, (3) H0+, (4) H0-, (5) H-+, (6) H++, (7) H--, (8) H+-
Please input here: [1 2 3 4 6 7]

Page 7:
Step 1 -- Calculation of each endpoint
Case 3: Two Endpoints: 1st Normal & 2nd Survival
  1) For the first normal endpoint:
     The number of looks this trial has: [5]
     Number of Monto carlo replications: [50000]
     Under Null Hypothesis: Mean = [0.00] Variance = [1.00]
     Under Alternative Hypothesis: Mean = [0.33] Variance = [1.00]
     The alpha for this endpoint is: [0.05]
     The beta for this endpoint is: [0.10]
     The spending number is: [1]

Page 8:
Step 1 -- Calculation of each endpoint
Case 3: Two Endpoints: 1st Normal & 2nd Survival
  1) For the first normal endpoint:
     Information Spending:
     relative information(1): [1] information(1): 0.2
     relative information(2): [2] information(2): 0.4
     relative information(3): [3] information(3): 0.6
     relative information(4): [4] information(4): 0.8

Page 9:
Step 1 -- Calculation of each endpoint
Case 3: Two Endpoints: 1st Normal & 2nd Survival

2) For the second survival endpoint:

The number of looks this trial has: 5
The number of Monte Carlo replications: 50000
The type I error (alpha) for the endpoint is: [0.05]
The type II error (beta) for the endpoint is: [0.1]

Page 10:
Step 1 -- Calculation of each endpoint

Case 3: Two Endpoints: 1st Normal & 2nd Survival

2) For the second survival endpoint:

------------------------------------
Information Spending:
relative information(1): [1]
relative information(2): [2]
relative information(3): [3]
relative information(4): [4]
relative information(5): [5]

Page 11:
Step 1 -- Calculation of each endpoint

Case 3: Two Endpoints: 1st Normal & 2nd Survival

2) For the second survival endpoint:

The alphaSpend for this endpoint is: [2]
The betaSpend for this endpoint is: [2]
The lambdaNull for this endpoint is: [0.1733]
The lambdaAlter for this endpoint is: [0.1118]
The entry for this trial is: [28]
The followup for this trial is: [6]
The lambdadrop for this trial is: [0]

Page 12:
Step 1 -- Calculation of each endpoint

Case 3: Two Endpoints: 1st Normal & 2nd Survival

The correlation is: [0]
The global alpha is: [0.05]
The global beta is: [0.1]

---------------------------------------------
Click "Calculate".

The calculated sample sizes and corresponding critical boundaries for hard (soft) decisions are also shown in Table 1. The plots of critical boundaries with information spending can be visualized from the interface. The same plots are shown in Figure 3 (for symmetric decision rule) and Figure 4 (for non-symmetric decision rule).
Experimental data from clinical trials stored in a certain format can be analyzed with our software. As in the design stage, we can analyze data from clinical trials with one (Normal or time-to-event type) or two endpoints (Normal-Normal, Normal-survival, survival-Normal, survival-survival). We demonstrate how to use our software to analyze data with the following SAMPLE data.

Example 2: Analysis of SAMPLE trial

Page 1:
Data Analysis of
Group Sequential Clinical Trials with Multiple Endpoints
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Page 2:
Section II -- Data Analysis of Group Sequential Clinical Trials
Step 1: Calculation of Marginal Critical Boundaries Satisfying Certain Alpha(beta) Spending Functions
Step 2: Use Global Alpha Spending Function to Control Overall Type I Error.
Step 3: Compare Test Statistics with Critical Boundaries
Software Homepage: http://www.biostat.wisc.edu/~kosorok/

Page 3:
Section II -- Data Analysis of Group Sequential Clinical Trials
How many endpoints does this trial have (1 or 2)?
Please input the number of endpoints: [2]

Page 4:
Section II -- Data Analysis of Group Sequential Clinical Trials
Number of endpoints: 2
-----------------------
Case Selection ?
  Case 1. Two Normal Endpoints.
  Case 2. Two Survival Endpoints.
  Case 3. A Normal Endpoint(first) and a Survival Endpoint(second).
  Case 4. A Survival Endpoint(first) and a Normal Endpoint(second).
Please select (1, 2, 3 or 4): [3]
Number of endpoints: 2

Choose decision rule: hard or soft?
Choose "h" or "s": [h]

Page 6:
Section II -- Data Analysis of Group Sequential Clinical Trials
Case 3: Two Endpoints: first Normal & second Survival
For the first Normal Endpoint:

Please Load Information Files. Two Files Needed.
Sample Information Files Available at:
http://www.biostat.wisc.edu/~kosorok/
Please input the name of the first information files: [new1a.txt]

Page 7:
Section II -- Data Analysis of Group Sequential Clinical Trials
Case 3: Two Endpoints: first Normal & second Survival
The following information received.

<table>
<thead>
<tr>
<th>Order</th>
<th>Alpha</th>
<th>Beta</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1959</td>
<td>0.3341</td>
</tr>
<tr>
<td>2</td>
<td>0.8380</td>
<td>0.0333</td>
</tr>
<tr>
<td>3</td>
<td>0.6456</td>
<td>0.2418</td>
</tr>
<tr>
<td>4</td>
<td>0.1246</td>
<td>0.8616</td>
</tr>
<tr>
<td>5</td>
<td>0.3180</td>
<td>0.2385</td>
</tr>
</tbody>
</table>

Page 8:
Section II -- Data Analysis of Group Sequential Clinical Trials
Case 3: Two Endpoints: first Normal & second Survival
For the first Normal Endpoint:

Please input the name of the second file: [new1b.txt]

Page 9:
Section II -- Data Analysis of Group Sequential Clinical Trials
Case 3: Two Endpoints: first Normal & second Survival

Page 10:
Section II -- Data Analysis of Group Sequential Clinical Trials
Case 3: Two Endpoints: first Normal & second Survival
For the first Normal Endpoint:
-------------------------------
Current Look Number:
Please input here: [3]

Page 11:
Section II -- Data Analysis of Group Sequential Clinical Trials
Case 3: Two Endpoints: first Normal & second Survival
For the first Normal Endpoint:
-------------------------------
Please Load Data File.
Please input the file name here: [newtest.txt]

Page 12:
Section II -- Data Analysis of Group Sequential Clinical Trials
Case 3: Two Endpoints: first Normal & second Survival
For the first Normal Endpoint:
-------------------------------
Data loaded successfully.

Page 13:
Section II -- Data Analysis of Group Sequential Clinical Trials
Case 3: Two Endpoints: first Normal & second Survival
For the second Survival Endpoint:
---------------------------------
Please Load Information Files. Two Files Needed.
Sample Information Files Available at:
http://www.biostat.wisc.edu/~kosorok/
Please input the name of the first information files: [survival2a.txt]

Page 14:
Section II -- Data Analysis of Group Sequential Clinical Trials
Case 3: Two Endpoints: first Normal & second Survival
For the second Survival Endpoint:
---------------------------------
The following information received.
Order = 2  Alpha = 0.05
Number of Looks = 5  Beta = 0.1
Number of Monte Carlo replications = 20000  Global Alpha = 0.05
Lambda (Null) = 0.1  Global Beta = 0.2
Lambda (Alter) = 0.164
Lambda (drop) = 0.005
Sample size control = 120
Sample size treat = 150

Page 15:
Section II -- Data Analysis of Group Sequential Clinical Trials
Case 3: Two Endpoints: first Normal & second Survival
For the second Survival Endpoint:
---------------------------------
Please input the name of the second information file: [survival2b.txt]

Page 16:
Section II -- Data Analysis of Group Sequential Clinical Trials
Case 3: Two Endpoints: first Normal & second Survival
For the second Survival Endpoint:
---------------------------------
<table>
<thead>
<tr>
<th>Global Alpha</th>
<th>Alpha</th>
<th>Beta</th>
<th>Look time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Look 1:</td>
<td>0.02</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Look 2:</td>
<td>0.02</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Look 3:</td>
<td>0.02</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Look 4:</td>
<td>0.02</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Look 5:</td>
<td>0.02</td>
<td>0.01</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Page 17:
Section II -- Data Analysis of Group Sequential Clinical Trials
Case 3: Two Endpoints: first Normal & second Survival
For the second Survival Endpoint:
---------------------------------
Current Look Number:
Please input here: [3]

Page 18:
Section II -- Data Analysis of Group Sequential Clinical Trials
Case 3: Two Endpoints: first Normal & second Survival
For the second Survival Endpoint:
---------------------------------
Please Load Data File.
Please input the file name here: [send333.txt]

Page 19:
Section II -- Data Analysis of Group Sequential Clinical Trials
Case 3: Two Endpoints: first Normal & second Survival
For the second Survival Endpoint:
---------------------------------
Data loaded successfully.
Click "Next" to run the program.

Page 20:
Section II -- Data Analysis of Group Sequential Clinical Trials
Case 3: Two Endpoints: first Normal & second Survival
Critical Boundaries: First endpoint Second endpoint
---------------------------------
<table>
<thead>
<tr>
<th>lower</th>
<th>upper</th>
<th>testZ</th>
<th>lower</th>
<th>upper</th>
<th>testZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Look 1: 0.0027</td>
<td>1.6502</td>
<td>-0.7219</td>
<td>0.0176</td>
<td>1.3175</td>
<td>1.1636</td>
</tr>
</tbody>
</table>
The information spending, global $\alpha$ spending, marginal critical boundaries for each interim analysis and test statistics are shown in Table 2. The numbers given in Table 2 correspond to absolute values of critical boundaries. The plots of the marginal critical boundaries and test statistics for the current look are shown in Figure 5 (symmetric decision rule) and Figure 6 (non-symmetric decision rule). Comparing the test statistics and critical boundaries, we conclude that we should continue this trial.

**Possible technical problems**

The software has been tested under standard Unix environment in the University of Wisconsin-Madison biostatistics computing systems. Minor modifications of the data loading function may be needed for other Unix systems. Only files in the correct format can be analyzed with our software.
Table 1. *Sample Size Calculation and Critical Boundaries for Design of SAMPLE Trial*

<table>
<thead>
<tr>
<th>Stage (j)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information Spending</td>
<td>0.2</td>
<td>0.4</td>
<td>0.6</td>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td>α Spending</td>
<td>0.0011</td>
<td>0.0025</td>
<td>0.0057</td>
<td>0.0126</td>
<td>0.0281</td>
</tr>
<tr>
<td>β Spending</td>
<td>0.0022</td>
<td>0.0050</td>
<td>0.0114</td>
<td>0.0252</td>
<td>0.0562</td>
</tr>
<tr>
<td>α Spending</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>β Spending</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Symmetric Decision Rule: Sample Size 114

**Endpoint 1**
Upper Bound 3.3273 3.1435 2.9664 2.5784 2.1928
Lower Bound 0.0094 0.0686 0.3423 1.2184 2.1928

**Endpoint 2**
Upper Bound 2.5376 2.5376 2.5376 2.4324 2.3218
Lower Bound 0.1425 0.3804 0.9498 1.5973 2.3218

Nonsymmetric Decision Rule: Sample Size 108

**Endpoint 1**
Upper Bound 3.3972 3.2096 3.0287 2.6326 2.2389
Lower Bound 0.0096 0.0700 0.3495 1.2440 2.2389

**Endpoint 2**
Upper Bound 2.5910 2.5910 2.5910 2.5495 2.3793
Lower Bound 0.1616 0.4039 1.0025 1.6596 2.3793
Table 2. *Critical Boundaries for SAMPLE Data at the Third Interim Analysis*

<table>
<thead>
<tr>
<th>Stage ((j))</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information Spending</td>
<td>0.2</td>
<td>0.4</td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global (\alpha) Spending</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Symmetric Decision Rule**

<table>
<thead>
<tr>
<th>Endpoint 1</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Bound</td>
<td>1.6502</td>
<td>1.6936</td>
<td>2.0106</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Bound</td>
<td>0.0027</td>
<td>0.0122</td>
<td>0.1176</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoint 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Bound</td>
<td>1.3175</td>
<td>1.4424</td>
<td>1.7833</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Bound</td>
<td>0.0176</td>
<td>0.0731</td>
<td>0.3259</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Nonsymmetric Decision Rule**

<table>
<thead>
<tr>
<th>Endpoint 1</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Bound</td>
<td>2.5562</td>
<td>2.4799</td>
<td>2.5064</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Bound</td>
<td>0.0041</td>
<td>0.0179</td>
<td>0.1467</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoint 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Bound</td>
<td>2.0408</td>
<td>2.1120</td>
<td>2.2230</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Bound</td>
<td>0.0272</td>
<td>0.1071</td>
<td>0.4063</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Test Statistics**

<table>
<thead>
<tr>
<th>Endpoint 1</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Endpoint 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endpoint 1</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Endpoint 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 1: Bivariate critical regions at the $j^{th}$ look and final look for symmetric decision rule. Regions 1–9 are stopping regions which conclude $H_{-0}$, $H_{+0}$, $H_{0+}$, $H_{00}$, $H_{-+}$, $H_{++}$, $H_{--}$ and $H_{+-}$ respectively. Blank areas are continuation regions. Dashed lines correspond to lower boundaries and dotted lines correspond to upper boundaries.
Figure 2: Bivariate critical regions at the $j^{th}$ look and final look for non-symmetric decision rule. Regions 1–6 are stopping regions which conclude $H_{-s}$, $H_{+s}$, $H_{0+}$, $H_{0-}$, $H_{00}$ and $H_{(-)}$ respectively. Blank areas are continuation regions. Dashed lines correspond to lower boundaries and dotted lines correspond to upper boundaries.
Figure 3: Marginal Critical Boundaries for Design of SAMPLE Trial (Symmetric Decision Rule).
Figure 4: Marginal Critical Boundaries for Design of SAMPLE Trial (Non-symmetric Decision Rule).
Figure 5: Marginal Critical Boundaries for Data Analysis of SAMPLE Trial (Symmetric Decision Rule). Dashed lines are lower boundaries and solid lines are upper boundaries.
Figure 6: Marginal Critical Boundaries for Data Analysis of SAMPLE Trial (Nonsymmetric Decision Rule). Dashed lines are lower boundaries and solid lines are upper boundaries.