1. Suppose we conduct a group sequential test with 2 looks where the accumulated information between the first and second look is half the information at the first look. What is the joint distribution of our test statistics \((T(t_1), T(t_2))^T\) under the null hypothesis?

2. The following data is from a traditional design comparing two treatments to lower blood pressures. The data is re-arranged in groups with every 60 patient increment (for a total of 4 groups):

<table>
<thead>
<tr>
<th></th>
<th>time 1</th>
<th></th>
<th>time 2</th>
<th></th>
<th>time 3</th>
<th></th>
<th>time 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n)</td>
<td>(\bar{Y})</td>
<td>(S^2)</td>
<td>(n)</td>
<td>(\bar{Y})</td>
<td>(S^2)</td>
<td>(n)</td>
</tr>
<tr>
<td>treatment 1</td>
<td>30</td>
<td>116</td>
<td>112</td>
<td>60</td>
<td>115</td>
<td>120</td>
<td>90</td>
</tr>
<tr>
<td>treatment 0</td>
<td>30</td>
<td>122</td>
<td>110</td>
<td>60</td>
<td>120</td>
<td>112</td>
<td>90</td>
</tr>
</tbody>
</table>

where \(n\) is the total sample size available at each time point, \(\bar{Y}\) is the sample mean of the blood pressures and \(S^2\) is the sample variance. Do the following:

(a) Use the (two-sided) two sample t-test at the last time point to test at the significance level \(0.05\) whether or not the mean blood pressures of the patients receiving treatment 1 and treatment 0 are the same.

(b) Conduct a (two-sided) group sequential test using Pocock boundaries at significance level \(\alpha = 0.05\). What is your conclusion?

(c) Conduct a (two-sided) group sequential test using O’Brien-Fleming boundaries at significance level \(\alpha = 0.05\). What is your conclusion?

3. Suppose we want to detect a difference in mean cholesterol values of 12 units between two treatments (new treatment and old treatment) with 95% power using the two-sample t-test (two-sided) at the 0.05 level of significance. Assume the standard deviation of the response \(\sigma_Y\) to be 60. Use equal allocation.
(a) Find the sample size for each treatment if a traditional design (analyze the data at the end of study) is used.

(b) Suppose we plan to have a maximum of 5 analyses of the data after equal increments of information using Pocock boundaries. How would you design such a study? What is the maximum sample size required?

(c) Repeat (b) using O’Brien-Fleming boundaries. If you have a strong belief that the new treatment will reduce 12 units of cholesterol more than the old treatment, which design do you prefer? If on the other hand there is a strong indication that there is no difference between these two treatments, which design do you prefer?

4. Suppose we want to detect a difference in mean response rates between a new treatment and the standard treatment where the outcome is whether or not a patient responds to the treatment. We would like to detect a 10% increase of response rate for the new treatment compared to the standard treatment with 95% power at the 0.05 level of significance. Assume 0.4 and 0.5 response rates for the new and standard treatments. Use equal allocation.

(a) Find the sample size for each treatment if a traditional design (analyze the data at the end of study) is used.

(b) Suppose we plan to have a maximum of 5 analyses of the data after equal increments of information using O’Brien-Fleming boundaries. How would you design such a study? What is the maximum sample size required? What is the cumulative information required at each interim analysis.

(c) Suppose the true response rates for the new and standard treatments turn out to be 0.35 and 0.45. Do you have enough information at each interim analysis?