Checking Symmetry in Predefined Time Assessments

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Introduction

- Phase III trials are mainly based on time-to-event-variables
  - In oncology, Overall Survival (OS) is the gold standard but
  - In some cases Progression Free Survival (PFS) may be used as its surrogacy
- PFS is usually defined as time from randomization to progression or death (irrespective the relationship)
- Tumor assessments are prefixed in function of time or in cycle visits
  - To avoid bias in comparisons the assessments should be done in parallel

![Diagram showing tumor assessments at different cycles]
Why symmetrical assessments?

Let’s see the reason with a simple and naive example

- Control/experimental arm assessments every 6 weeks/ 9 weeks

Imagine 100 patients (50 per arm) and all patients progress in the first evaluation they have, then if we compare them:

- log rank test associated is <0.0001
- consequently experimental arm seems better than control arm
- but what would happen if symmetrical assessments?
Symmetrical assessments

- Although prior example is an extreme situation, in real clinical practice we may find several situations that can affect PFS assessments (e.g. logistic disponibility of the hospital unit)

- A crucial check (if not the first) would be to ensure that symmetry in the assessments cannot be rejected

- Different ways to conduct this check using SAS© will be described herein
Hypothetical scenario

• Suppose a new clinical trial with primary endpoint PFS

• A new treatment arm compared with the standard of care
  – $\alpha=0.025$ (one-sided), $\beta=0.1$ (power=90%)
  – Control median is 24 weeks and 30% risk reduction with the experimental is expected

• According these assumptions 331 events out of 400 patients are necessary

• So two samples of 200 patients following the expected exponential distributions are simulated
PFS graph

Cumulative probability

Time (weeks)

0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54

Experimental
Standard of care
Censored

HR: 0.698 95%CI (0.572-0.85)
(p-value=0.0003)
Check symmetry

- Boxplot
- Wilcoxon test
- “Kaplan-Meier” plot

To maintain simplicity in the presentation only the first two assessments are going to be used
<table>
<thead>
<tr>
<th>Disease assessment</th>
<th>Treatment arm</th>
<th>n</th>
<th>Median (weeks)</th>
<th>p-value</th>
</tr>
</thead>
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<tr>
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<td>Standard of care</td>
<td>200</td>
<td>6.0</td>
<td>0.7624</td>
</tr>
<tr>
<td></td>
<td>Experimental</td>
<td>200</td>
<td>6.1</td>
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<td>0.9616</td>
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<tr>
<td></td>
<td>Experimental</td>
<td>164</td>
<td>11.9</td>
<td></td>
</tr>
</tbody>
</table>
"KAPLAN-MEIER" PLOT

Time to first disease assessment

- Standard of care
- Experimental

Proportion of patients*

Time (weeks)

* Proportion of patients for whom the time from randomization to the disease assessment is greater than a given time t (in weeks)
Take home message

Before reach a conclusion in a global treatment comparison the assumption that any potential time to event variable affected by assessments are asymmetrically measured should be discarded.