

Checking Symmetry in Predefined Time Assessments

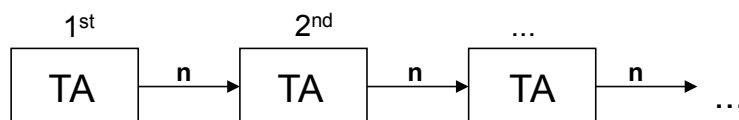


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Introduction

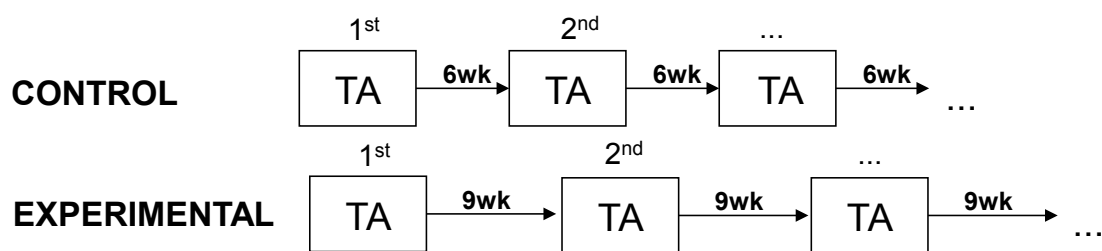
- Phase III trials are mainly based on time-to-event-variables
 - In oncology, Overall Survival (OS) is the gold standard but
 - In some cases Progression Free Survival (PFS) may be used as its surrogacy
- PFS is usually defined as time from randomization to progression or death (irrespective the relationship)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



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



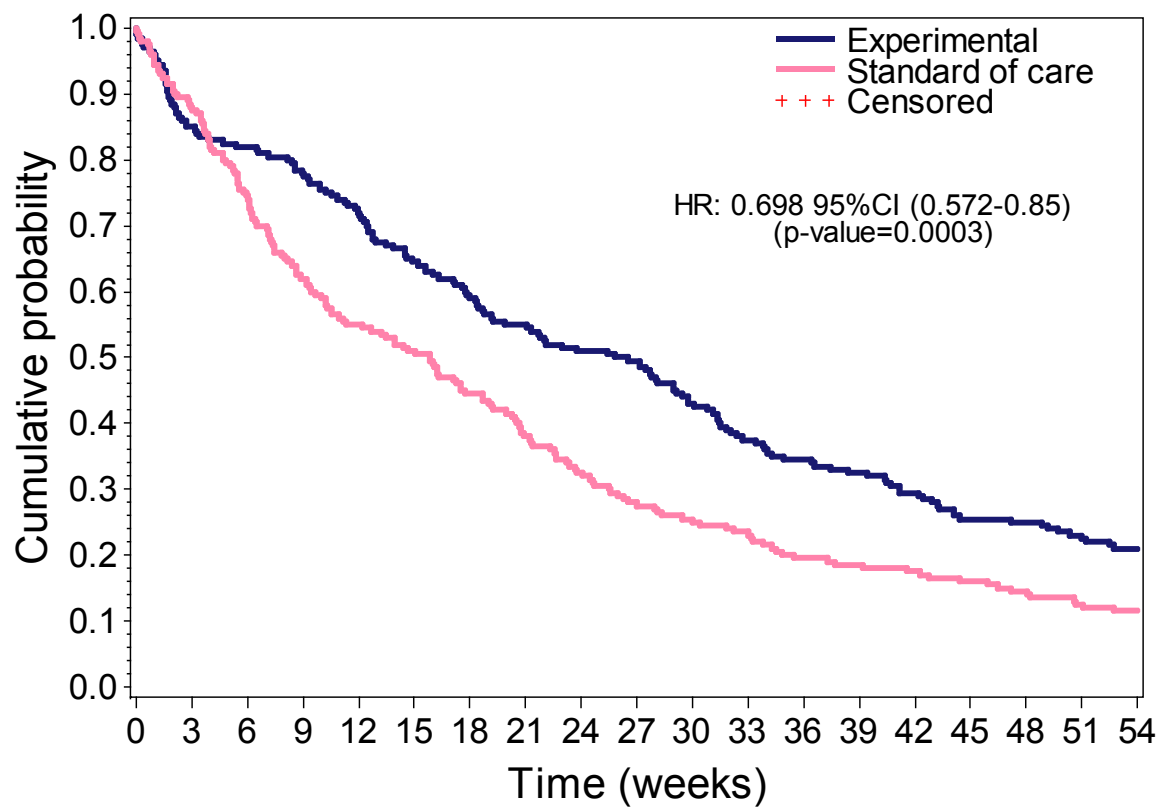
- Although prior example is an extreme situation, in real clinical practice we may find several situations that can affect PFS assessments (e.g. logistic disponibility of the hospital unit)
- A crucial check (if not the first) would be to ensure that symmetry in the assessments cannot be rejected
- Different 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



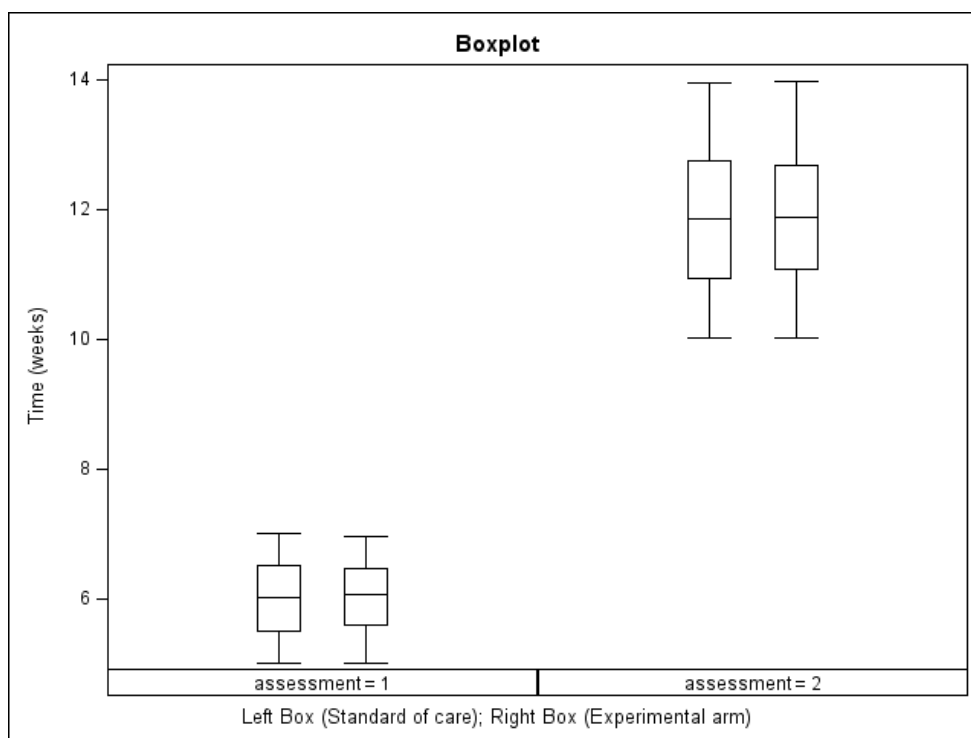
Check symmetry



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

To maintain simplicity in the presentation only the first two assessments are going to be used

Boxplot



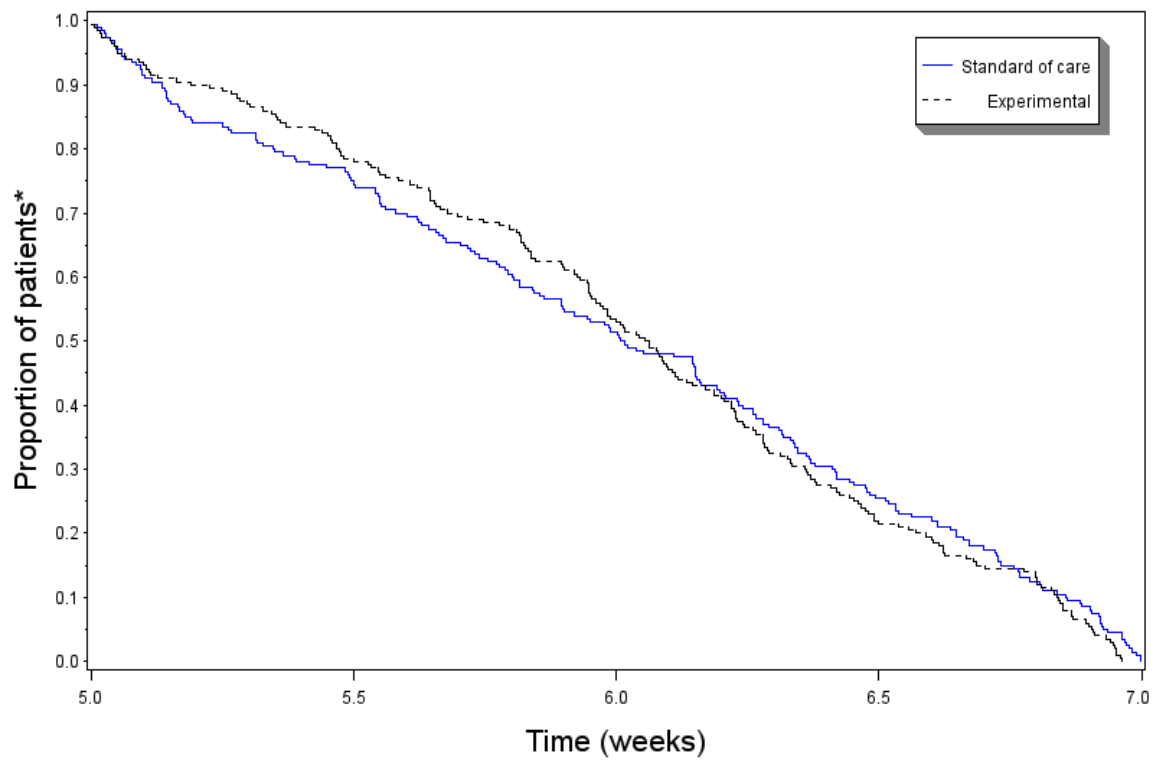
Wilcoxon Test



Disease assessment	Treatment arm	n	Median (weeks)	p-value
1	Standard of care	200	6.0	0.7624
	Experimental	200	6.1	
2	Standard of care	149	11.8	0.9616
	Experimental	164	11.9	

“KAPLAN-MEIER” PLOT

Time to first disease assessment



* 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

Questions

