Multivariate Analysis of treatment in Multiple Sclerosis using the Wei-Lachin procedure

Thomas Zwingers
CROS DE GmbH
Augsburg, Germany

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Multivariate Analysis of treatment in MS using the Wei-Lachin procedure

The problem

- Multiple endpoints with equal priority in MS:
  - o progression of the disease measured through the Expanded Disability Status Scale (EDSS),
  - o Standard Neurological Status (SNS),
  - o Ambulation Index (AI),
  - o the number of attacks requiring corticosteroid treatment,
  - o time to the first attack requiring such treatment.

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Nature of endpoints

- EDSS is a scale ranging from 0 to 10 in steps of 0.5;
- AI is a scale ranging from 0 to 9 in steps of 1,
- SNS is a scale ranging from 0 to 99 in steps of 1;
- Number of attacks is a count variable and
- Time to 1st attack is a duration.

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- There was no generally acceptable composite score that could be adopted.

- A Bonferroni adjustment was impractical due to the large number of endpoints.

➔ **Multivariate Analysis**

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Additional medical requirement

- None of the endpoints is allowed to be worse in the active treatment group

➔ **directional test**

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The solution

Multivariate test which is able

- to combine variables of different nature and
- to test directional alternatives

H_0 : $\Theta_k = 0$ for all k=1,2,3,4,5 (variables tested)

H_1 : $\Theta_k >= 0$ for all k=1,2,3,4,5 with at least one k>0;

➔ **non-parametric test of O'Brien type**

Wei-Lachin test

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The test statistic Z derived from the Wei-Lachin procedure has an asymptotic normal distribution and is defined as:

$$Z = (J' \Theta) / [J' S J] 1/2$$

with

- Θ being the vector of Mann-Whitney-differences between the treatment groups;
- S being the covariance-matrix of Q and
- J being a vector of weights.

This test statistic is the nonparametric equivalent to Hotelling's one-sided parametric T^2 test.

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Study results

	Placebo vs. 12 mg MTX	
	Mann-Whitney-difference (95% confidence interval)	p-value
Global difference	0.2941 (0.1644 – 0.4239)	<0.0001
Change in EDSS	0.2393 (0.0414 – 0.4373)	0.0194
Change in AI	0.2107 (0.0240 – 0.3974)	0.0306
No. Of attacks	0.3693 (0.1740 – 0.5645)	0.0002
Time to 1st treated attack	0.4431 (0.1974 – 0.6888)	0.0004
Change in SNS	0.2302 (0.0299 – 0.4305)	0.0269

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Summary

- Endpoints often have different nature (counts, scores, mean values, time to event)
- Non-parametric tests using the Mann-Whitney difference can be a solution
- Such tests are of special interest in closed testing procedures