Nonparametric Statistics (t_{max}, t_{lag})

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Recap: Distributions

Theoretically t_{max} and t_{lag} follow a continuous distribution

- *Maybe* a truncated normal distribution where the lowest value is zero
- However, we sample at certain time points
  - Hence, both PK metrics follow a *discrete* distribution
  - Shall we transform the data or use them as they are?
    - Whereas one would say
      'C_{max} of the test is 10% higher than the one of the reference'
      everybody would say
      't_{max} of the test is observed 30 minutes earlier than the one of the reference'
    - Therefore, we should use an *additive* model (*i.e.*, *not* transform the data)
- ANOVA or what else?
  - It would be a major statistical flaw to perform any analysis (ANOVA, *t*-tests, …) which requires normal distributed data
  - By comparing data from a discrete distribution we need a *nonparametric* test

Nonparametric Statistics?

Review of Guidelines

- EMA (NfG, Jul 2001 and earlier ones)
  - If appropiate to the evaluation the analysis technique for t_{max} should be non-parametric and should be applied to untransformed data. […] in addition to the appropriate 90% confidence intervals for the comparison of the two formulations, summary statistics such as median, minimum and maximum should be given.
    […] Statistical evaluation of t_{max} only makes sense if there is a clinically relevant claim for rapid release or action or signs related to adverse effects. The non-parametric 90% confidence interval for this measure of relative bioavailability should lie within a clinically determined range.

Nonparametric Statistics?

Review of Guidelines

- EMA (BE GL, Jan 2010)
  - A statistical evaluation of t_{max} is not required. However, if rapid release is claimed to be clinically relevant and of importance for onset of action or is related to adverse events, there should be no apparent difference in median t_{max} and its variability between test and reference product.
- EMA (MR GL, Nov 2014)
  - A statistical evaluation of t_{max} is not required. However, there should be no apparent difference in median t_{max} and its range between test and reference product.
- EMA (Dimethyl fumarate gastro-resistant capsules, Draft Jul 2017)
  - Comparable median and range for t_{lag} and t_{max}.

Guessing instead of Statistics?

Problematic Issues

- 'no apparent difference in median t_{max} and its variability between test and reference product'
  - What is 'no apparent difference in median t_{max}'?
  - How to assess the 'variability of median t_{max}' and compare it between products?
    - What is meant be the variability of the median? Quartiles?
    - In section 4.1.8 the GL states 'A non-parametric analysis is not acceptable' though in the context of other PK parameters.
- 'no apparent difference in median t_{max} and its range between test and reference product'
  - Even worse, since only two (!) values of the entire data set (minimum and maximum) are used and everything else is ignored
  - The range has a *breakdown point* of one (*i.e.*, a single extreme value distorts the estimate towards this value)

Guessing instead of Statistics?

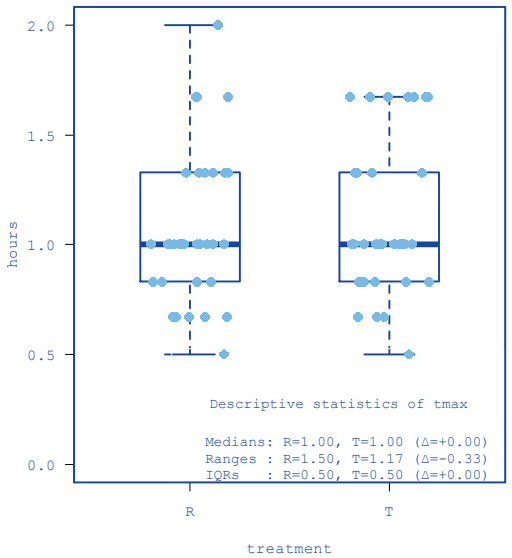
Problematic Issues

- 'no apparent difference in median t_{max} and its range between test and reference product'
  - Examples (valid for any sample size)
  - # 1
    - All t_{max} values after both the test and reference product are identical and 2
    - If we add another subject with $t_{max,T} = 2$ and $t_{max,R} = 8$, the medians will be still be 2 for both products
    - For the test product the range will be 0 but for the reference it will be 6
    - IMHO, this lacks any relevance…
  - # 2
    - t_{max} of R {1, …, 1, 2} median 1, range 1
    - t_{max} of T {1, …, 1, 3} median 1, range 2 → apparent difference?
    - t_{max} of T {1, …, 1, 1} median 1, range 0 → superior product?

Guessing instead of Statistics?

Problematic Issues

- 'no apparent difference in median t_{max} and its range between test and reference product'
  - Simulated data (n = 36, identical medians of T and R)
    - Identical medians of 1.0 h
    - Identical interquartile ranges (upper quartile – lower quartile) of 0.5 h
    - The single t_{max} of 2.0 h in one of the subjects after R distorts the range
    - Is this an 'apparent difference of the range' or not?



Nonparametric Statistics!

Problematic Issues

- Could easily resolved by using a statistical test
  - Data of the previous example
  - Δ of $\pm$20 minutes is considered clinically not relevant

```
Data structure       : Crossover design (dependent samples)
Dependent variable   : Tmax (h)
Data transformation  : none
α = 0.05             : 90% CI (exact), ≥90% CI (asymptotic)
Acceptance range for
equivalence (AR)     : -0.3333, +0.3333
Descriptive statistics
```

	R	T
Minimum	0.50	0.50
Lower whisker	0.50	0.50
1st quartile	0.83	0.83
Median	1.00	1.00
3rd quartile	1.33	1.33
Upper whisker	2.00	1.67
Maximum	2.00	1.67

```
Observations in sequence RT: 18
Observations in sequence TR: 18
72 total observations on 36 subjects; balanced sequences.
Tied ranked data; average ranks used.

Hodges-Lehmann (HL) estimates
Periods     (1, 2): 1.08, 1.00
Treatments  (T, R): 1.00, 1.00
```

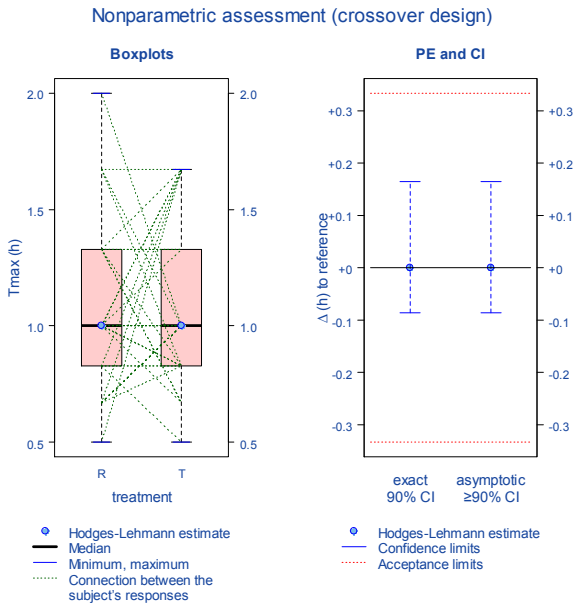
Nonparametric Statistics!

Problematic Issues

- Could easily resolved by using a statistical test
  - Data of the previous example
  - Δ of ±20 minutes is considered clinically not relevant

```
                Wilcoxon signed rank test
Data          : data$pdiff by treatment / sequence (RT, TR)
                (i.e., adjusted for period effects)
Expectation   : 333
Statistic     : 347
Exact         : Z = 0.4544, p-value = 0.6595
95% p-interval: 0.6479, 0.6595; mid p-value = 0.6537
Asymptotic    : Z = 0.4544, p-value = 0.6495
Alternative hypothesis: True μ is not equal to 0.
  Testing for a shift in location assumes equal distribu-
  tions - which is reasonable in a crossover design.
  The level of the test never exceeds nominal α, i.e., for
  normal distributed data the test is conservative.
  α of the exact test: 0.04999.

Sample estimates (difference in location)
  HL exact         : +0.00  interval midpoint: +0.04
  HL asymptotic    : +0.00  interval midpoint: +0.04
Confidence intervals (CI)
  Exact (90.00%)   : -0.09, +0.16,   Asymptotic (≥90%): -0.09, +0.16
```



Problematic Issues

- 'Comparable median and range for t_{lag}…'
  - Why at all?
    - For gastric-resistant formulations any difference in t_{lag} is reflected in t_{max} as well, *i.e.*, any shift in t_{lag} will lead to *exactly* the same shift in t_{max}
    - Whereas rich sampling close to the expected t_{max} likely is already applied in the study (in order to get reliable estimates of C_{max}) this is generally not the case around the expected t_{lag}
      In order to get reliable estimates of t_{lag}, additional samples have to be drawn in the very early part of the absorption phase
      - » Unnecessary burden to the subjects renders this requirement ethically doubtful
      - » Contrary to C_{max}, early concentrations might be close to the LLOQ – which leads to high variability and hence, possible ill-defined estimates of t_{lag}

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Thank You!
Open Questions?

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