Understanding variation in n-of-1 trials

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Introduction

- N-of-1 trials are performed on a single individual with the purpose of estimating individual treatment effects.
- Series of n-of-1 trials can be used to estimate an overall treatment effect as well as individual treatment effects.
- Distinct individual treatment effects arise as a consequence of a treatment by patient interaction.
- N-of-1 trials are undertaken in small populations when there is expectation a priori of a treatment by patient interaction.
Running the trial

1st period
Treatment A

2nd period
Treatment B

3rd period
Treatment B

4th period
Treatment A

5th period
Treatment A

6th period
Treatment B

1st Cycle

2nd Cycle

3rd Cycle

Wash-out

Wash-out

Wash-out

Wash-out

Wash-out

Utrecht, 24 August, 2015
Collecting the data

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<th>Period</th>
<th>Treatment</th>
<th>Outcome</th>
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Methods

\[ y_{ij[k]} = 100 + \tau_{[k]} + b_i + c_{i[k]} + e_{ij} \]

\[ b_i \sim N(0,25) \]
\[ c_{i[k]} \sim N(0,\sigma_c^2) \]
\[ e_{ij} \sim N(0,9) \]

\[ i = 1, \ldots, 30 \]
\[ j = 1, \ldots, n_i \]
\[ k = 0,1 \]
\[ \tau_0 = 0 \]
\[ \tau_1 = 20 \]
\[ \max(n_1, \ldots, n_{30}) = 8 \]
\[ \min(n_1, \ldots, n_{30}) = 4 \]

Simulate data → Fit models → \[ \hat{\tau}_1 \]
\[ \text{Var}(\hat{\tau}_1) \]
\[ E[\text{Var}(\hat{\tau}_1)] \]
\[ E[\text{Var}(\hat{\tau}_1)] / \text{Var}(\hat{\tau}_1) \]
4 cycles balanced n-of-1 trials

30 subjects

Utrecht, 24 August, 2015
2 to 4 cycles unbalanced n-of-1 trials

30 subjects

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4 cycles balanced n-of-1 trials

30 subjects
2 to 4 cycles unbalanced n-of-1 trials

30 subjects
Conclusions

When the treatment by patient interaction is significant:

• The t-test and fixed effects meta-analysis underestimate the variance of the overall treatment effect estimate.
• The t-test does not permit the estimation of distinct individual treatment effects.
• Both the full mixed-effects model and the mixed-effects model of difference produce unbiased or near unbiased estimates of the variance of the overall treatment effect estimate.
References

Thanks for your attention