Are multiple primary outcomes analysed appropriately in RCTs?

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Why use multiple outcomes?

- A single outcome may not be sufficient

- In complex conditions several outcomes may need to be investigated to fully assess all aspects of the disorder

- Example: relapse to drug use and frequency of substance use in 90 days (Bowen et al, 2014)
Statistical methods to account for multiplicity

• Separate univariate analyses and adjust the p-values (using Bonferroni, Holm, Hochberg etc.)

• Composite primary outcome

• Multivariate regression
Separate univariate analysis with an adjustment to the p-values

- Easy to implement
- Conservative approach when there are many outcomes or when the outcomes are correlated
Composite outcome

Combine multiple measurements into a single variable

✓ Takes account of multiplicity without the need to adjust the p-values

✗ It is not clear where the main effect is

✗ Misleading conclusions can be drawn when a number of disparate outcome are combined
Multivariate regression model

✓ Takes account of correlations between outcomes

✓ Can either measure the intervention effect for each outcome or measure an overall intervention effect

If the intervention effect is measured for each outcome then an adjustment for the multiplicity will be required
Review

• Review of randomised trials

• Between July 2011 and June 2014

Results

• 289 RCTs identified
  – 209 trials included
  – 80 phase 2 trial excluded

• 32% (67) reported > 1 primary outcomes
• 68% (142) reported 1 primary outcome
Results

> 1 primary outcome reported
  n= 67

Multiple primary outcomes
  n=60

Separate testing
  n=58
  Multiplicity adjustment
    n=13
  No multiplicity adjustment
    n=45

Co-primary outcomes
  n=7

Simultaneous testing
  n= 2

32% of all RCTs

Adjustments:
  Bonferroni (6)
  Holm (2)
  Hochberg-Benjamini (1)
  Sidak (1)
  Dunnett (1)
  Sequential (2)
Recommendations for reporting

• Specify the primary and secondary outcomes, methods of measurements and time points of interest

• Any aspects of multiplicity “should be identified in the protocol; adjustment should always be considered and the details of any adjusting procedure…should be set out in the analysis plan” (ICH guidelines)
Current research

• Multivariate methods are infrequently used in the analysis of clinical trials

• Comparing multivariate method to univariate method using a simulation study

• Various outcomes types
  – Continuous, binary, mixture of continuous and binary

• Various types of missingness
  – Complete data, MCAR, MAR, MNAR
Simulations: Complete data

The power graph will be amended!
Simulations: MCAR 30%, 50%

![Graph showing power and FWER across correlation for Uni and MV with Bonferroni and No adjustment]
Results

• Multivariate methods may increase the power when
  – the outcomes are correlated ($\rho > 0.4$) and
  – there are missing data

• When using 2 outcomes, the Bonferroni adjustment keeps the FWER at the desired level
References


