Statistics•Collaborative

design and analysis for biomedical research

Use of meta-analysis in the setting where a small number of studies are available

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Overview

- Motivating examples
- Example 1 – use of meta-analysis to provide information for a noninferiority margin
- Fixed effects
- Random effects
- Random effects for small number of studies
- Example 2 – application of methods for an orphan indication
- Summary

Uses of meta-analysis in a regulatory setting

- Non-inferiority studies
  - Meta-analysis is used to derive a confidence limit for the placebo-adjusted treatment effect
  - The lower bound of this confidence limit then becomes the benchmark for the computation of the non-inferiority margin

- Orphan diseases/subgroups
  - Meta-analysis can be used to estimate treatment effect for a well-defined subgroup of individuals across studies, for example, genetic mutations

Example 1

- Non-inferiority study
  - Two treatment modalities – standard is a nasal administration, experimental treatment is a pill
  - Three studies available to estimate placebo-adjusted effect of the standard treatment
  - One study had a large number of subjects (548), the other two had a small number of subjects (40, 17)
  - The largest placebo-adjusted effect was seen in the two small studies
  - Meta-analysis was used to estimate the effect

Example 1

Study	TRT	N	Var	Mean % change	Placebo-adjusted
1	Pill	280		1.40	
	Std	268	4.1	0.21	1.19
2	Pill	20		1.40	
	Std	20	5.5	-0.70	2.10
3	Pill	9		7.6	
	Std	8	?	1.9	5.70

Example 1

- No variance estimate for the third study.
- Regulatory agency decided to use 2.5 as the estimate of the variance
- Inverse variance method used to combine results

Example 1

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	Std	8	? 2.5	1.9	5.70
Effect size +/- std error	1.56 +/- 0.33				
95% CI	(0.91, 2.21)				

Example 1

Assumption	Placebo-adjusted trt effect	95% CI
Var = 2.5	1.56	(0.91, 2.21)
Var = 4.1	1.35	(0.69, 2.01)
Var = 5.5	1.29	(0.63, 1.97)
Study 1	1.19	(0.40, 1.98)

Example 1

- Assumptions make a substantial difference
- Lower bound of the CI ranges from 0.40 to 0.91 as the variance ranges from 2.5 to 5.1
- Meta-analyses involving a small number of studies are sensitive to changes in the assumptions

Meta-analytic techniques – fixed effects

- Assumptions
  - One true effect size
  - Inferences based on the studies included in the meta-analysis and cannot be extended beyond the collection of studies included
  - Properties of estimates, tests, and CIs depend on the **total number of subjects** across all studies
  - Weights used to combine studies are $\frac{w_i}{\sum w_i}$, where $w_i = \frac{1}{v_i}$ and v_i is the within study variance. Note that this weight function is ~ proportional to n, so that studies with a larger n receive greater weight

Meta-analytic techniques – random effects

- Inferences related to treatment effect can be made to the full population
- Sample size is **number of studies**
- Between study variability is included in all computations
- Best if approximately 25 or more studies are included in the analysis. This insures that the type 1 error is accurate
- Weights used to combine studies are generally similar in size. Thus small studies receive a weight that is approximately the same as a large study.

Estimation of overall treatment effect – fixed effects

- K = number of studies
- $\hat{\theta}_i$ = estimate of treatment effect in ith study (i = 1, …, K)
- $\widehat{var}(\hat{\theta}_i)$ = variance of the estimated treatment effect
- $w_i = \frac{1}{\widehat{var}(\hat{\theta}_i)}$
- $\hat{\theta}_F = \sum_{i=1}^{K} \frac{\hat{\theta}_i w_i}{\sum w_i}$
- $\hat{V}_F = \frac{1}{\sum w_i}$ = variance of $\hat{\theta}_F$
- $Z_{1-\alpha/2}$ = (1 – α/2) percentile of the standard normal distribution (1.96 for a two-sided 95% CI)

Estimation of overall treatment effect – fixed effects

- Test statistic for $\hat{\theta}_F$ is

$$Z_F = \frac{\hat{\theta}_F}{\sqrt{\frac{1}{\sum w_i}}}$$

- Confidence interval (two-sided 95%) is as follows:

$$(\hat{\theta}_F - 1.96\sqrt{\frac{1}{\sum w_i}}, \hat{\theta}_F + 1.96\sqrt{\frac{1}{\sum w_i}})$$

Estimation of overall treatment effect – random effects (DerSimonian and Laird)

- $\hat{\tau}^2 = \max\left(0, \frac{\sum w_i \left(\hat{\theta}_i - \hat{\theta}_R\right)^2 - K - 1}{\sum w_i - \frac{\sum {w_i}^2}{\sum w_i}}\right)$
- $\hat{\theta}_R = \sum_{i=1}^{K} \hat{v}_i \, \hat{\theta}_i$
- $\hat{v}_i = \frac{\left(\hat{\tau}^2 + \frac{1}{w_i}\right)^{-1}}{\sum\left(\hat{\tau}^2 + \frac{1}{w_i}\right)^{-1}}$
- $\widehat{var}\left(\hat{\theta}_R\right) = \left(\sum \frac{1}{\hat{\tau}^2 + \frac{1}{w_i}}\right)^{-1}$

Estimation of overall treatment effect – random effects (DL)

- Test statistic for $\hat{\theta}_R$ is given by

$$Z_R = \frac{\hat{\theta}_R}{\sqrt{\widehat{var}(\hat{\theta}_R)}}$$

- Confidence interval (two-sided 95%) is given by

$$(\hat{\theta}_R - 1.96 * \sqrt{\widehat{var}(\hat{\theta}_R)}\ , \hat{\theta}_R + 1.96 * \sqrt{\widehat{var}(\hat{\theta}_R)}\ )$$

Performance of Random effects approach when the number of studies is small

- Simulation results: Meta-analysis including only 2 studies:
  - Studies of equal size type 1 error ranged from 6% to 25%
  - One large, one small type 1 error ranged from 13.8% to 30.9%

- Three studies:
  - Type 1 error ranged from 5.9% to 22.1%

- Ten studies: type 1 error is below 10%
- Range of 2-10 studies is unpredictable

IntHout J, Ioannidis JPA, Borm GF (2014)

Methods for small number of studies – random effects

- Three reasons why methods are inaccurate: normal approximation is questionable, weights that are used are estimates and not fixed, sample size is number of studies and not number of subjects
- Hartung, Knapp, Sidik, Jonkman (HKSJ) address some of these issues by modifying the variance estimate to account for the fact that the weights are estimated and base the proposed test and confidence intervals on the t-distribution rather than the normal distribution

HKSJ method – random effects

- Define $\hat{q} = \frac{1}{K-1} \sum \frac{v_i}{\sum v_i} \left(\hat{\theta}_i - \hat{\theta}_R\right)^2$
- Modified test statistic is given by

$$\frac{\left|\hat{\theta}_R\right|}{\sqrt{\hat{q}}}$$

- Modified 95% confidence interval is given by

$$\hat{\theta}_R - t_{K-1;1-\alpha/2} * \sqrt{\hat{q}}, \hat{\theta}_R + t_{K-1;1-\alpha/2} * \sqrt{\hat{q}}$$

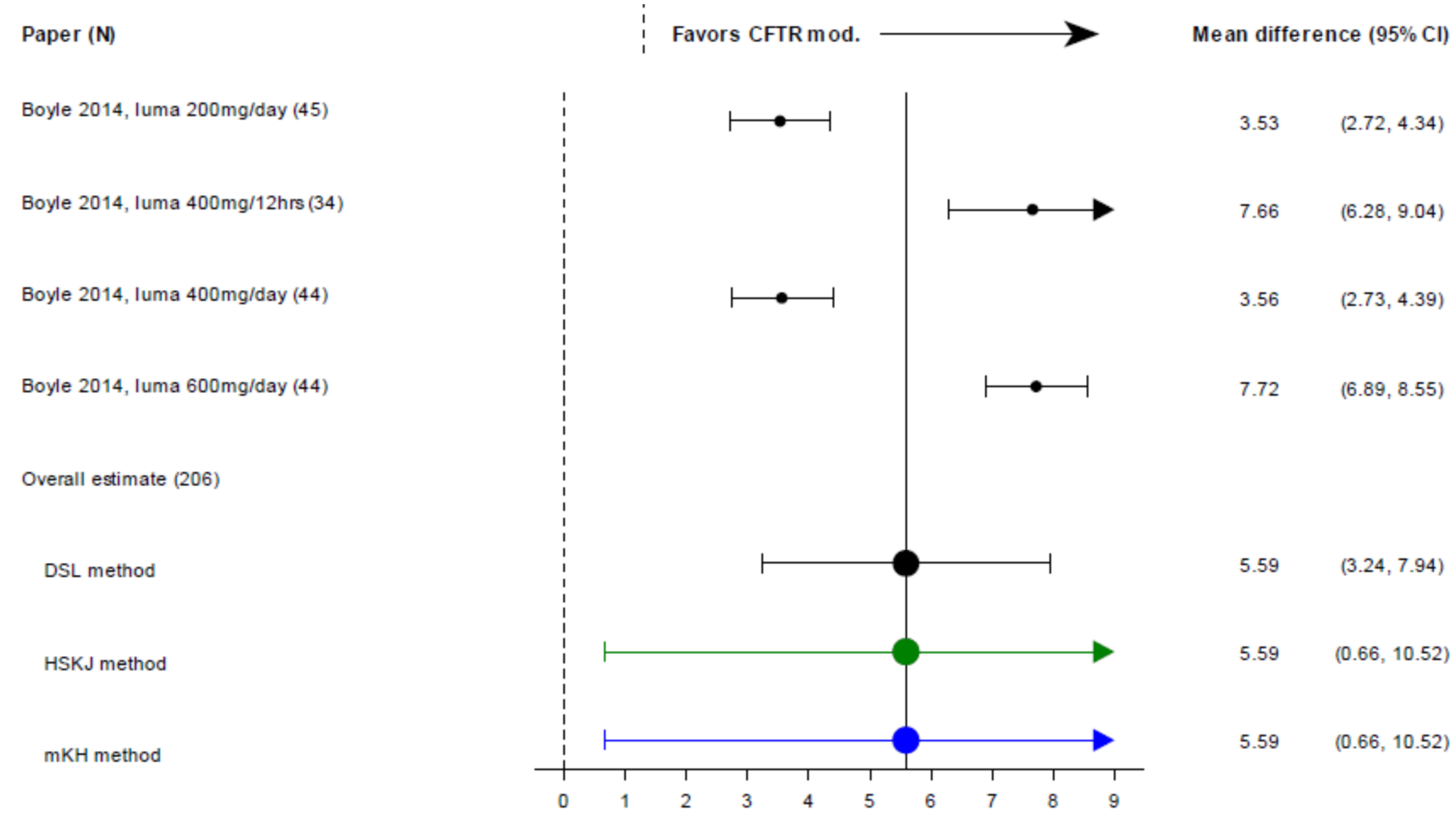
where $t_{K-1;1-\alpha/2}$ denotes a t distribution with K -1 df

HKSJ method – random effects

- Confidence intervals will be larger when compared to standard methods
- Multiplier for DerSimonian and Laird is always 1.96. For HKSJ this is 12.71 and 4.30 for two and three studies, respectively. For nine studies it is 2.31 and for 10 studies it is 2.25.
- Modified Knapp Hartung method (mKH) replaces q with $q^{*}=\max[1,q]$.

Example 2

- Use of Ivacaftor for treating cystic fibrosis in groups with specific genetic defects
- Limited number of studies available
- Outcome is percent predicted FEV_1
- Patients aged 18 and older with CF, baseline PPFEV1 >90%, and two copies of the F508del mutation



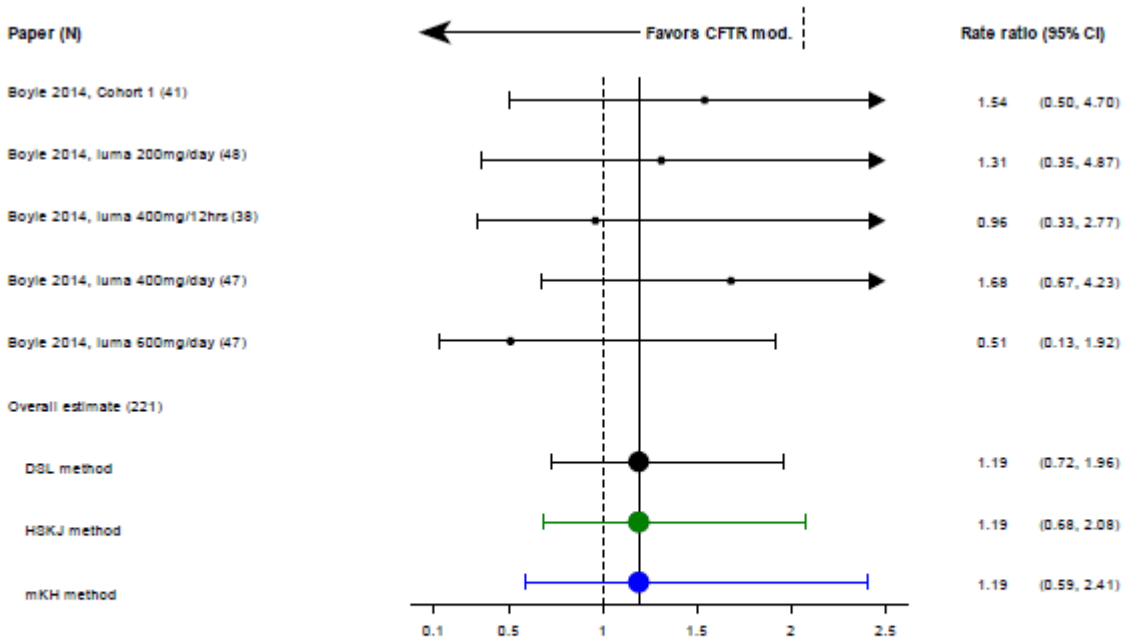
Outcome of interest in this plot is pulmonary function as measured by absolute change in percent predicted FEV1 for research question 30. Weights are computed within each ivacaftor dosage subgroup. Only research questions with three or more sources of outcome data in an ivacaftor dosage subgroup included in the random effects analysis.

CFTR mod.=cystic fibrosis transmembrane conductance regulator modulator. For research questions 21-40, active treatment is Orkambi®. CI=Confidence interval; DSL=DerSimonian and Laird method; HKSJ=Hartung-Knapp-Sidik-Jonkman method; mKH=Modified Knapp-Hartung method.

RevMan database as of 21OCT2016
E:\Proj\RCA CFF meta\Programs\f_forest_con.sas v.001 (last run: 12/20/2016, 13:21), f_forest_con_nopool_PICO30_FEVabs.rtf

Example 2 - Continued

- Upper respiratory symptoms: percentage of subjects reporting symptoms
- baseline PPFEV1 >90%, and two copies of the F508del mutation: Upper respiratory symptoms
- Rate ratio 1.19
  - DL (0.72, 1.96)
  - HKSJ (0.68, 2.08)
  - mKH (0.59, 2.41)



Outcome of interest in this plot is upper respiratory symptoms for research question 30. Weights are computed within each ivacaftor dosage subgroup. Only research questions with three or more sources of outcome data in an ivacaftor dosage subgroup included in the random effects analysis.

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Conclusions

- Newer methods can be very helpful when the number of studies is small
- If 2 – 3 studies are being combined, it is probably best to use a fixed effects approach
- If a small number of studies are available and the studies differ in size, the HKSJ or mKH should be used when random effects are taken into account.

Other considerations

- The approach should fit the application
- Studies may "reuse" the placebo groups, particularly in the case of subgroup analyses. Thus, the same data may appear in multiple computations.
- Care should be taken in all analyses

References

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