

**Siebert & Saverno:
Meta-Analysis and Indirect Treatment Comparisons from RCTs with Small Patient Numbers
ISPOR 2011, Madrid**

Meta-Analysis and Indirect Treatment Comparisons from RCTs with Small Patient Numbers

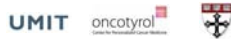
ISPOR Madrid, 2011

Uwe Siebert, MD, MPH, MSc, ScD^{1,2,3}
Kim Saverno, PhD, RPh^{1,2}

¹Department of Public Health and HTA, UMIT, Austria

²Oncotyrol – Center for Personalized Cancer Medicine, Innsbruck, Austria

³Center for Health Decision Science and MGH-ITA, Harvard University, Boston, USA



Contact Data:

Uwe Siebert, MD, MPH, MSc, ScD

Professor of Public Health (UMIT)

Adjunct Prof. of Health Policy and Management (Harvard Univ.)

Chair, Dept. of Public Health and HTA, UMIT - University for Health Sciences, Medical Informatics and Technology,

Director, Area of Public Health Decision Modelling, Health Technology Assessment and Health Economics, ONCOTYROL Center for Personalized Cancer Medicine, Innsbruck, Austria

Mail address: Eduard Wallnoefer Center I, A-6060 Hall i.T., AUSTRIA,

Tel.: +43(0)50-8648-3930, Fax: +43(0)50-8648-673931,

Email: public-health@umit.at



Dept. of Public Health & HTA



Acknowledgment

This work was supported by the ONCOTYROL Center for Personalized Cancer Medicine.



ONCOTYROL is a K1-COMET Center and funded by the Federal Ministry for Transport Innovation and Technology (BMVIT) and the Federal Ministry of Economics and Labour/the Federal Ministry of Economy, Family and Youth (BMWA/BMWFJ), the Tyrolean Future Foundation (TZS) and the State of Styria represented by the Styrian Business Promotion Agency (SFG) and supported by UMIT - University for Health Sciences, Medical Informatics and Technology.



Dept. of Public Health & HTA



Overview

- „Regular“ Meta-Analysis
 - Fixed Effects and Random Effects
- Indirect Treatment Comparison
- Small sample sizes and small number of studies
- Challenges



Dept. of Public Health & HTA



Fixed-Effects (FE) Meta-Analysis

- Assumption: One true effect size which all studies are estimating
- Within-study error is the only source of sampling error
- Study weight = $1/(\text{within-study variance})$
- Study weight strongly depends on sample size

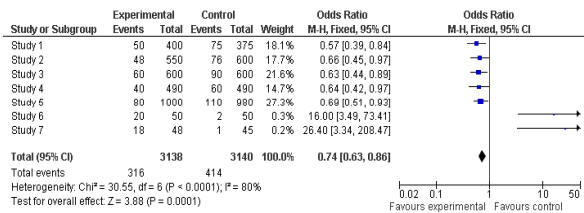
Borenstein M et al., *Introduction to Meta-Analysis*, 2009

Fixed-Effects (FE) Meta-Analysis

- What happens when there are studies with small sample sizes?
 - Smaller studies generally receive smaller weights in FE meta-analysis
 - Assumption = one true effect size among studies => smaller studies provide less information than larger studies about overall effect estimate
 - Smaller studies may be considered a less dependable source of true effect estimate than larger studies

Borenstein M et al., *Introduction to Meta-Analysis*, 2009

Example of Fixed-Effect Meta-analysis



Random-Effects (RE) Meta-Analysis

- Does not assume one true effect size among all included studies
- Each study estimating a different (true) effect size
- Want to estimate average of distribution of all (true) effects
- Studies considered a random sample of distribution of (true) effects
- Weight of each study in meta-analysis takes into account both within- and between-study variance

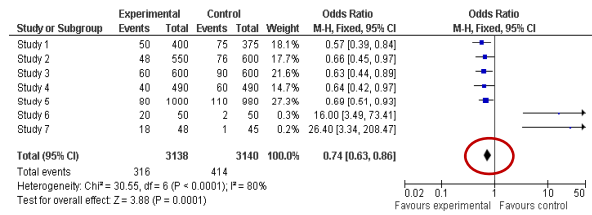
Borenstein M et al., *Introduction to Meta-Analysis*, 2009

Random-Effects (RE) Meta-Analysis

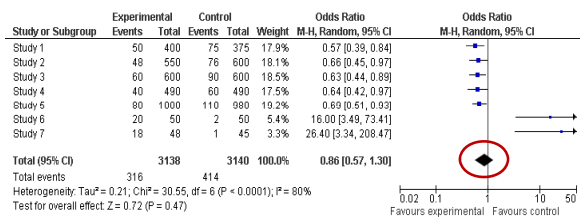
- What happens when there are studies with small sample sizes?
 - Weights assigned to studies in RE are more balanced (i.e., similar) than in FE
 - In RE, each study estimates different effect size, so information from a small study in a RE model may be more informative than a small study in FE model where all true effect sizes assumed to be the same
 - As long as between-study variation > 0, confidence intervals for the overall effect size are generally larger in RE than FE

Borenstein M et al., *Introduction to Meta-Analysis*, 2009

Example of Fixed-Effect Meta-analysis

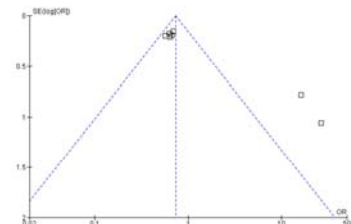


Example of Random-Effect Meta-Analysis

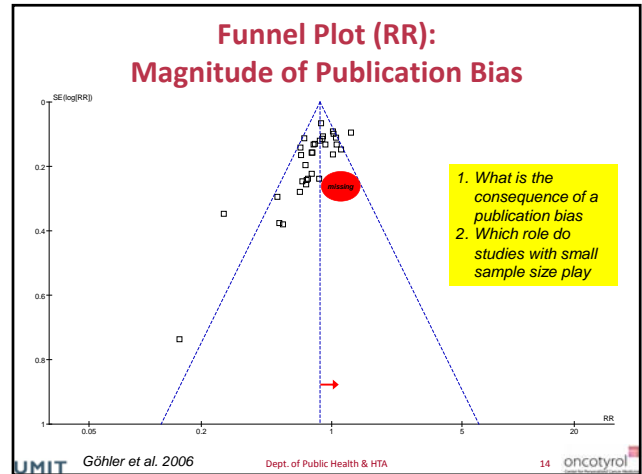
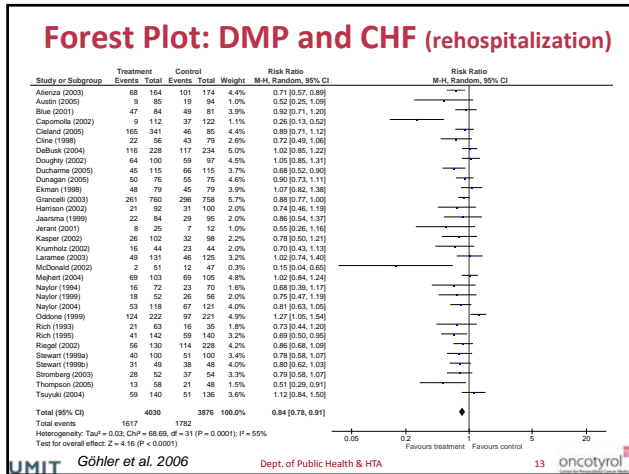


Other Considerations

- Publication Bias
 - Funnel Plot
 - Correction for Publication Bias
 - Small pat. No
 - Interpretation difficult for REM
- Study Quality
- Subgroup Analysis
 - May not be feasible with small numbers of studies



Siebert & Saverno:
Meta-Analysis and Indirect Treatment Comparisons from RCTs with Small Patient Numbers
ISPOR 2011, Madrid



Meta-Analysis: Small No of Studies

- Assessing heterogeneity in meta-analysis
 - Cochran's Q = Dependent on # of studies in analysis
 - Low power when number of studies is small
 - I^2 = Proportion of variation across studies due to real differences (heterogeneity)
 - Not directly dependent on # of studies in analysis

Higgins JP et al., Measuring inconsistency in meta-analyses, BMJ 2003
Borenstein M et al., Introduction to Meta-Analysis, 2009

UMIT Dept. of Public Health & HTA 15 oncotyrol

Meta-Analysis: Small No of Studies

- How to decide between FE and RE?

Borenstein et al. suggest...

"The selection of the model must be based solely on the question of which model fits the distribution of effect sizes, and takes account of the relative source(s) of error. When studies are gathered from published literature, the random-effects model is generally a more plausible match."
- It is not recommended to base choice of model on tests of heterogeneity.

Borenstein M et al., Introduction to Meta-Analysis, 2009

UMIT Dept. of Public Health & HTA 16 oncotyrol

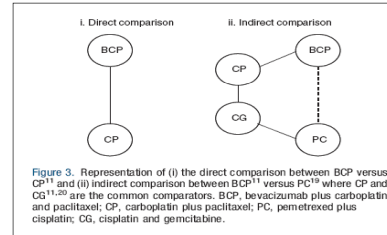
Meta-Analysis: Small Number of Studies

- If number of studies is small, may not be able to precisely determine between-study variance
- Suggestions for how to handle this type of situation:
 - Do not attempt to compute overall combined effect estimate
 - FEM instead of REM
 - Bayesian framework using informative prior for between-studies variance
 - Problem: all suggested alternatives have inherent limitations

Borenstein M et al., *Introduction to Meta-Analysis*, 2009

Network Meta-analysis - Example

Nuijten MJ et al. An indirect comparison of the efficacy of bevacizumab plus carboplatin and paclitaxel versus pemetrexed with cisplatin in patients with advanced or recurrent non-squamous adenocarcinoma non-small cell lung cancer. *Curr Med Res Opin.* 2011



Network Meta-Analysis

- Similarity assumption
 - Studies should be combined only if believed to be methodologically and clinically similar
- Consistency assumption
 - Consistency between direct and indirect comparisons
- Meta-regression
 - May be used to overcome violations of similarity and consistency assumptions
 - Reduces bias
 - Can explain sources of heterogeneity

Jansen JP et al. *Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices; part 1. Value in Health* 2011
 Hoaglin DC et al. *Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices; part 2. Value in Health* 2011

Network Meta-Analysis: Small No of Studies - Challenges

- Meta-regression
 - May not be feasible with small number of studies
 - Over-specification
 - Ecological bias
 - Patient level meta-regression if data are available

Jansen JP et al. *Value in Health* 2011

**Siebert & Saverno:
Meta-Analysis and Indirect Treatment Comparisons from RCTs with Small Patient Numbers
ISPOR 2011, Madrid**

ISPOR Task Force on ITCs states:

“Hence, the objective is to use a model that sufficiently fits the data (and reduces confounding bias) but that provides stable parameter estimates. The choice of a fixed- or random-effects meta-analysis model, with or without covariate interactions, can be made by comparing different competing models regarding their goodness-of-fit to the data.”

Jansen JP et al. *Value in Health* 2011

When are Meta-Analysis and ITC Used in the Context of HTA?

- Chapter benefit assessment of HTA report
 - Usually, Cochrane-type meta-analysis
 - Increasing use of ITC, e.g. IQWiG (cave assumptions)
- Chapter economic model of HTA report
 - Both types of metaanalyses
- Development of clinical guidelines
- Informing further research priorities (value-of-information analysis)
- **ITCs do not replace head-to-head RCTs, but may have to be used as best available evidence**

More about evidence synthesis?
→ HTADS Continuing Education Program Certified Courses
www.htads.at