Random-effects network meta-analysis of studies of binary outcomes: Comparison of frequentist, MCMC and INLA method with data on exacerbations in COPD patients

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Workshop of Bayes WG and SFB 876, Dortmund

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Overview

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(1) Introduction

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Network meta-analysis investigates several treatments in several trials, but not all treatments in every trial. E.g. in patients with Chronic Obstructive Pulmonary Disease (COPD), the following comparisons have been performed:

- Salmeterol (SAL) – Placebo (PLA)
- Formoterol (FOR) – PLA
- Indacaterol (IND) – PLA
- Tiotropium (TIO) – PLA
- TIO – SAL

Specific problems:

(a) Some direct comparisons are missing, e.g. between TIO and IND, and indirect comparisons are necessary.

(b) The comparison TIO-SAL is also informed through the comparisons SAL-PLA and TIO-PLA.

(1) Introduction

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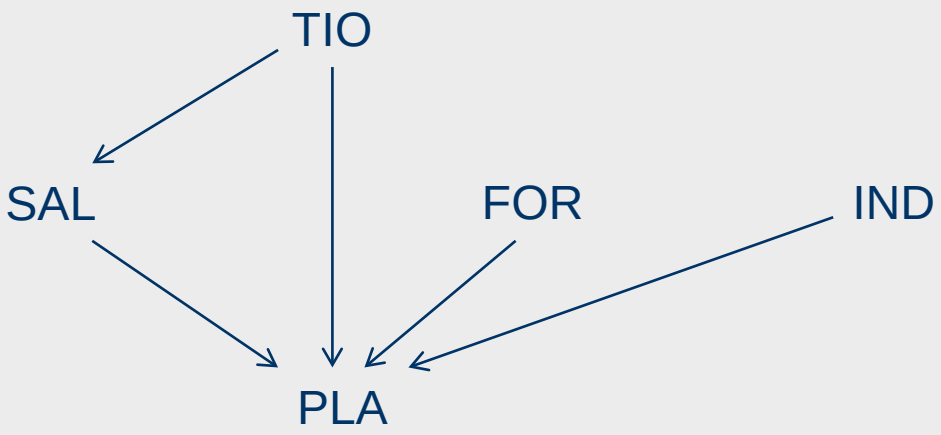
Network representation of available comparisons (instead of list):



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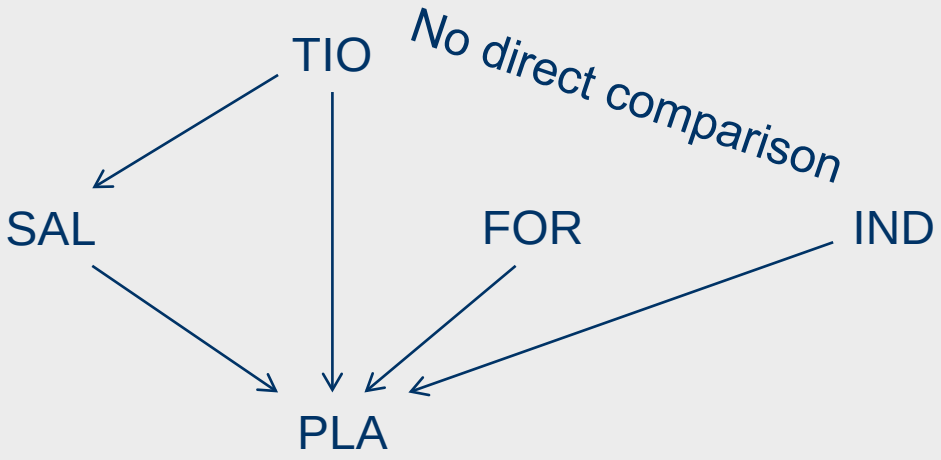

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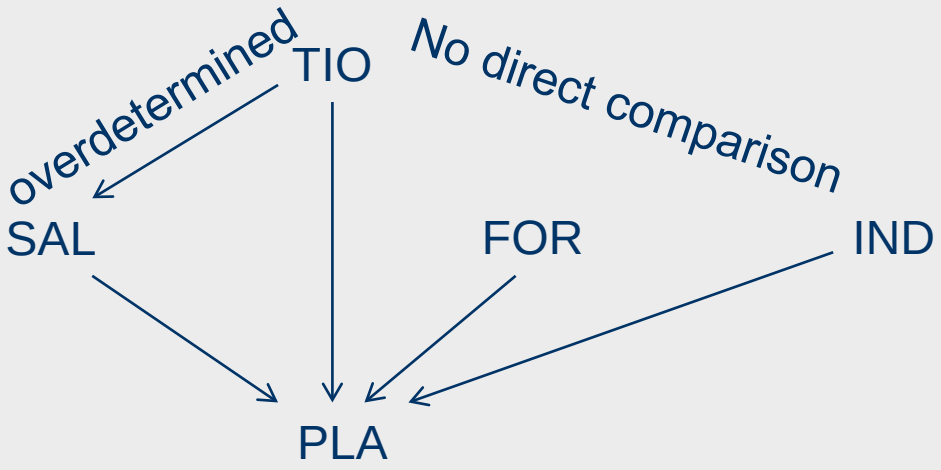

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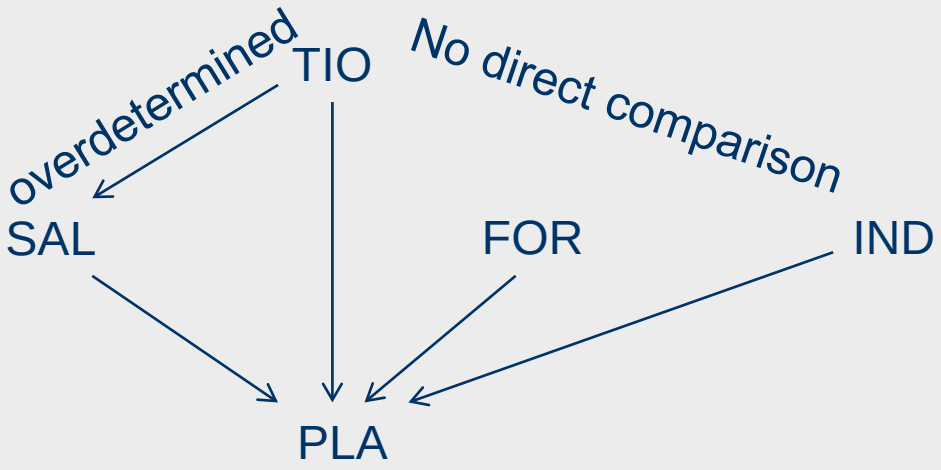

The overdetermination in the triangle TIO/SAL/PLA may lead to „inconsistency“ of the effect estimates – not to be mixed up with „heterogeneity“, which comes from multiple measurement of the same paired comparison

Krahn et al., BMC 2013; Cipriani et al., AIM 2013

(1) Introduction

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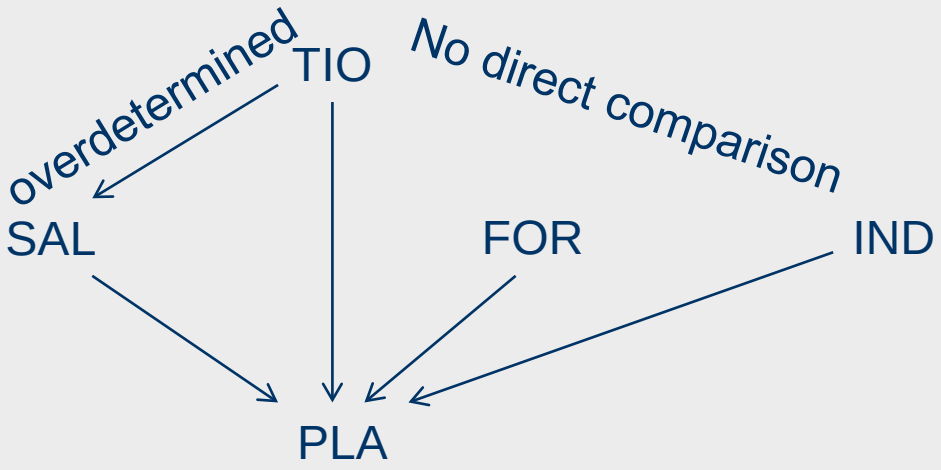

The GLMM for the proportions of patients with event, in study k with treatment i, is:

$$\text{Logit}(\pi_{ik}) = \tau_i + \mu_k + a_{ik}$$

with τ_i fixed for all i, μ_k fixed for all k, a_{ik} random, and $\tau_1 = 0$ (Placebo) and $\mu_1 = 0$ (Study 1).

Jones et al., Pharm.Stat. 2011; Senn et al., S.M.M.R. 2013

(2) Estimation methods for the parameters in the GLMM
(a) frequentist (likelihood-based)

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Investigate the likelihood (or better: its LN) around its estimated maximum:

As a function of the parameters, the inverse of the expected value of the matrix of the 2nd derivatives of LN (likelihood) is asymptotically (with the number of groups↑ or the denominators in each group↑) multi-normally distributed. That means, it can be interpreted as a „standard error“ for the parameters.

As an approximation, calculate the inverse of the matrix of the 2nd derivatives, evaluated at the estimated maximum.

Random effects are treated as nuisance parameters. We investigate the marginal likelihood of the fixed-effect parameters, and the behaviour at its maximum, through deterministic integration over a grid of values of the random parameters.

Now not shown: details of further variants of the likelihood (pseudo-L., penalized quasi-L., profile L.)

McCullagh/Nelder 1989 p. 469-473+114-117; Jones et al., Pharm.Stat. 2011

(2) Estimation methods for the parameters in the GLMM
(b) MCMC

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The Markov chain Monte Carlo (MCMC) method scans the posterior distribution of all parameters together in a step-by-step manner. The empirical distribution of the sampled parameter values converges point-wise to the correct distribution of the parameters. The results of a converged, sufficiently long MCMC run are therefore, with probability 1 and with vanishing simulation error, the reference with which the results of all other methods can be compared.

Geman/Geman, IEEE Trans. Pattern Analysis 1984; Gelfand/Smith, J.A.S.A. 1990; Higgins et al., J.R.S.S.A 2009; Lunn et al. 2013

(2) Estimation methods for the parameters in the GLMM
(c) INLA

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Also the integrated nested Laplace approximation (INLA) investigates the posterior distribution of the parameters. The GLMM shown above falls in its range of definition, as follows.

Rue et al., J.R.S.S.B 2009

www.imbei.uni-mainz.de/bayes/programm/2009-Rue-Lecture1.pdf

(2) Estimation methods for the parameters in the GLMM
(c) INLA

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We have per trial arm (study k, treatment i): $r_{ik} \sim \text{Bin}(n_{ik},\pi_{ik})$
with the already known dependencies between the π_{ik}:

$\eta_{ik} := \text{logit}(\pi_{ik}) = \tau_i + \mu_k + a_{ik}$

fixed, i.i.d.random $N(0,\sigma^2)$

$\tau_1 = 0, \mu_1 = 0$

With normal prior distributions for $\tau_2, ..., \tau_I$ and $\mu_2, ..., \mu_K$, the composite variable $x := (\tau_2, ..., \tau_I, \mu_2, ..., \mu_K, \eta)$ is multivariate-normal. Re-write this in a hierarchical manner, and let the parameter vector of the multinormal distribution be $\theta := (\tau_2, ..., \tau_I, \mu_2, ..., \mu_K)$ with variance σ^2:

$r \mid x, \theta \sim \text{Product}_{i,k}\, p(r_{ik} \mid \eta_{ik}, \theta)$

$x \mid \theta \sim p(x|\theta) = N(0, \Sigma(\theta))$

$\theta \sim p(\theta)$ prior distribution, low dimension.

This model class is called a „latent Gaussian model“.

See also Higgins et al., J.R.S.S.A 2009, p.144

(2) Estimation methods for the parameters in the GLMM
(c) INLA

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If now most components of x are conditionally independent, i.e.

x_i indep. from x_j | all other x's (Markov property) ,

the precision matrix (not the variance-covariance matrix) of x will be sparse, and we have a „Gaussian Markov Random Field" (GMRF).

Note that this re-parameterisation could be done in any case. It is the estimation method where the differences between the 3 methods come in.

INLA integrates over x through Laplace integration, which sets up a truncated Taylor series for LN(posterior), then integrates the posterior through application of the chain rule. This is exact for normally-distributed parameters. The variance σ^2 is integrated deterministically over a grid.

(3) The COPD/exacerbation example

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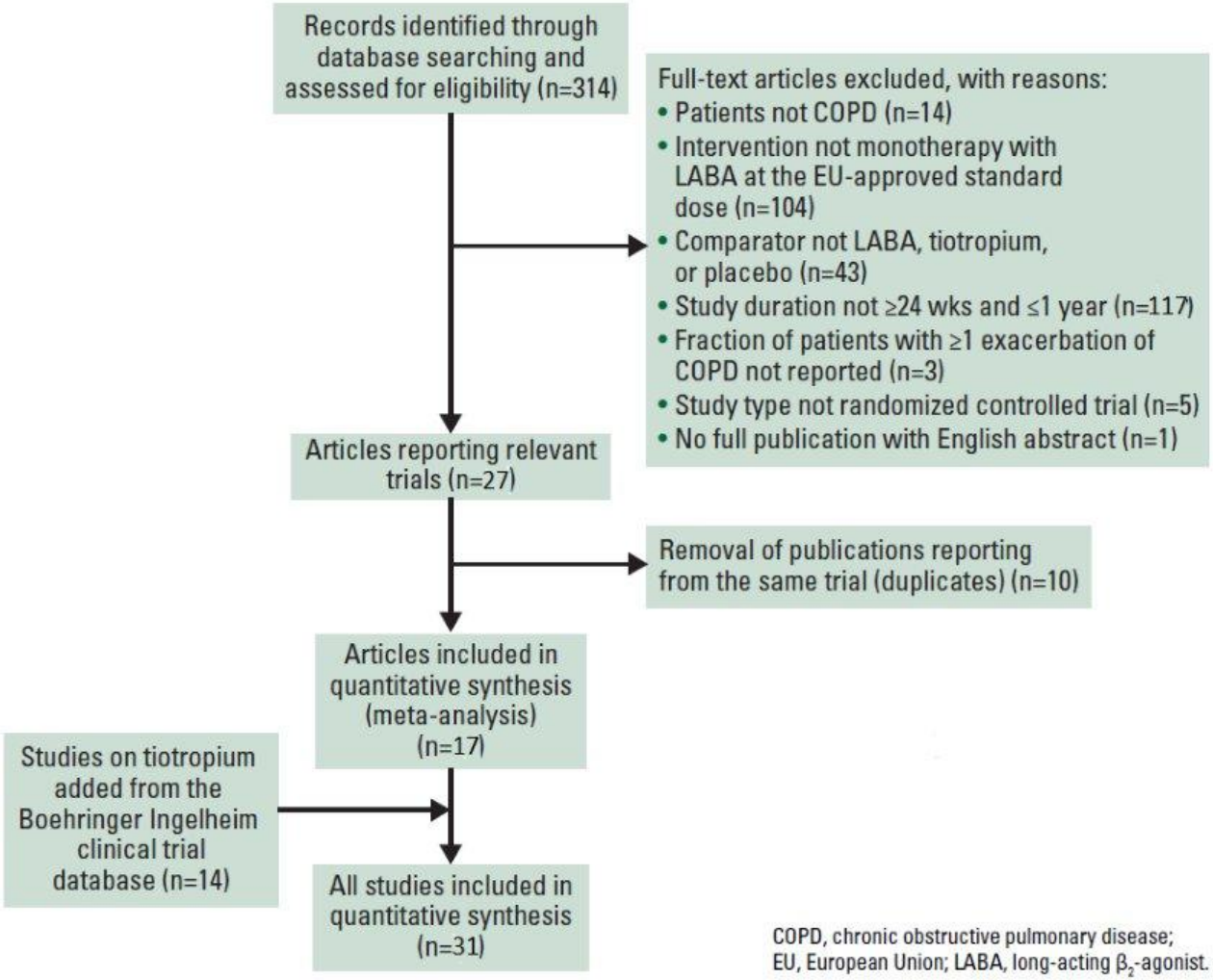
Studies were selected that were comparable in length (≥ 6, ≤ 12 months), in the patient characteristics, and in the treatments (double-blind inhalations) and doses.

The endpoint was in all cases binary (patient had exacerbation no/yes), and the definition was uniform across studies. Note that all patients who dropped out with no observed event were counted as „no“.

See the warning example of Thorlund 2013 (for rheumatoid arthritis).

Thorlund et al., Ann.Rheum.Dis. 2013

(3) The COPD/exacerbation example



COPD, chronic obstructive pulmonary disease; EU, European Union; LABA, long-acting β_2-agonist.

This is the PRISMA diagram. K=31.

Moher et al., B.M.J. 2009; Buhl et al., poster ATC 2013

(4) Results and comparison

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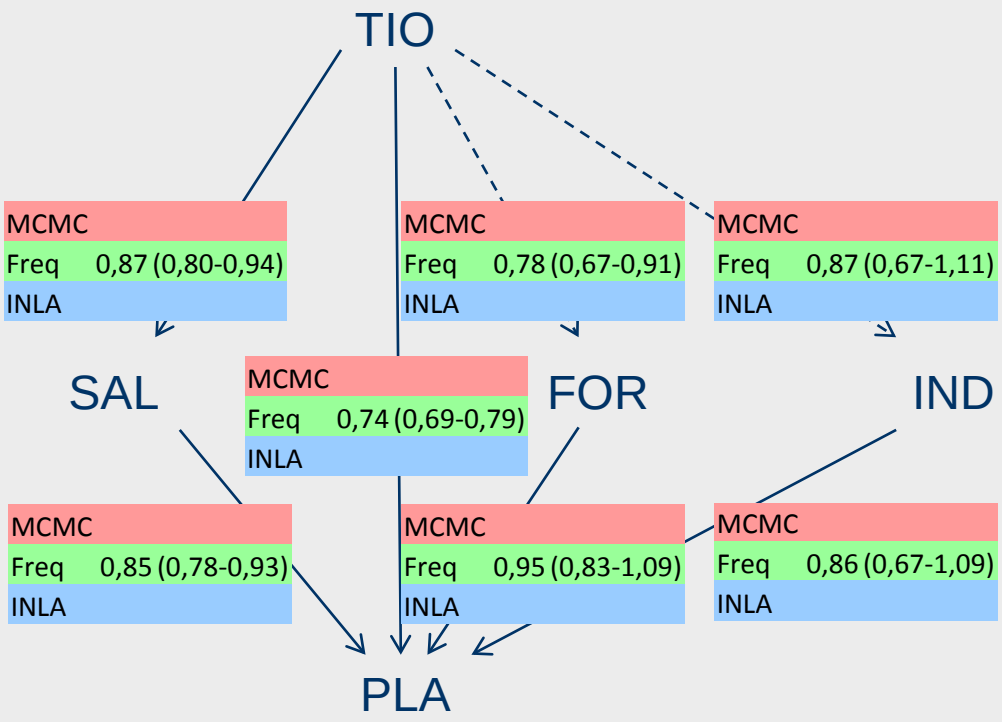
In the network diagram, the results for the odds ratios are as follows:



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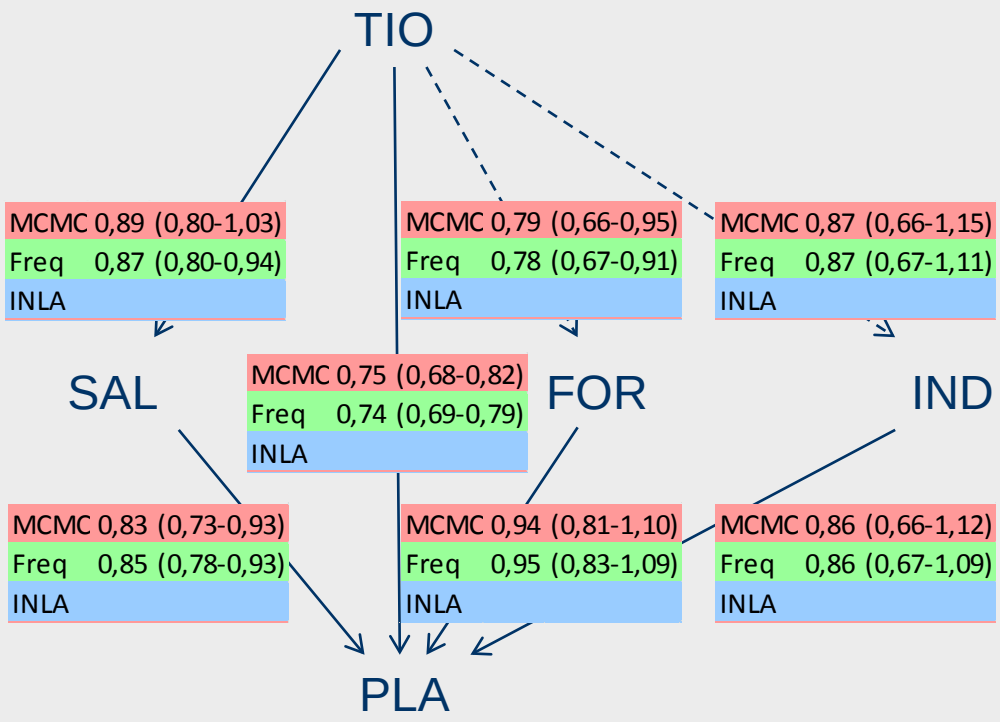

The number of iterations was 10000 + 200000/20, which is high. No problems with starting values.

Dias et al. 2011/2014; Jansen et al., Value in Health 2008; Rücker/Schwarzer, Stat.Med. 2014

(4) Results and comparison

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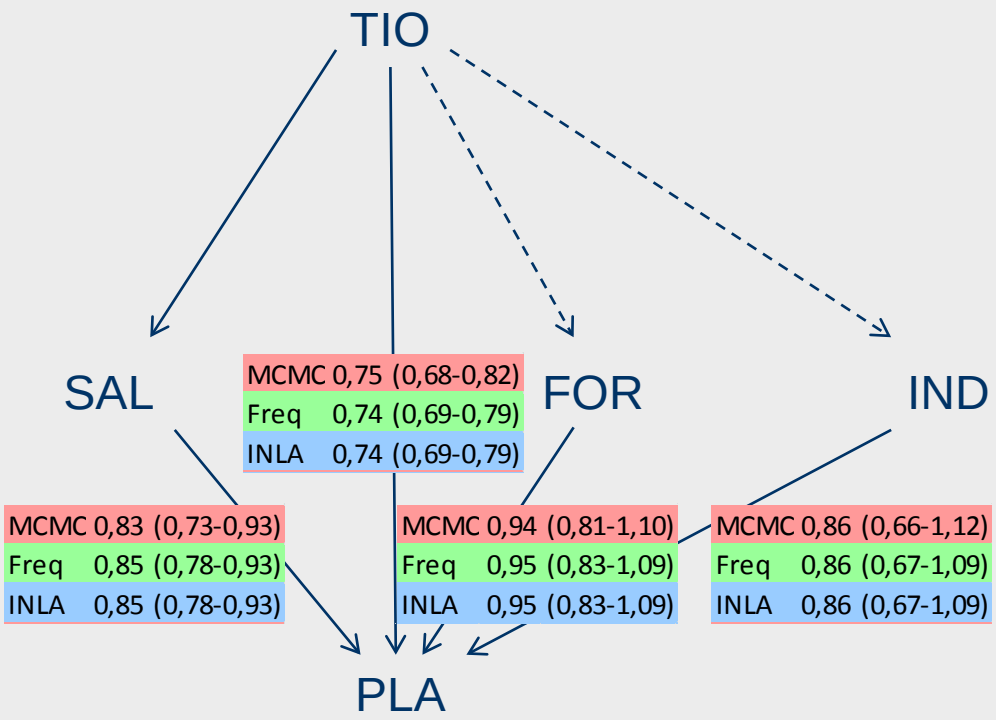

We were regrettably not able to extract results for comparisons other than with PLA.

www.imbei.uni-mainz.de/bayes/programm/2009-Rue-Lecture1.pdf

(4) Results and comparison

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The sampled points from the MCMC sequence can be post-processed to obtain a ranking.
Calculate the degree of certainty that treatment i assumes rank m:

Treatment	Degree of certainty for rank				
	1	2	3	4	5
PLA					
SAL					
FOR					
IND					
TIO					

Circle areas are proportional to degree of certainty.

Salanti et al., J.Clin.Epi. 2011; Woods et al., BMC 2010

(5) Discussion, conclusion

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In this example we see no fundamental problems; the distribution of the π_{ik}'s and a_{ik}'s is approximately normal and therefore both the ML estimation and the INLA method perform well.

Some small divergences in the CI could not be resolved. One possible explanation is MCMC simulation error.

It is worth-while to move the investigation closer to the limits, namely to let the r_i's (numerators) go closer towards zero.

Medically, the drop-out question needs more attention, and the time to drop-out (including unspecific mortality) should be considered as censoring time. This comes in addition to the consideration of event times (➔ HR models). The transformation of Woods 2010 projects counted events on a time scale. Note however that this assumes a constant hazard over the observation time and implies an exponential distribution for the event times.

Fong et al., Biostatistics 2010; Capanu et al., Stat.Med. 2013; Woods et al., BMC 2010

(5) Discussion, conclusion

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In the process of drug development, network meta-analysis will probably have most of its value either in Phase 4 (e.g. reimbursement discussions), in Marketing (ranking) or in the early stages of a project (internal planning and decision making). We do currently not see much application in Phase 3 and registration-related discussions.

Schmidli et al., S.M.M.R. 2013; Di Scala et al., Stat. Med. 2013

(6) Literature

Krahn U, Binder H, König J:
A graphical tool for locating inconsistency in network meta-analyses.
BMC Medical Research Methodology 2013; 13 (35): 1-18

Cipriani A, Higgins JPT, Geddes JR, Salanti G:
Conceptual and Technical Challenges in Network Meta-analysis.
Annals of Internal Medicine 2013; 159: 130-137

Jones B, Roger J, Lane PW, Lawton A, Fletcher C, Cappelleri JC, Tate H, Moneuse P:
Statistical approaches for conducting network meta-analysis in drug development.
Pharmaceutical Statistics 2011;10: 523-531

Senn S, Gavini F, Magrez D, Scheen A:
Issues in performing a network meta-analysis.
Statistical Methods in Medical Research 2013; 22: 169-189

(7) References

McCullagh P, Nelder JA:
Generalized Linear Models (2nd ed.).
London / Glasgow / Weinheim / New York / Tokyo / Melbourne / Madras:
Chapman & Hall 1989

Geman S, Geman D:
Stochastic Relaxation, Gibbs Distributions, and the Bayesian Restoration of Images.
IEEE Transactions of Pattern Analysis and Machine Intelligence 1984; 6: 721-741

Gelfand AE, Smith AFM:
Sampling-Based Approaches to Calculating Marginal Densities.
Journal of the American Statistical Association 1990; 85: 398-409

Higgins JPT, Thompson SG, Spiegelhalter DJ:
A re-evaluation of random-effects meta-analysis.
Journal of the Royal Statistical Society A 2009; 172: 137-159

(7) References

Lunn D, Jackson C, Thomas A, Best N, Spiegelhalter D:
The BUGS Book.
Boca Raton/FL: Chapman&Hall / CRC 2013

Rue H, Martino S, Chopin N:
Approximate Bayesian inference for latent Gaussian models by using integrated nested Laplace approximations [with discussion].
Journal of the Royal Statistical Society B 2009; 71: 319-392

Rue H:
Bayesian computing using INLA. Presentation, Lübeck 2009-12-03
www.imbei.uni-mainz.de/bayes/programm/2009-Rue-Lecture1.pdf

Thorlund K, Druyts E, Aviña-Zubieta JA, Wu P, Mills EJ:
Why the findings of published multiple treatment comparison meta-analyses of biologic treatments for rheumatoid arthritis are different: an overview of recurrent methodological shortcomings.
Annals of Rheumatic Diseases 2013; 72: 1524-1535

(7) References

Moher D, Liberati A, Tetzlaff J, Altman DG:
Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.
British Medical Journal 2009; 339: 332-336

Buhl R, Vogelmeier C, Kögler H, Schmidt H, Geier S, Glaab T, Rabe KF, Welte T:
Network Meta-analysis Comparing Tiotropium With long-acting β_2-agonists.
Poster, American Thoracic Society congress, Philadelphia 2013

Dias S, Welton NJ, Sutton AJ, Ades AE:
NICE DSU technical support document 2: A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. Report by the Decision Support Unit August 2011 (last updated April 2014)
http://www.nicedsu.org.uk/TSD2%20General%20meta%20analysis%20corrected%2015April2014.pdf

(7) References

Jansen JP, Crawford B, Bergman G, Stam W:
Bayesian Meta-Analysis of Multiple Treatment Comparisons: An Introduction to Mixed Treatment Comparisons.
Value in Health 2008; 11: 956-964

Rücker G, Schwarzer G:
Reduce dimension or reduce weights? Comparing two approaches to multi-arm studies in network meta-analysis.
Statistics in Medicine 2014; 33: 4353-4369

Salanti G, Ades AE, Ioannidis JPA:
Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial.
Journal of Clinical Epidemiology 2011; 64: 163-171

(7) References

Woods BS, Hawkins N, Scott DA:
Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: A tutorial.
BMC Medical Research Methodology 2010; 10 (54): 1-9

Fong Y, Rue H, Wakefield J:
Bayesian inference for generalized linear mixed models.
Biostatistics 2010; 11: 397-412

Capanu M, Gönen M, Begg CB:
An assessment of estimation methods for generalized linear mixed models with binary outcomes.
Statistics in Medicine 2013; 32: 4550-4566

(7) References

Schmidli H, Wandel S, Neuenschwander B:
The network meta-analytic-predictive approach to non-inferiority trials.
Statistical Methods in Medical Research 2013; 22: 219-240

Di Scala L, Kerman J, Neuenschwander B:
Collection, synthesis, and interpretation of evidence: a proof-of-concept study in COPD.
Statistics in Medicine 2013; 32: 1621-1634