The NEtwork meta-analysis with Missing Outcome data (NEMO) project: a combination of a systematic overview, empirical and simulation study

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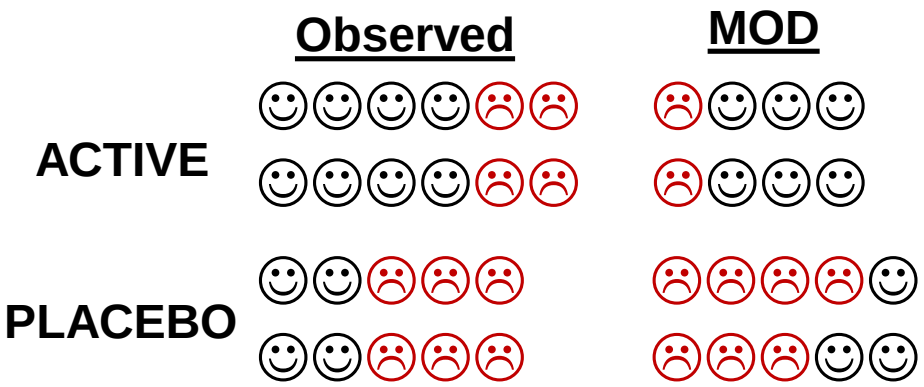
Why the NEMO project was proposed? (1)

- **Missing outcome data** (MOD) are ubiquitous in clinical trials…
- ... and in systematic reviews, inevitably!
- Implications of MOD on results:
  - **loss of precision**, if MOD are excluded;
  - **risk of bias**, if MOD are handled inappropriately

(i.e. exclusion or imputation before analysis).



%MOD: 40% vs 50% (active vs placebo)

Truth	14/20	7/20	4.3 (1.2, 16)
Exclude	8/**12**	4/**10**	3.0 (0.5, 17)
Impute ☹	8/20	4/20	2.7 (0.6, 11)
Impute ☺	16/20	14/20	1.7 (0.4, 7.3)

Why the NEMO project was proposed? (2)

- Several strategies to address MOD in systematic reviews* **but without evidence on their performance:**
  - exclude before analysis with & without uncertainty due to MOD;
  - impute before analysis & ignore uncertainty due to MOD;
  - model using pattern-mixture or selection model.

*Higgins JPT, Deeks JJ, Altman DG on behalf of the Cochrane Statistical Methods. Chapter 16: Special topics in statistics. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration; 2011

Why the NEMO project was proposed? (3)

- **Intention-to-treat (ITT)** principle preferred in the presence of MOD.
- Appropriate application of ITT in systematic reviews requires:
  - Distinction between observed outcomes and MOD;

  (observation-carried-forward methods hinder such an accurate distinction)

  - Information on the reasons for MOD;

  (transparent and detailed reporting of trials is required)

  - Sensitivity analyses that include all randomised individuals under plausible scenarios about MOD.

  (to evaluate the robustness of the results of primary analysis)

.

Why the NEMO project was proposed? (4)

- Reviewers fail to provide an accurate extraction of outcome data from the included trials.

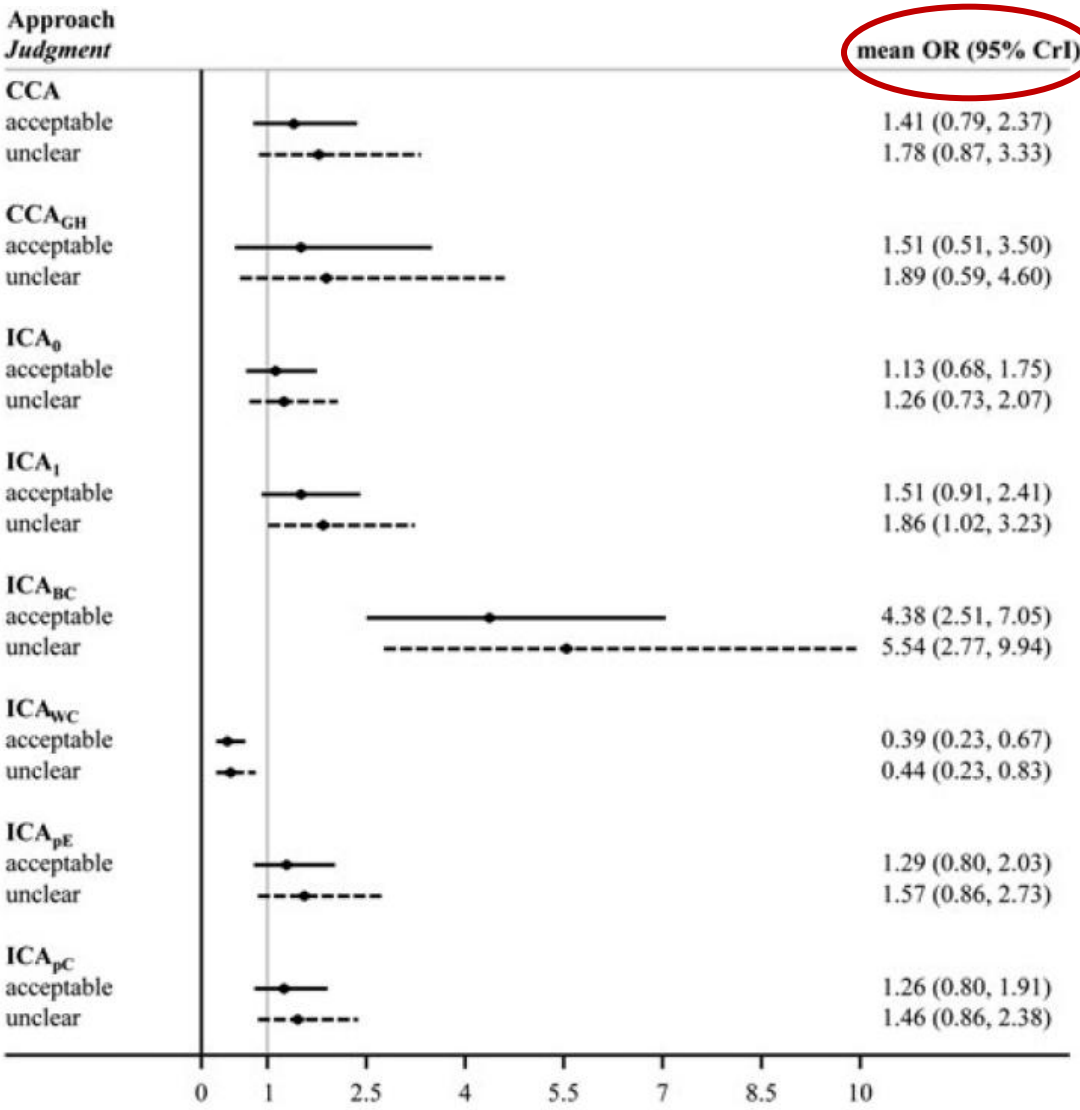
Item	Aspects reported in the systematic review	Extraction evaluation		
		Acceptable	Unclear	Unacceptable[a]
i.	Information on outcome of completers for all included studies	✓		
ii.	Information on outcome "withdrawal" for all included studies	✓	✓	✓
iii.	Explicit description of how missing outcome data in meta-analyses is handled	✓	✓	
iv.	Information on outcome of completers and/or outcome "withdrawal" but only for a minority of included studies			✓

[a]Meta-analyses that included at least one study with calculated negative non-events were immediately considered to be "unacceptably" extracted.

Cochrane Mental Health Group	Extraction Is Judged		
	Acceptable	Unclear	Unacceptable
Depression, anxiety and neurosis	10	17[a]	25
Schizophrenia	0	42[a]	16
Developmental, psychosocial and learning problems	1	1	1
Total	***11***	***60***	***42***

[a]Three systematic reviews in the Schizophrenia Group and one in the Depression, Anxiety and Neurosis Group did not provide adequate information for indicate "acceptable" extraction but reported attrition rates below 5%, which were too low to raise accuracy concerns.

Why the NEMO project was proposed? (5)



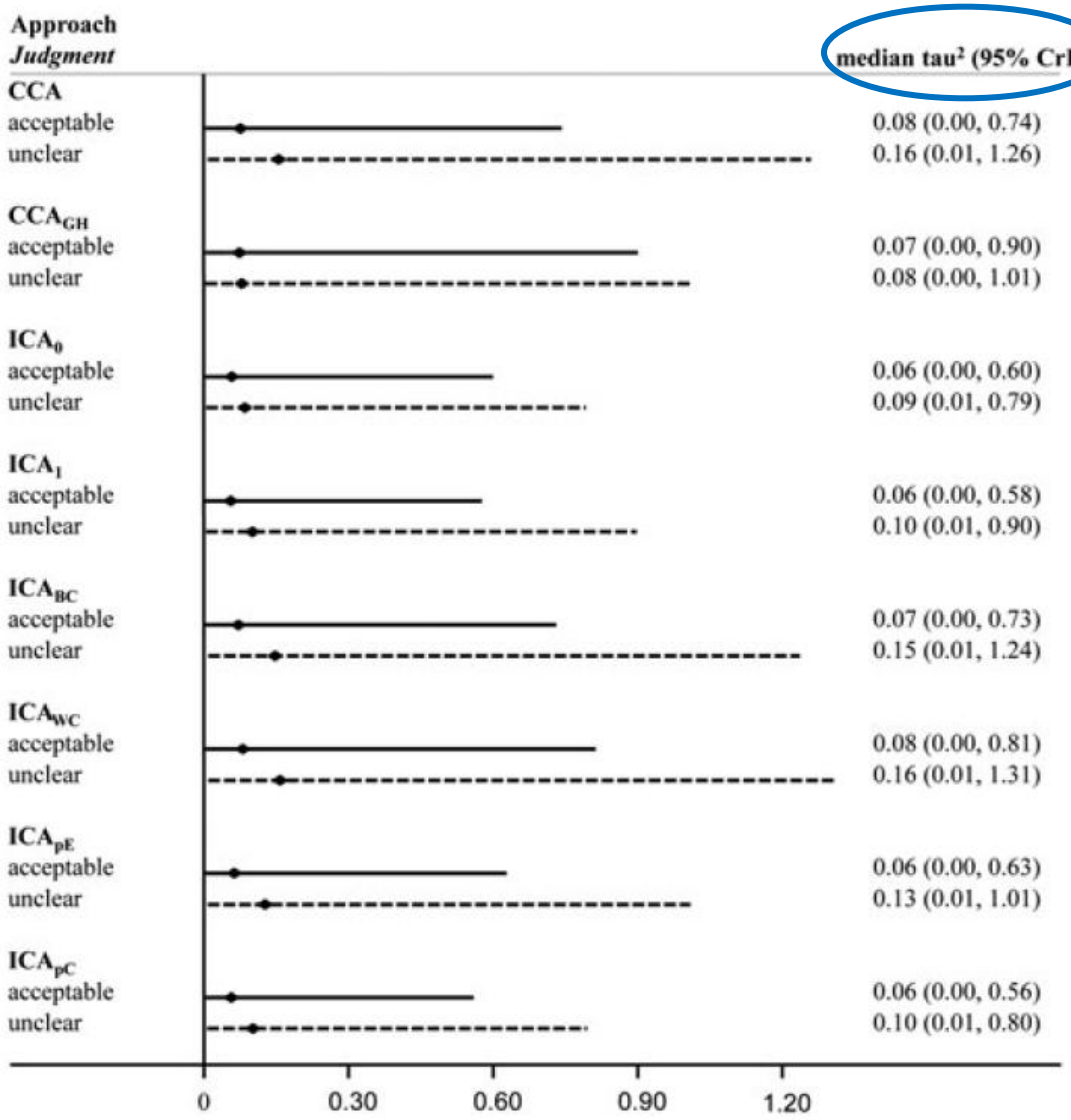
➢ Inaccurate extraction of trial data may :

- lead to **biased meta-analysis results**;
- **hinder the performance** of methods to handle MOD.

*From a systematic review with a meta-analysis with **‚acceptable‘** extraction and the same meta-analysis on LOCF data (**‚unclear‘**).*

Hetrick SE, McKenzie JE, et al. Newer generation antidepressants for depressive disorders in children and adolescents. Cochrane Database Syst Rev. 2012;11: CD004851.

Why the NEMO project was proposed? (6)



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‘What is the **reporting quality of systematic reviews of multiple interventions** in terms of MOD?’

Search strategy

Published databases considered:

- Zarin et al. → **inception – 14/04/2015**; **≥ 4** interventions
- Tan et al.
- Bafeta et al.

→ **1997 – 07/2012**; **≥ 3** interventions

- Nikolakopoulou et al. → **inception – 12/2012**; **≥ 4** interventions

Our own search:

08/2012 – 03/2017; **≥ 3** interventions; using **Petropoulou et al. search strategy** in MEDLINE, EMBASE and the CDSRs.

Eligibility strategy (1)

Following Zarin et al.:

- ✓ Systematic reviews of randomized controlled trials (RCTs);
- ✓ No language restriction;
- ✘ Diagnostic test accuracy studies;
- ✘ Genetic studies;
- ✘ Observational studies;
- ✘ Mixture of RCTs and observational studies;
- ✘ Number of included trials **<** number of interventions.

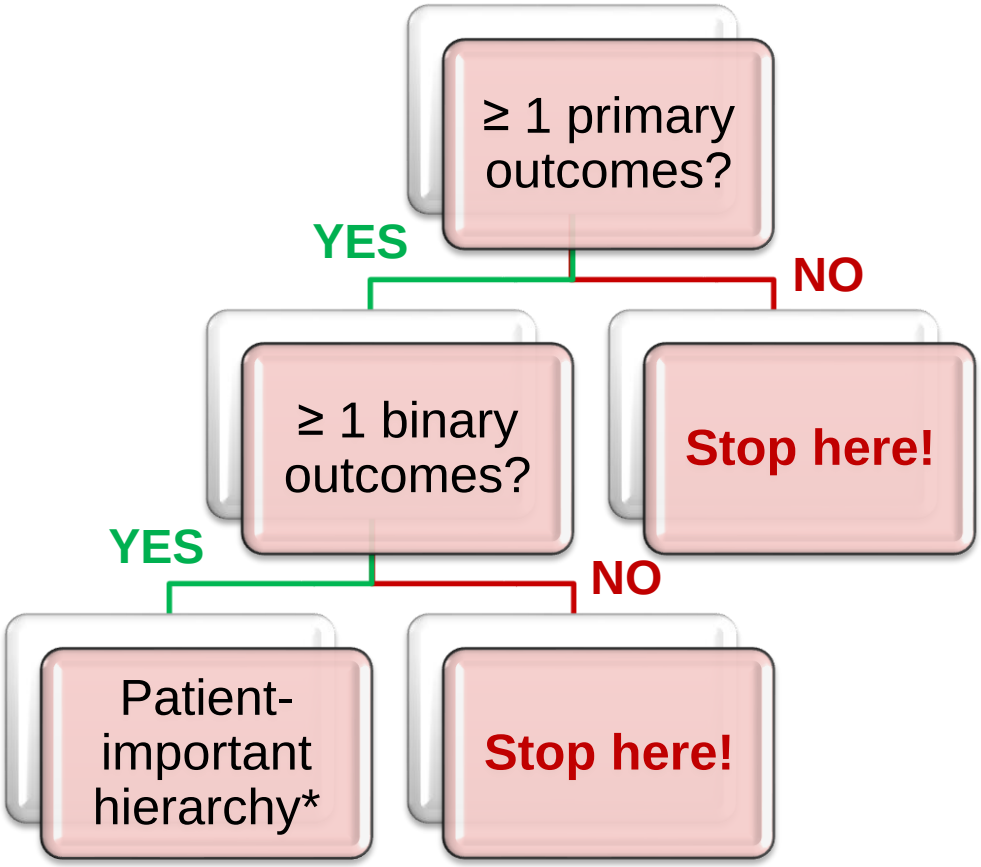
Eligibility strategy (2)

Our own criteria:

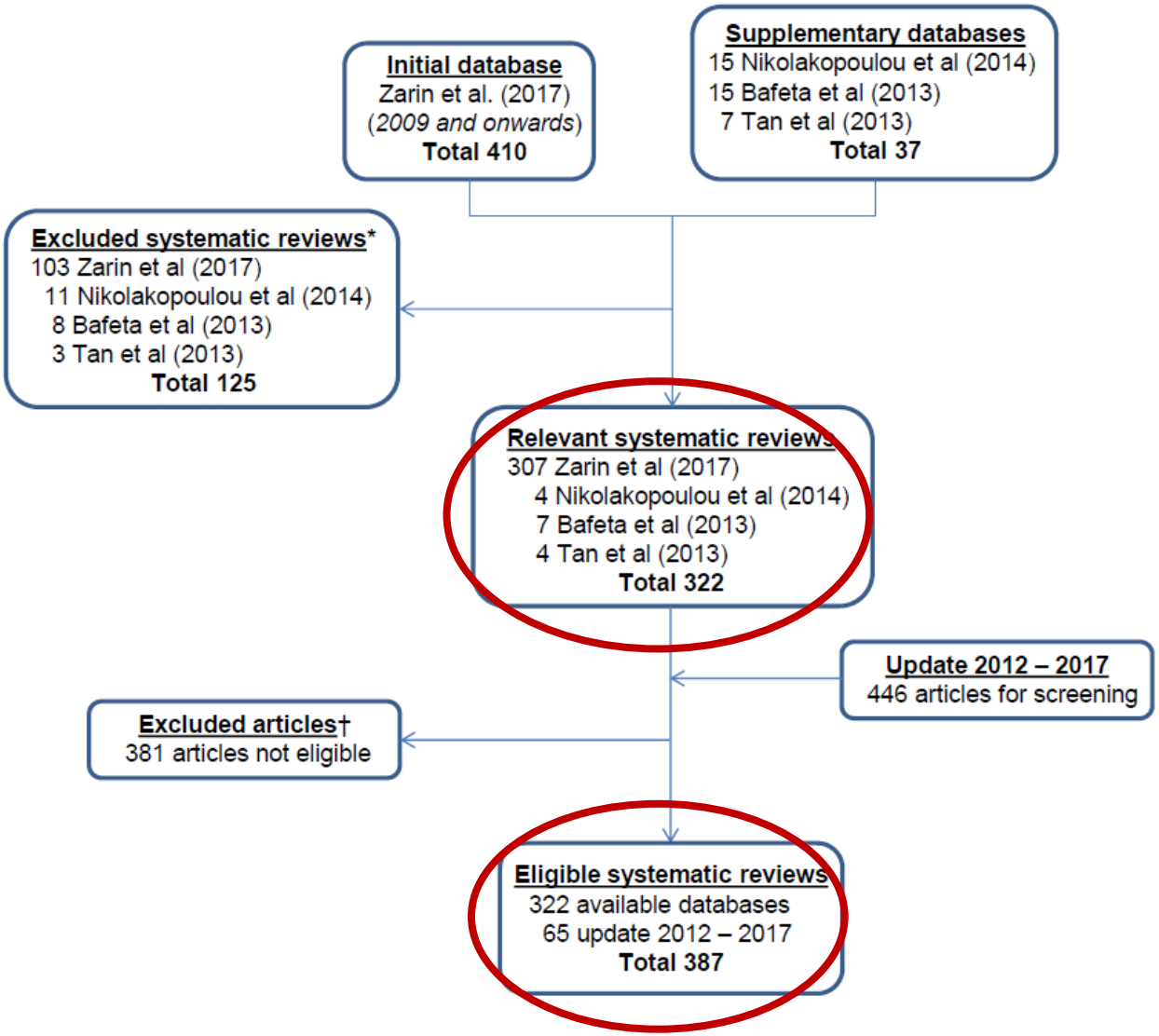
- ✓ At least 3 interventions are investigated;
- ✓ Systematic reviews published from **2009 and onwards**;
  - ❖ *the new Cochrane risk of bias tool was published during 2009*
- ✗ RCTs with non-standard design;
  - ❖ e.g. *quasi, crossover, factorial, cluster, split-mouth.*
- ✗ Overviews of systematic reviews;
- ✗ MOD investigated as single primary outcome.

Eligibility strategy (4)

For each eligible Systematic review:



*Akl EA, Kahale LA, Agarwal A, et al. Impact of missing participant data for dichotomous outcomes on pooled effect estimates in systematic reviews: a protocol for a methodological study. Syst Rev 2014;3:137



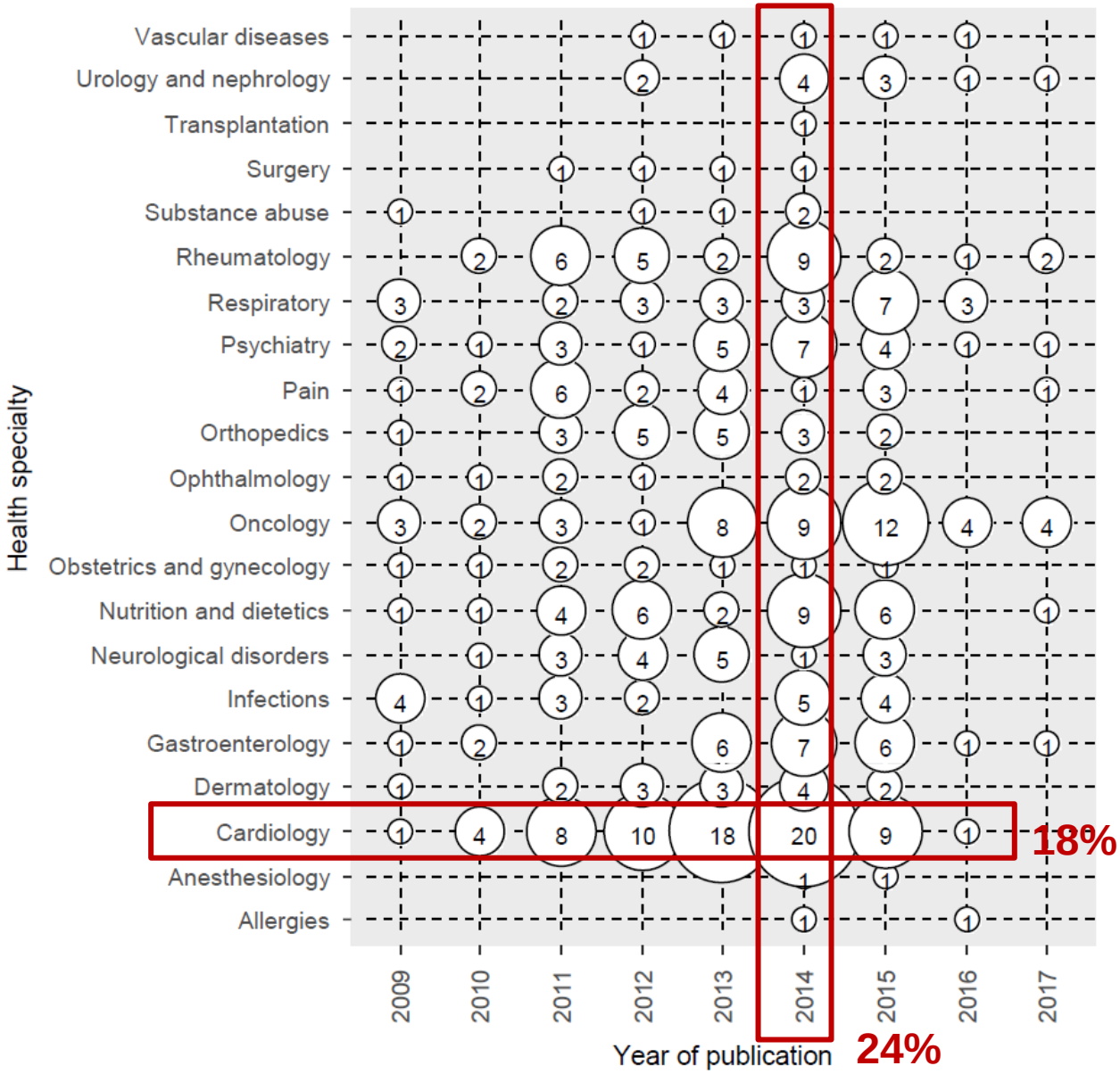
***Reasons for exclusion**

- 3 articles in Chinese
- 1 article in Hungarian
- 9 dropout as the primary outcome
- 3 letter to editor, editorial, commentary
- 6 meta-epidemiological or empirical studies
- 14 methodological articles
- 57 mixture of RCTs with non-standard design
- 16 mixture of RCTs with observational studies
- 6 number of interventions ≥ number of trials
- 6 overviews of systematic reviews
- 1 protocol of systematic review
- 4 published before 2009 (incident in Zarin et al)

†Reasons for exclusion

- 1 article in Russian
- 5 NMA/MA of diagnostic studies
- 2 disconnected network
- 18 letter to editor, editorial, commentaries
- 12 literature reviews on NMA/MA
- 6 meta-epidemiological or empirical studies
- 46 methodological articles on NMA/MA
- 13 mixture of RCTs with non-standard design
- 10 mixture of RCTs with observational studies
- 3 NMA on laboratory or animal studies
- 21 number of interventions ≥ number of trials
- 4 overviews of systematic reviews
- 15 Post-hoc NMA/ITCs from several published MAs or selected clinical trials
- 13 protocol of systematic review
- 3 software reports on NMA
- 4 systematic reviews of observational studies
- 5 systematic reviews on 2 interventions
- 14 tutorials on NMA
- 3 valid NMA was reported not to be feasible
- 137 no systematic reviews
- 46 duplicates

387 selected Systematic Reviews



Non-Cochrane reviews: 98%

Addressing MOD in the PROTOCOL

Protocol availability

- **37 (10%) reviews only**

Strategy for MOD

- **14 (38%) reviews only**

Actually addressed MOD

- **12 (86%) reviews only**

24% intention-to-treat

13% MOD as secondary

5% exclude MOD

Addressing MOD in the REVIEW

Explicitly reported **MOD** are **present**

- **273 (70%) reviews**

Addressed MOD with ≥1 strategy

- **153 (56%) reviews only**

71% intention-to-treat

40% MOD as secondary

10% sensitivity analyses

Applied intention-to-treat analysis

- **42%** as reported in trials;
- **28%** applied ITT *de novo*;
- **12%** combination of both.

Addressing MOD in the REVIEW

Assessed attrition bias?

- **198 (51%) reviews**

74% Cochrane RoB tool

34% Jadad scale

10% sensitivity analyses

Justified the risk of bias level

- **18 (9%) reviews only**

Ambiguous assessment of attrition bias (19%)

- **51%** overall score is provided;
- **26%** results on RoB omitted;
- **21%** results on attrition bias omitted.

Addressing MOD in the REVIEW

Implications of MOD?

- **88 (32%) out of 273 reviews**

66% MOD as secondary

18% sensitivity analysis

12% MOD prevalence

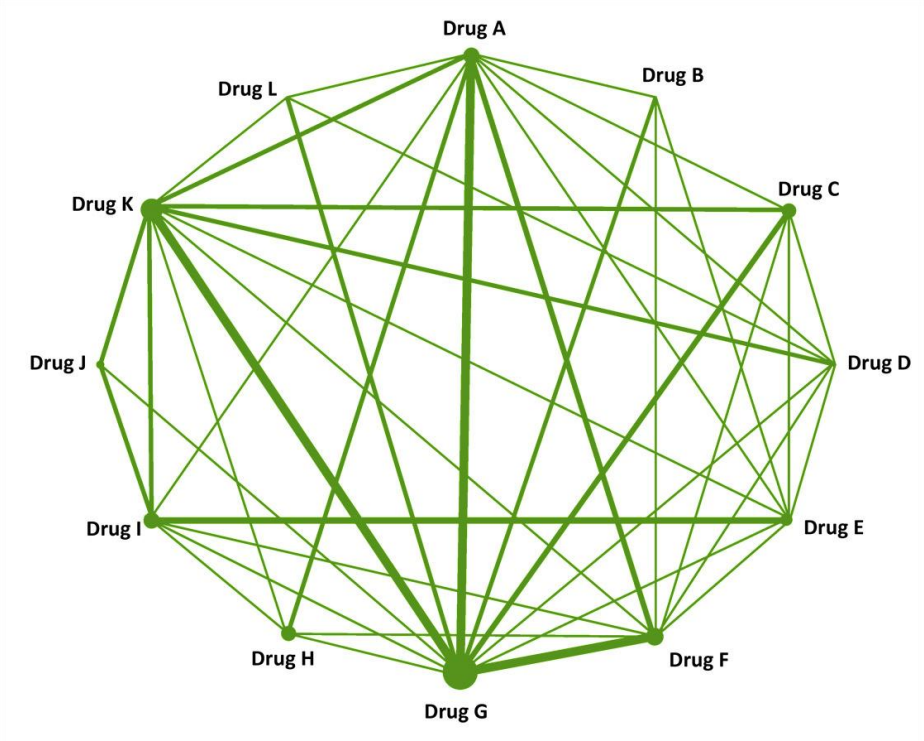
Where reported mainly?

- **74 (84%) in Discussion**
- **46 (52%) in Abstract**

Which NMA components mainly?

- **84 (95%)** NMA effects;
- **13 (15%)** intervention ranking.

273 NMAs with present MOD



https://www.quantics.co.uk/blog/software-bayesian-network-meta-analyses/

Addressing MOD in the **NMA**

Strategy explicitly reported

- **in 113 (40%) reviews only**
  - ***92% claimed intention-to-treat***

60% as reported in trials

22% exclusion of MOD

17% intention-to-treat

Actual strategy judged

- **agreed with 14 (12%) reviews**
- **able to judge in 95 (35%) reviews**

Intention-to-treat analysis (16; 17%)

- **8** all MOD as non-events;
- **1** all MOD as events;
- **7** no scenario is provided.

Addressing MOD in the **NMA**

Applied sensitivity analysis

- **16 (6%) reviews only**

7 trial exclusion

5 available case analysis

3 imputation

Reported any changes

- **2 reviews only**

‘To carry out a clinically sound analysis, we used a conservative approach and imputed outcomes for the missing participants assuming that they did not respond to treatment’

Justified strategy used in primary & sensitivity analysis

- **12 out of 273** reviews

Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet. 2009;373(9665):746-58.

Conclusions

- The **quality of reporting and handling MOD** in systematic reviews with NMAs is **particularly inadequate**!
- Reviewers remain **unaware of the presence and importance of MOD** in systematic reviews of multiple interventions.
- Poor handling of MOD attests to **limited knowledge of the reviewers** regarding the existing relevant methodology.
- **Education** amongst reviewers, peer reviewers and journal editors is deemed **necessary**!

‘Do **different models for binary MOD agree** in terms of core components of NMA ?’

Informative Missingness Odds Ratio (IMOR)

Pattern-mixture model (White at al., 2008)

$$IMOR = \frac{p^m/(1-p^m)}{p^o/(1-p^o)}$$

'Odds of an event being missing to odds of an event being observed'

$$log(IMOR) = \delta_{ik} \sim \mathrm{N}\left(\Delta_{ik}, \sigma_{ik}^2\right)$$

arm k of trial i

Δ	interpretation
$\Delta > 0$	more likely that a missing case to be an event
$\Delta < 0$	less likely that a missing case to be an event
$\Delta = 0$	Missing at random (on average)

$$\sigma_{ik}^2 = \sigma^2 = 1$$

Prior structures of logIMOR (1)

Identical structure*

… log IMORs are considered identical depending on further assumptions on whether missingness mechanisms are:

- **common in the whole network**
- **intervention-related**
- **trial-related**

Assumption	Prior specification
Common-within-network	$\delta_{ik} = \delta,\ \delta \sim N(0,1)$
Intervention-specific	$\delta_{ik} = \delta_{t_{ik}},\ \delta_{t_{ik}} \sim N(0,1)$
Trial-specific	$\delta_{ik} = \delta_i,\ \delta_i \sim N(0,1)$

***Turner NL**, Dias S, Ades AE, Welton NJ. A Bayesian framework to account for uncertainty due to missing binary outcome data in pairwise meta-analysis. Stat Med 2015;34:2062-80

Prior structures of logIMOR (2)

Hierarchical structure (Turner et al. 2015)

… log IMORs are considered different yet related to each other by borrowing information either across:

- **the whole network**
- **different trials for the same intervention**
- **different interventions in the same trial**

Assumption	Prior specification
Common-within-network	$\delta_{ik} \sim N(\Delta, \sigma^2)$ $\Delta \sim N(0,1),\ \sigma \sim U(0,1)$
Intervention-specific	$\delta_{ik} \sim N\left(\Delta_{t_{ik}}, \sigma_{t_{ik}}^2\right)$ $\Delta_{t_{ik}} \sim N(0,1),\ \sigma_{t_{ik}} \sim U(0,1)$
Trial-specific	$\delta_{ik} \sim N\left(\Delta_i, \sigma_i^2\right)$ $\Delta_i \sim N(0,1),\ \sigma_i \sim U(0,1)$

Missingness scenarios

$$\delta_{t_{ik}} \sim \mathbf{N}\left(\boldsymbol{\Delta}_{\boldsymbol{t_{ik}}}, \mathbf{1}\right)$$

Scenario*	Interpretation	Abbrev.
$e^{\Delta_{ik}} = 1$	Missing at random more likely	**MAR**
$e^{\Delta_{t_{ik}}} = 2$	More missing are events	**MME**
$e^{\Delta_{t_{ik}}} = 1/2$	More missing are non-events	**MMNE**
$e^{\Delta_{t_{ik}}} = 2$ & $e^{\Delta_R} = 1/2$	**MME** for non-references; **MMNE** for reference	**BC**
$e^{\Delta_{t_{ik}}} = 1/2$ & $e^{\Delta_R} = 2$	**MMNE** for non-references; **MME** for reference	**WC**

*Spineli LM, Higgins JP, Cipriani A, Leucht S, Salanti G. Evaluating the impact of imputations for missing participant outcome data in a network meta-analysis. Clin Trials 2013;10:378-88

Classification of networks based on MOD (1)

Prevalence: low, moderate, large

- **Low** MOD → 12/29 (41%) networks
- **Moderate** and **balance** MOD → 14/29 (48%) networks
- **Moderate** and **imbalance** MOD → 2/29 networks
- **Large and imbalance** MOD → 1/29 networks

Characterising networks

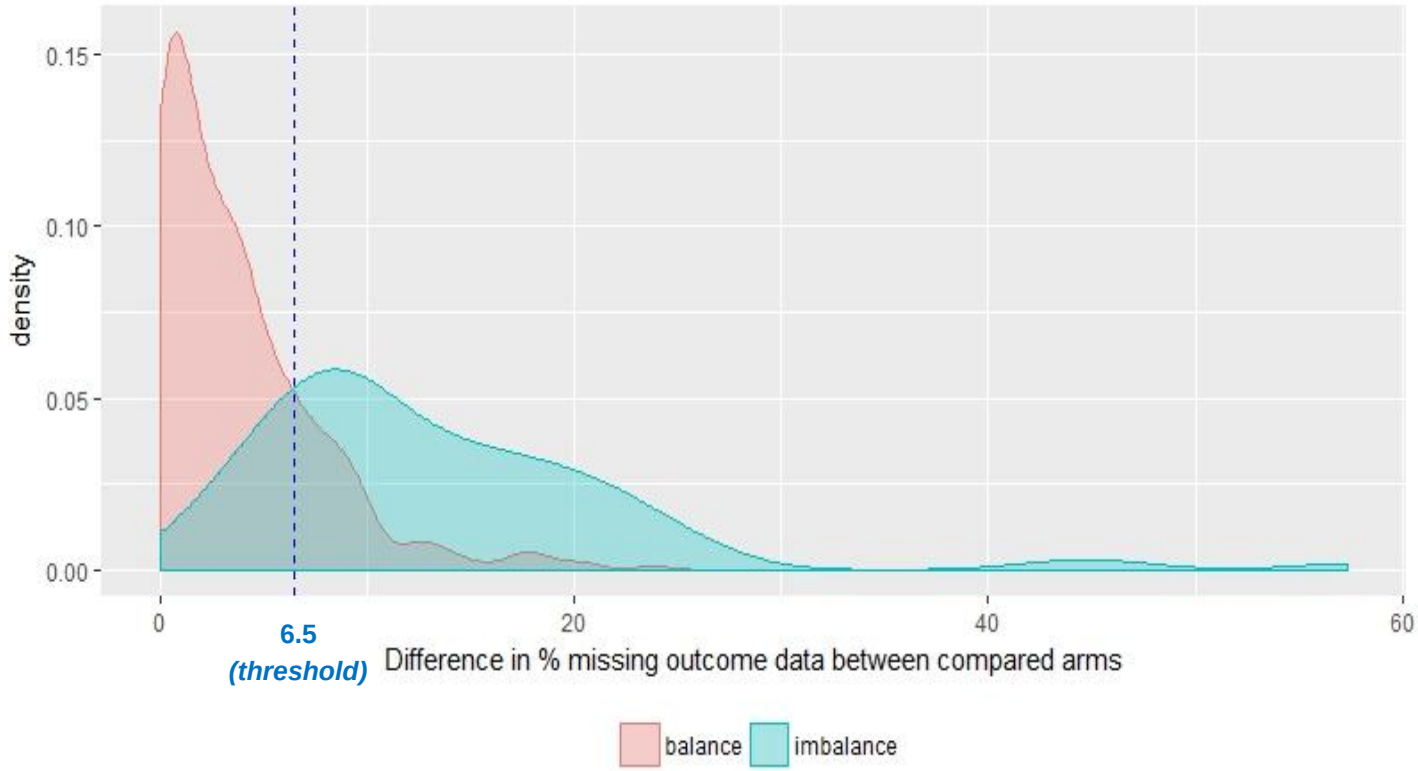
Use of the *'five to twenty' rule* based on Sackett et al (1997) ***in each network***:

- **low** → median of total %MOD across trials < 5%
- **high** → median of total %MOD across trials > 20%
- **moderate** → otherwise

Classification of networks based on MOD (2)

Balance vs. Imbalance in the compared arms

Calculate difference in %MOD between compared arms ***within each trial*** :



Model specification & Presentation of results

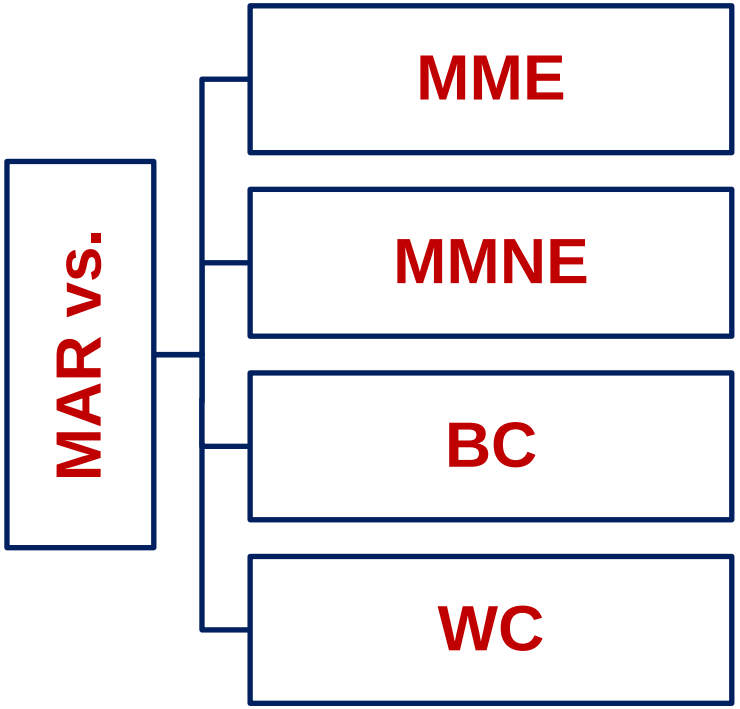
JAGS/R2jags

- Bayesian random-effects NMA model by Dias et al (2013);
- Incorporation of log IMOR as described in Turner et al (2015);
- For location parameters use of N(0, 10 000);
- Use of empirical priors on between-trial variance based on Turner et al (2015);
- 3 chains for 10 000 updates and 1 000 burn-in.
- Bland-Altman plots to investigate the agreements in the compared methods

Research questions (1)

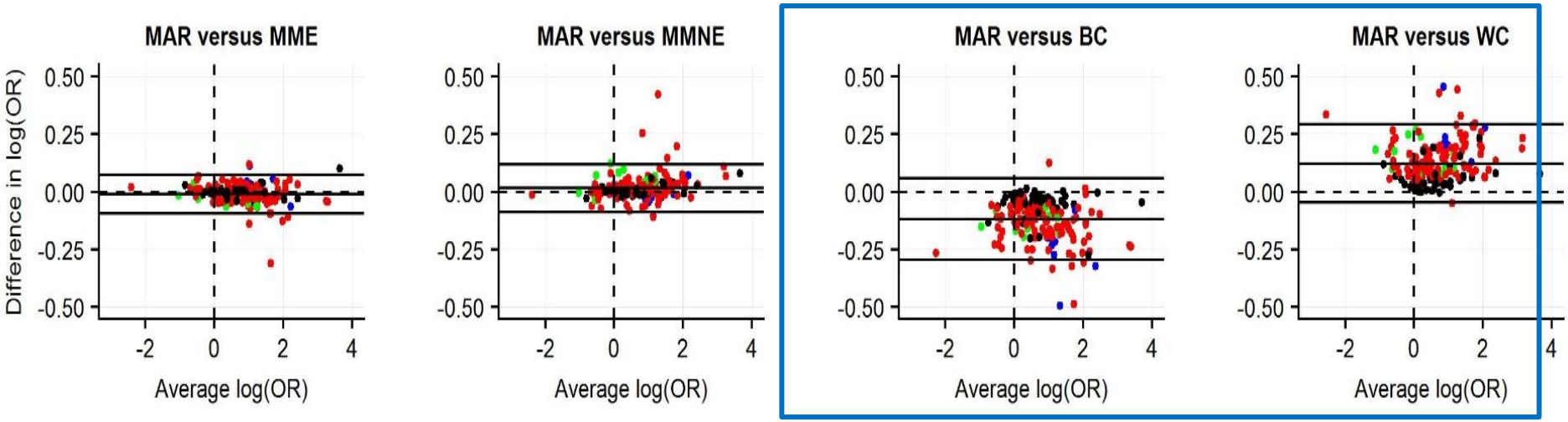
Agreement between on average MAR and extreme scenarios

- Identical log IMORs with intervention-specific normal prior distribution



$$\delta_{ik} = \delta_{t_{ik}},\ \delta_{t_{ik}} \sim N\left(\boldsymbol{\Delta_{t_{ik}}}, 1\right)$$

Posterior mean



Research questions (2)

Agreement between accountability & ignorance of uncertainty due to MOD

- Identical log IMORs with intervention-specific normal prior distribution

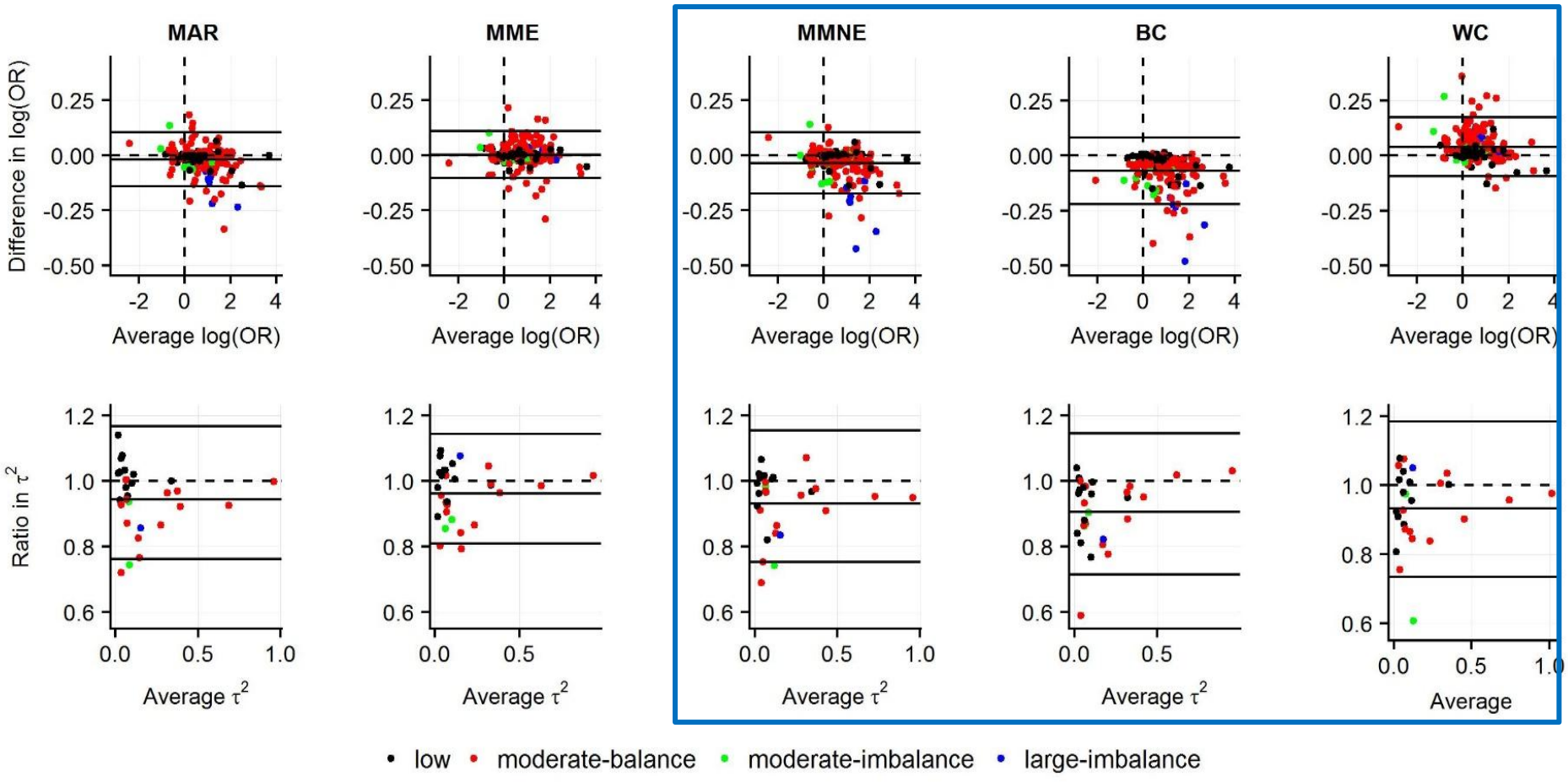
$$\delta_{ik} = \delta_{t_{ik}},\ \delta_{t_{ik}} \sim N\left(\boldsymbol{\Delta_{t_{ik}}}, 1\right)$$

- Scenarios considered: MAR, MME, MMNE, BC and WC

uncertainty about the scenario considered	
Accounted for vs.	**ignored**
$\delta_{t_{ik}} \sim N\left(\boldsymbol{\Delta_{t_{ik}}}, 1\right)$	$\delta_{t_{ik}} = \boldsymbol{\Delta_{t_{ik}}}$

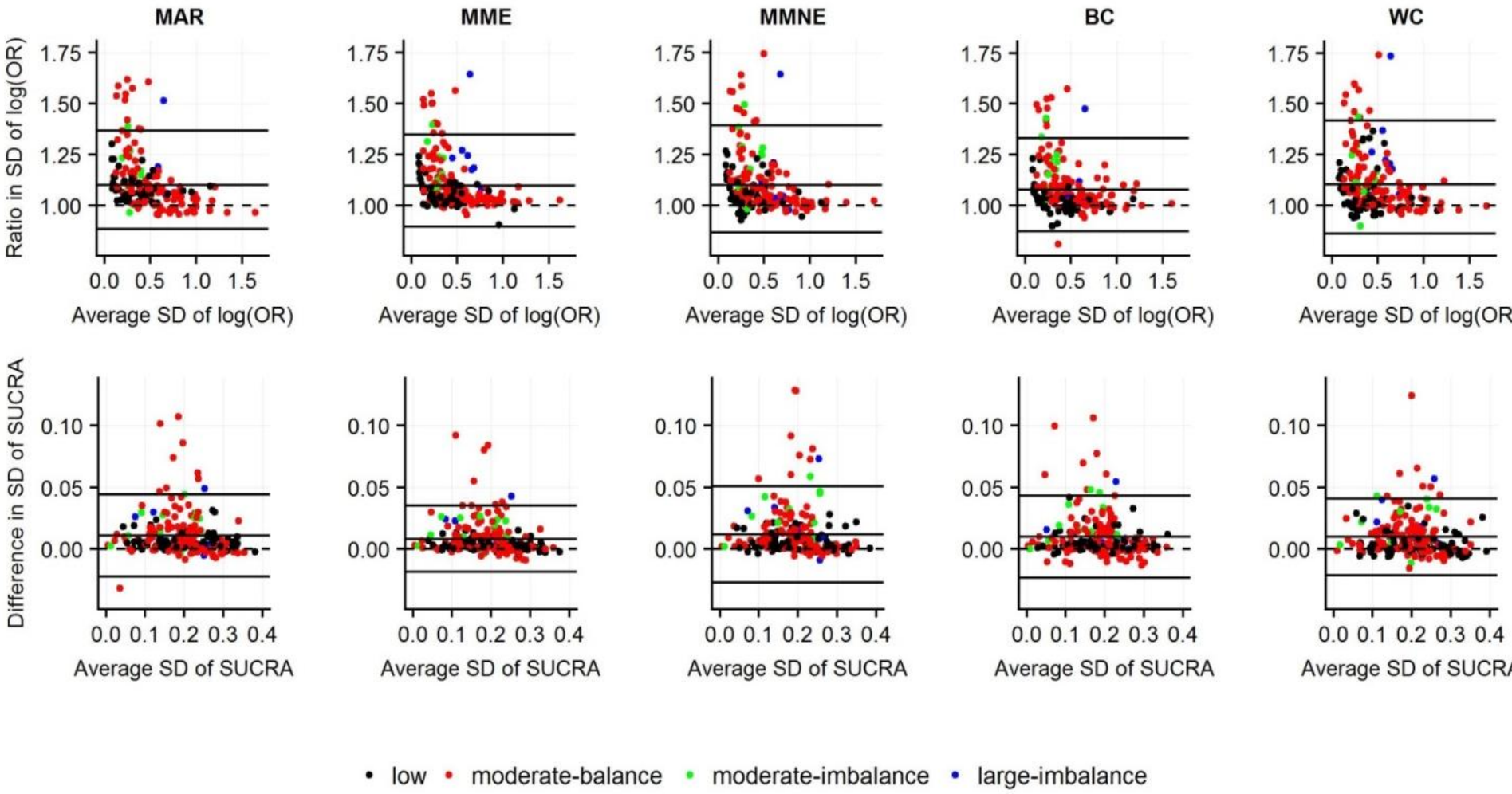
Posterior mean/median

Accounting vs ignoring uncertainty due to MOD



Posterior standard deviation

Accounting vs ignoring uncertainty due to MOD

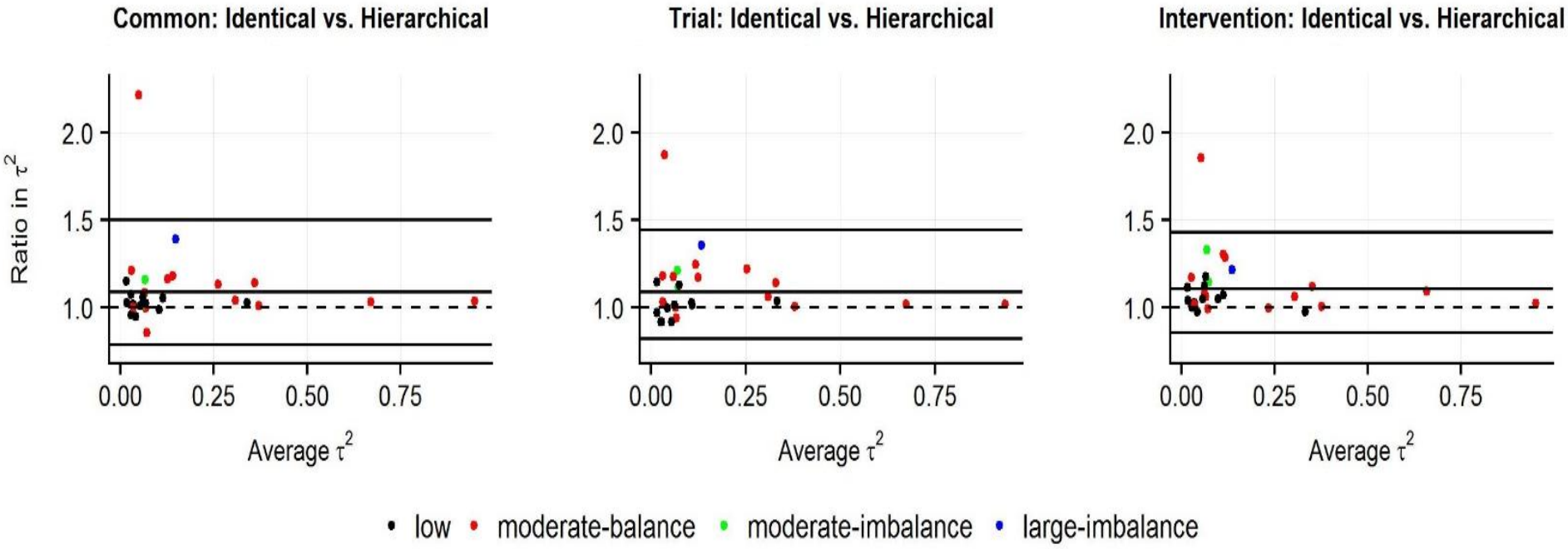


Research questions (3)

Agreement between identical and hierarchical structure of log IMOR

- MAR on average scenario
- In both structures use of normal prior distribution on log IMORs assumed:
  - Common-within network
  - Intervention-specific
  - Trial-specific

Posterior median



Take-home message

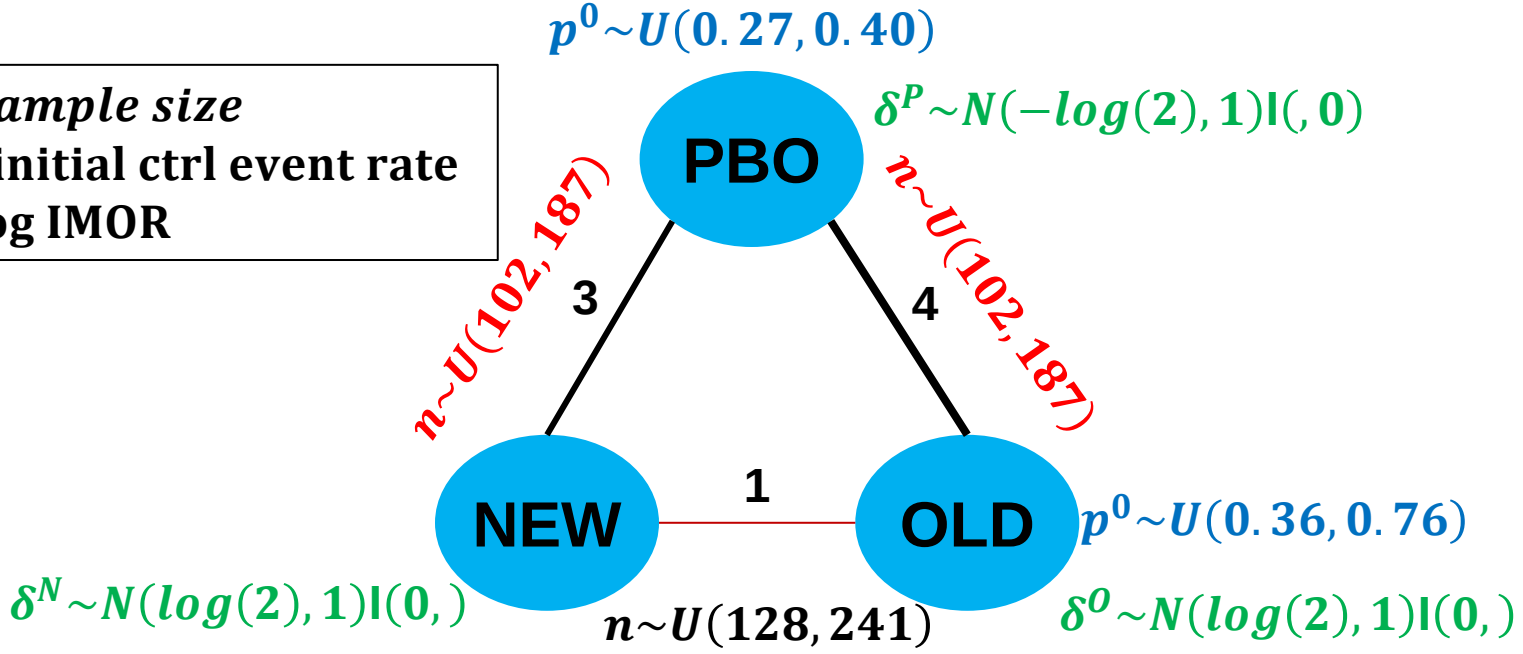
- ✓ Use **'on average MAR' for primary analysis** and **assumptions with clinical plausibility as sensitivity analyses**.
- ✓ **Model the missingness mechanism via the IMOR parameter** in order to accommodate the uncertainty about the missingness scenarios considered.
- ✗ **Avoid imputing or excluding MOD <u>either</u> before analysis <u>or</u> by fixing the missingness parameter!**

👍 Simulation study follows ...

Which **factors may affect the performance of different models for binary MOD** in terms of core components of NMA?

Simulation set-up (1)

n: *sample size*
p^0: initial ctrl event rate
δ: log IMOR

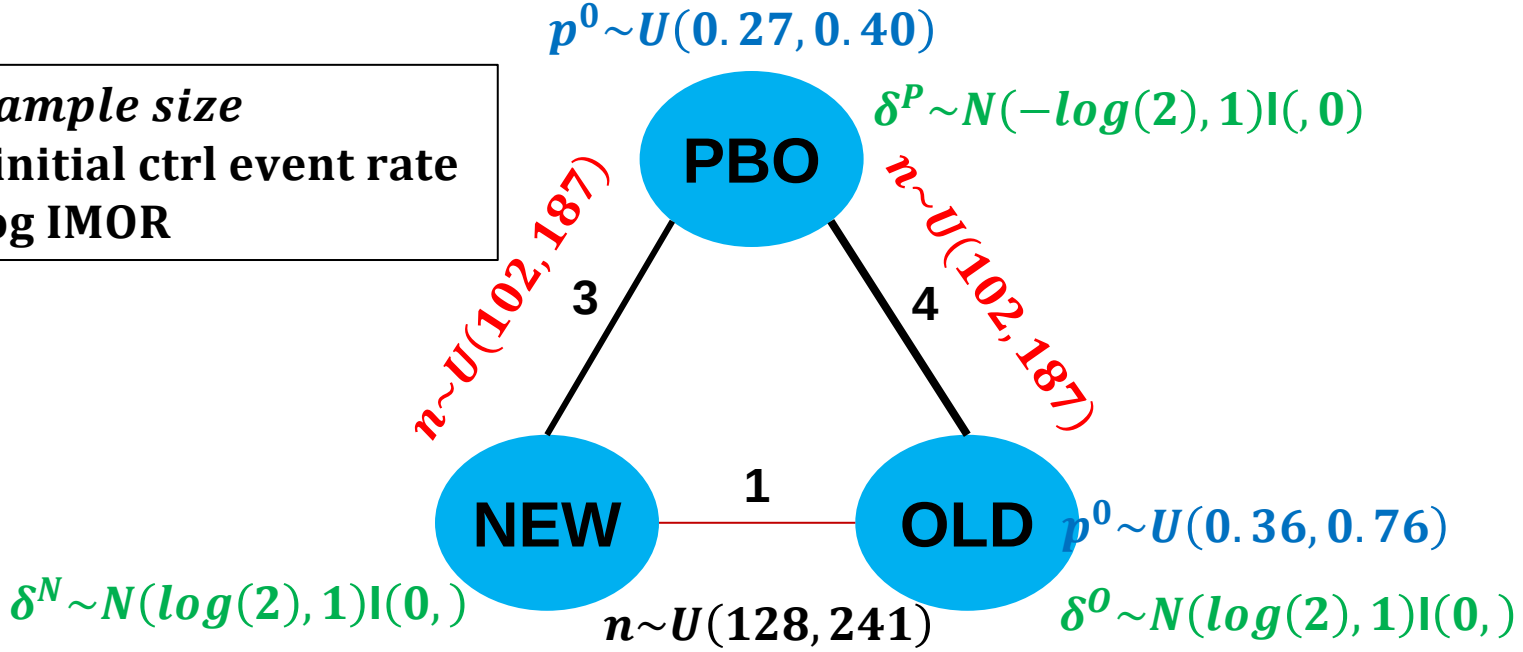


Comparison		Moderate %MOD		Large %MOD	
NEW	PBO	$U(0.05,0.10)$	$U(0.11,0.20)$	$U(0.21,0.30)$	$U(0.31,0.40)$
OLD	PBO				
NEW	OLD				

Veroniki AA, Mavridis D, Higgins JPT, Salanti G. Characteristics of a loop of evidence that affect detection and estimation of inconsistency: a simulation study. BMC Med Res Methodol. 2014;14:106. doi:10.1186/1471-2288-14-106

Simulation set-up (2)

n: *sample size*
p^0: initial ctrl event rate
δ: log IMOR



	small/low	substantial	$LOR_{NP} = log(2)$
τ^2	all-cause mortality	generic health	$LOR_{OP} = log(1.5)$
IF	$t(0, 0.44, df = 3)$	$t(1, 0.44, df = 3)$	$LOR_{NO} = LOR_{NP} - LOR_{OP} + \text{IF}$

Hartung & Knapp data generating model

1. Obtain **initial** event risks for the experimental arms, $\boldsymbol{p^E}$:

$$\boldsymbol{p^{E,0} = \frac{p^{C,0} \cdot exp(LOR)}{1 - p^{C,0} + p^{C,0} \cdot exp(LOR)}}$$

2. Obtain **initial** log odds for experimental and control arms, respectively:

$$\boldsymbol{logit^{E,0} = log\left(\frac{p^{E,0}}{1-p^{E,0}}\right)} \text{ and } \boldsymbol{logit^{C,0} = log\left(\frac{p^{C,0}}{1-p^{C,0}}\right)}$$

3. Generate **true** log odds for experimental and control arms, respectively:

$$\boldsymbol{logit^{E} \sim} \text{N}\left(\boldsymbol{logit^{E,0}}, \boldsymbol{\frac{2\tau^2}{3}}\right) \text{ and } \boldsymbol{logit^{C} \sim} \text{N}\left(\boldsymbol{logit^{C,0}}, \boldsymbol{\frac{\tau^2}{3}}\right)$$

4. Finally, obtain **true** event risks for experimental and control arms, respectively:

$$\boldsymbol{p^E = \frac{1}{1 + exp(-logit^E)}} \text{ and } \boldsymbol{p^C = \frac{1}{1 + exp(-logit^C)}}$$

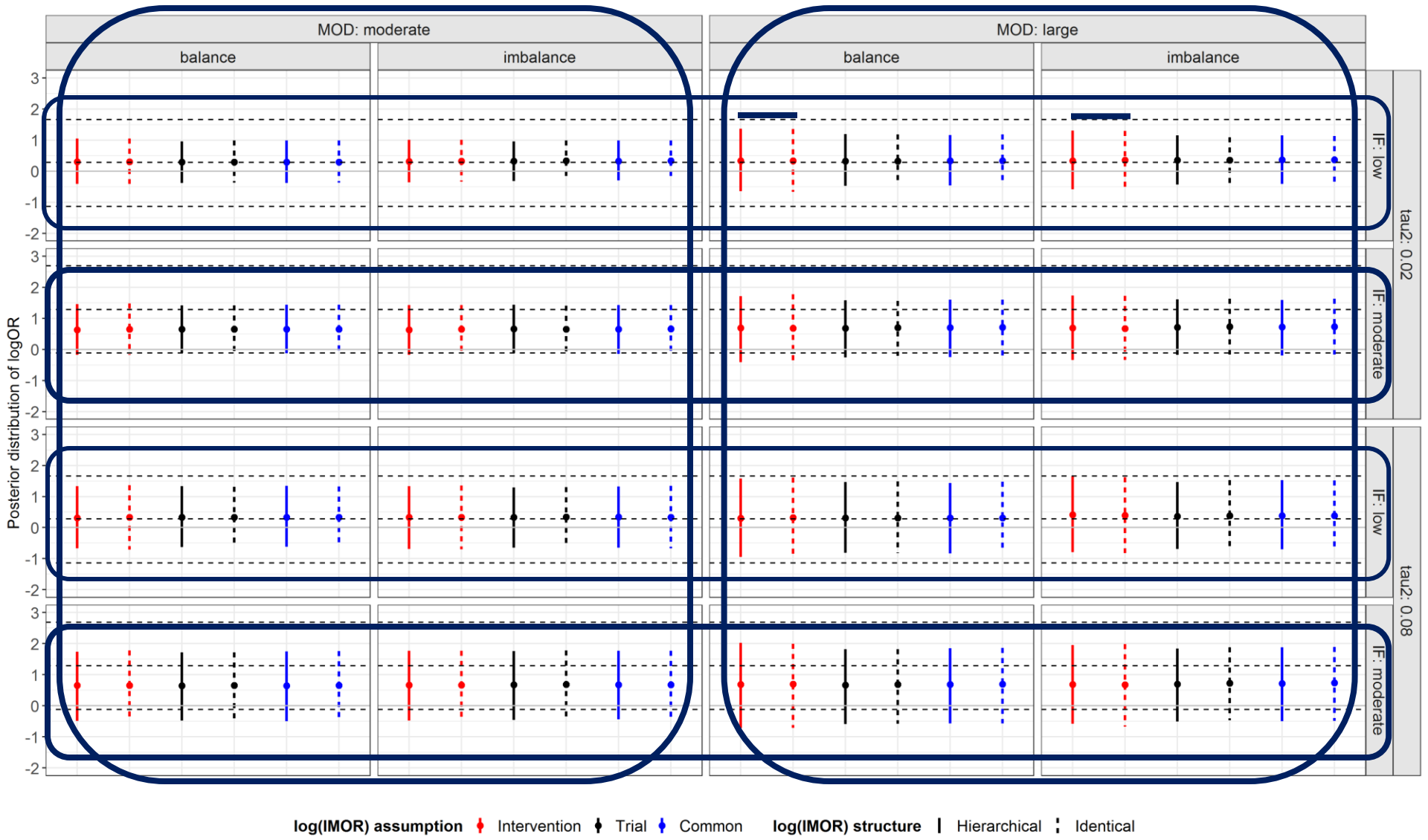
Hartung J, Knapp G. A refined method for the meta-analysis of controlled clinical trials with binary outcome. *Stat Med*. 2001;20(24):3875-3889. doi:10.1002/sim.1009.

Model specification & Presentation of results

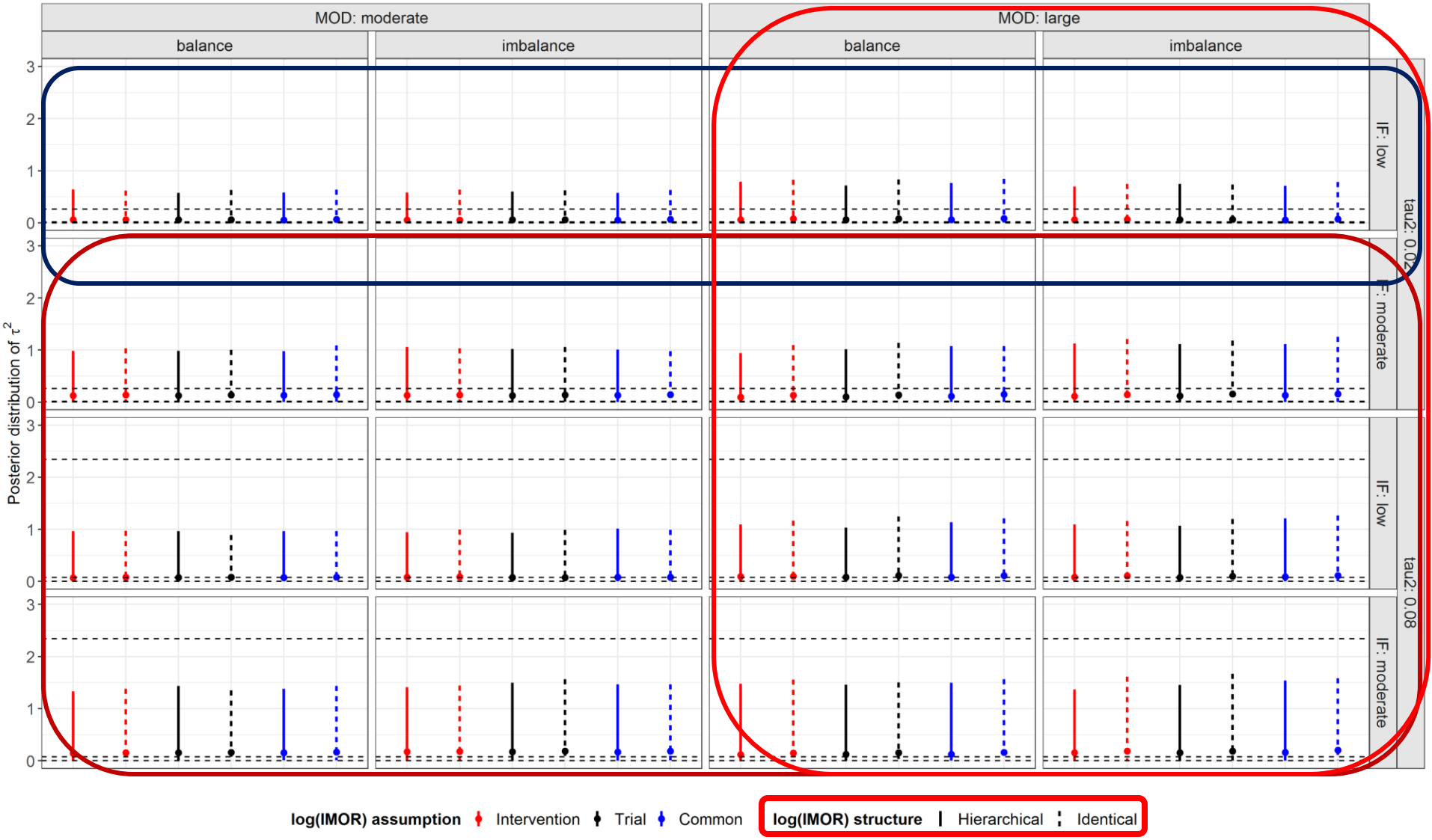
- **Bayesian random-effects NMA model** by Dias et al (2013);
- Application of the **node-splitting model** as developed by Dias et al (2010);
- Incorporation of log IMOR as described in Turner et al (2015);
- **Pattern-mixture model** for **identical** and **hierarchical logIMOR** (*common-within-network, trial-specific, and intervention-specific*).
- For **location parameters**, we used **N(0, 10 000)**;
- For **between-trial variance**, we used **N(0, 1)I(0,)**;
- For **logIMOR**, we used **N(0,1)** (on average MAR) in **all arms**;
- **1 000 triangles**, 3 chains for 20 000 updates and 2 000 burn-in;
- **Interval plots** for LOR (new vs old) and between-trial variance to correctly present results from Bayesian methods (prior distribution is presented with dotted parallel lines).

JAGS/R2jags

Posterior distribution of LOR (new vs old)



Posterior distribution of between-trial variance



Limitations of the study

- ❑ We considered a simple network of **3 interventions and 2-arm trials**;
- ➢ Simulating **a complex network with multi-arm trials*** will shed more light on implications of different prior structures of log IMOR on NMA estimates;
- ❑ We investigated only **frequent events**;
- ➢ Carpenter et al (2007): '***if an event is rare***, *missing data on very few patients can markedly alter estimated event rates*' → **affect NMA estimates**.
- ❑ **The degree of unbalanced MOD** was much smaller than the total extent of MOD in each trial → **We observed that much in the empirical study!**
- ➢ **Larger imbalance of MOD** may have resulted in more imprecise log OR **under common-within-network and trial-specific prior structures**.

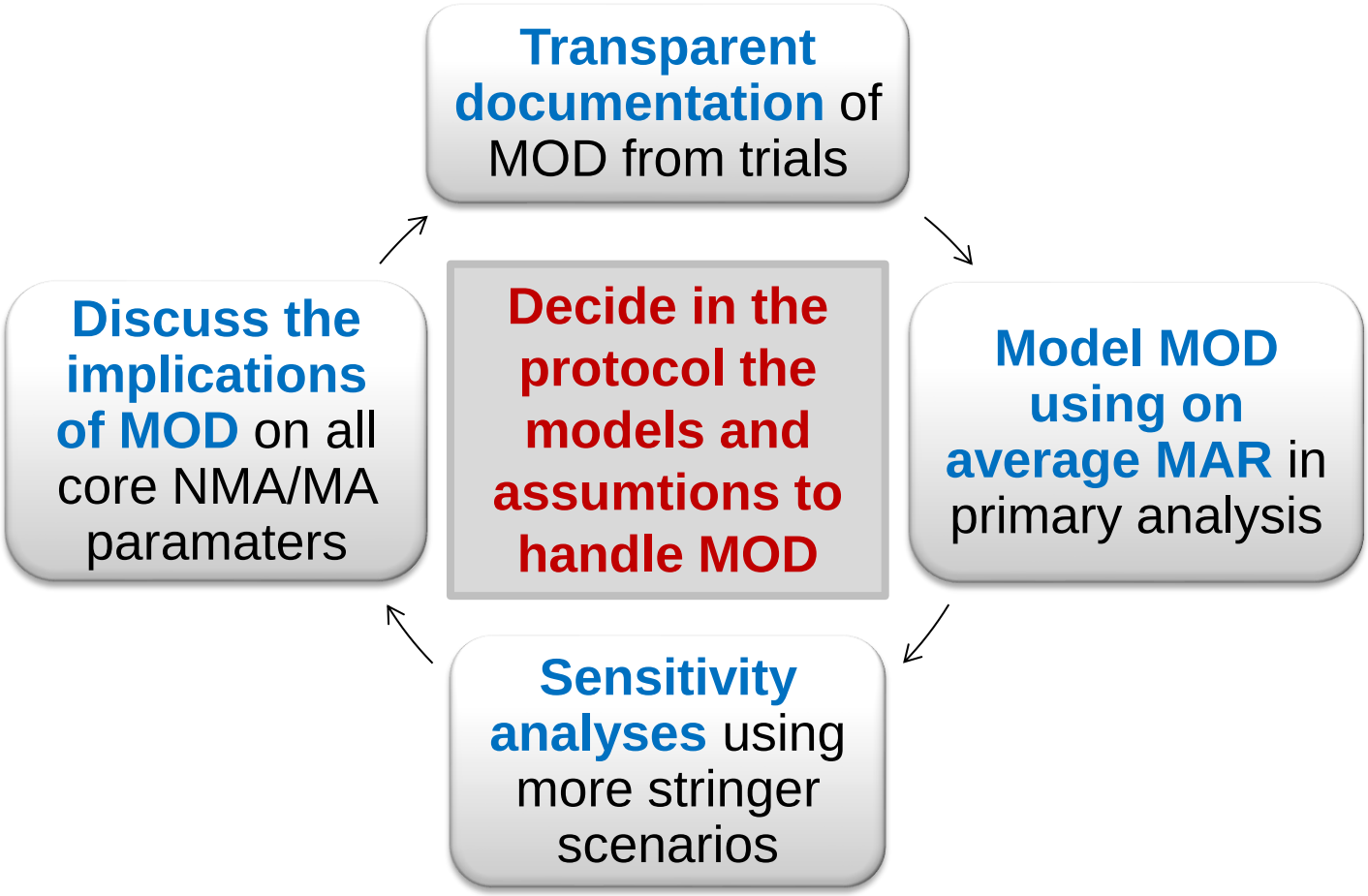
*Seide SE, Jensen K, Kieser M. Simulation and data-generation for random-effects network meta-analysis of binary outcome. Stat Med. 2019 May 9. doi: 10.1002/sim.8193. [Epub ahead of print]

Take-home message

- **Always decide <u>at the protocol</u>** on the proper prior structure of log IMOR that best aligns with the condition and interventions investigated;
- **Misspecification of the prior structure** may lead to spurious estimation of the uncertainty around log OR with implications for the conclusions;
- **Both identical and hierarchical structure may be considered** in the context of a sensitivity analysis;
- Though, we regard **hierarchical structure to be more plausible** in practice.
- **Results may** be also **generalize**d **to conventional meta-analyses** with binary outcome.
- **Inferences are greatly restricted by the scenarios considered!!!**

Future work in NEMO

- To assess and refine **methods to address continuous MOD in one-stage** (empirical and simulation study);
- Develop **a graphical tool for** comprehensive **sensitivity analyses** on plausible scenarios for MOD;
- **Develop an R-package** to ‚accommodate' all strategies that have been investigated within the project;
- **Submit Habilitation** on ‚NMA with MOD'.


Transparent documentation of MOD from trials
Model MOD using on average MAR in primary analysis
Sensitivity analyses using more stringer scenarios
Discuss the implications of MOD on all core NMA/MA paramaters
Decide in the protocol the models and assumtions to handle MOD

Publications within NEMO

1. Spineli LM, Kalyvas C, Pateras K. Participants' outcomes gone missing within a network of interventions: Bayesian modeling strategies. *Stat Med* 2019. DOI: 10.1002/sim.8207 [in press]
2. Spineli LM. An empirical comparison of Bayesian modelling strategies for missing binary outcome data in network meta-analysis. *BMC Med Res Methodol* 2019;19(1):86.
3. Spineli LM. Modeling missing binary outcome data while preserving transitivity assumption yielded more credible network meta-analysis results. *J Clin Epidemiol* 2019;105:19-26.
4. Spineli LM, Yepes-Nuñez JJ, Schünemann H. A systematic survey shows that reporting and handling of missing outcome data in networks of interventions is poor. *BMC Med Res Methodol* 2018;18(1):115.
5. Spineli LM. Missing binary data extraction challenges from Cochrane reviews in mental health and Campbell reviews with implications for empirical research. *Res Synth Methods* 2017;8(4):514-525.

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Thank you for your attention!