Sharing-of-Information in Evidence Synthesis to Strengthen HTA Decisions

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ISPOR Vienna, 2022

HTA in support of decision making

- Worldwide, formal or informal **HTA assessments** support decision making on the use of health care interventions

- HTA assesses evidence of comparative effectiveness/accuracy, and cost-effectiveness

- Evidence considered in HTA is typically restricted to the PICOS pertaining to the decision problem

PICOS: Population, **I**ntervention, (**C**omparator), **O**utcome, **S**tudy Design

Evidence-base

- But, there may be issues with the ‘direct’ evidence base:
  - Limited, e.g. disconnected networks, single-arm studies
  - Complex, e.g. surrogate/multiple outcomes, complex interventions
  - Sparse e.g., rare conditions or indications in children

- Or, simply, an extended evidence-base may plausibly retain relevance
  - e.g. chemotherapy similarly effective across solid tumors,
  - e.g. evidence on an adult population may be relevant to inform effectiveness in children

Sharing of information

- Considering an **extended evidence-base** with appropriate **sharing of information** can make best use of evidence to support decision making

- In practice, an extended evidence base can be:
  - Evidence that does not conform to the PICOS of interest but that has been collected as part of the directly relevant study set (e.g. other outcomes, non-licensed doses)
  - An extended evidence set that includes studies pertaining to a different PICOS

- Sharing of information is facilitated by evidence synthesis methods, complemented with expert judgement.

Sharing of information

- Sharing of information may be necessary/desirable to:
  - Strengthen decisions ("borrowing strength"), avoiding judgements
  - Better characterize heterogeneity (may "borrow weakness")
  - Better characterise uncertainty

- Sharing of information methods are already used in HTA, but:
  - haphazardly
  - with insufficient consideration for the strength of sharing imposed,
  - with insufficient consideration for the impact that the choice of sharing method can have on the strength of sharing

‘Core’ relationships facilitating information sharing in evidence synthesis


Nikolaidis et al. BMC Medical Research Methodology (2021) 21:107
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BMC Medical Research Methodology

RESEARCH ARTICLE Open Access

Classifying information-sharing methods

Georgios F. Nikolaidis[1,2*], Beth Woods[1], Stephen Palmer[1] and Marta O. Soares[1]

1. functional relationships: indirect parameters expressed as a function of the direct parameters, e.g. network meta-analysis, dose response models (sharing across interventions)
2. exchangeability-based relationships: random effects across both indirect and direct parameters, e.g. class effect hierarchical models (share across interventions)
3. prior-based relationships: where prior distributions complement or weight the direct evidence, e.g. informative priors (share across populations or study designs)
4. multivariate methods: assume indirect and direct parameters are correlated, e.g. surrogate outcomes (share across outcomes)

relationships have been preferentially used in specific contexts

Workshop

This workshop aims to introduce information-sharing methods and discuss with the audience opportunities and challenges of using these methods for decision making from a range of stakeholders' perspectives.

- Speakers will each present applications where a range of core relationships for sharing has been used

- Structured audience discussion (with polling) on the expected opportunities and challenges of introducing information-sharing in decision-making

University of BRISTOL

Sharing of dose-response information using functional relationships

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Use of bivariate network meta-analysis and RWE to borrow information across lines of therapy in rheumatoid arthritis: Bayesian evidence synthesis with target trial emulation

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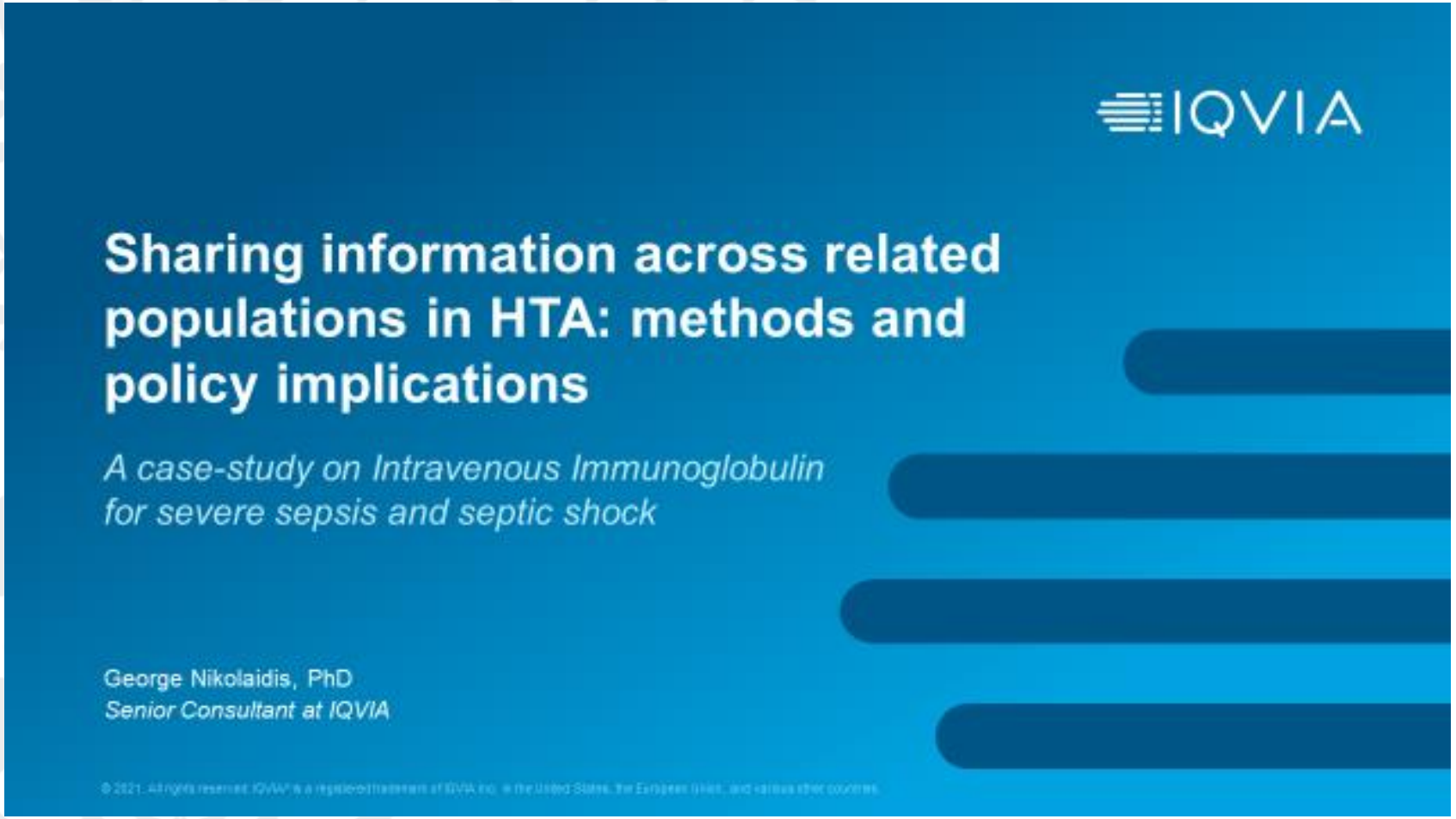
9 November 2022


IQVIA
Sharing information across related populations in HTA: methods and policy implications
A case-study on Intravenous Immunoglobulin for severe sepsis and septic shock
George Nikolaidis, PhD
Senior Consultant at IQVIA

Conflicts of Interest

- I have no conflicts of interest relating to this work

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Sharing of dose-response information using functional relationships

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Overview

- Information sharing in Network Meta-Analysis
- Incorporating functional dose-response relationship using “Model-Based” NMA
- Illustrative dataset: Triptans for migraine
- Analysis of different dose-response information sharing scenarios

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Network Meta-Analysis

- Synthesises study-specific relative effects on multiple treatments
- Respects randomisation in included RCTs
- Used in HTAs and by reimbursement agencies to support decision-making
- Information shared:
  - From multiple studies
  - From both direct and indirect evidence

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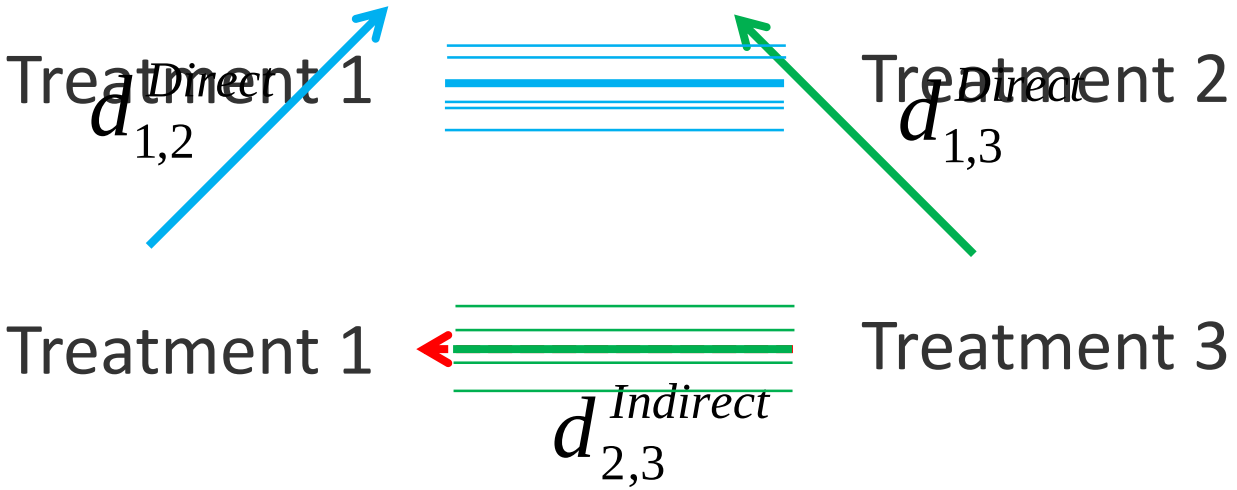
Network Meta-Analysis



Consistency assumption: $d^{Indirect}_{2,3} = d^{Direct}_{1,3} - d^{Direct}_{1,2}$

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Dose-response Network Meta-Analysis

- Information sharing via “model-based” approach that functionally incorporates a dose-response relationship
- Dose-response function fitted to study-specific **relative effects**
  - Preserves within-study randomisation
  - Model fit can be compared to “split” NMA where possible
  - Consistency assumption can be assessed
- Easily implemented in R package `MBNMAdose`

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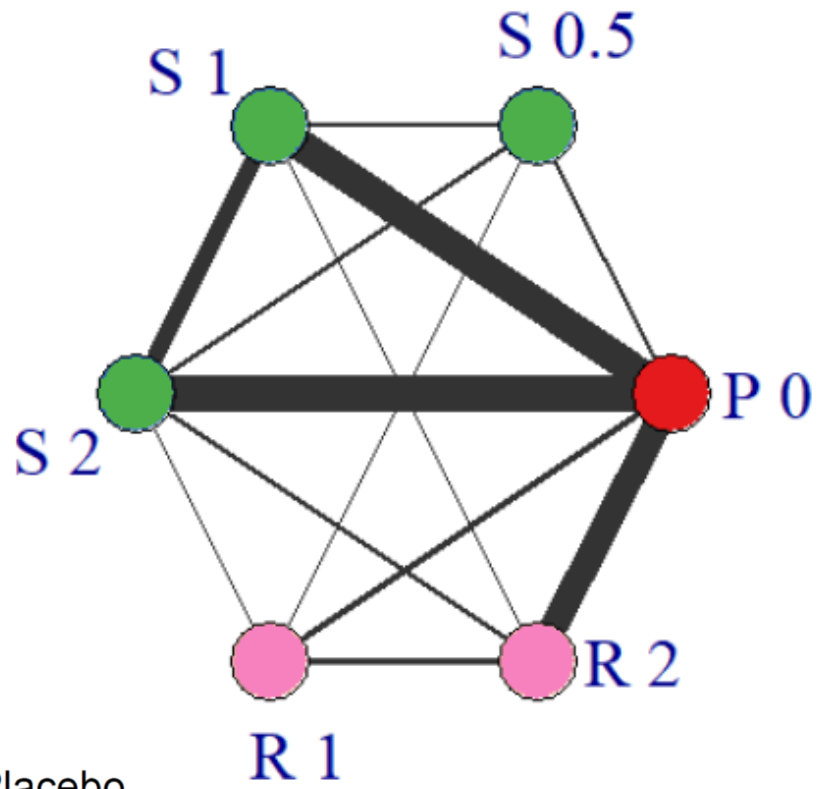
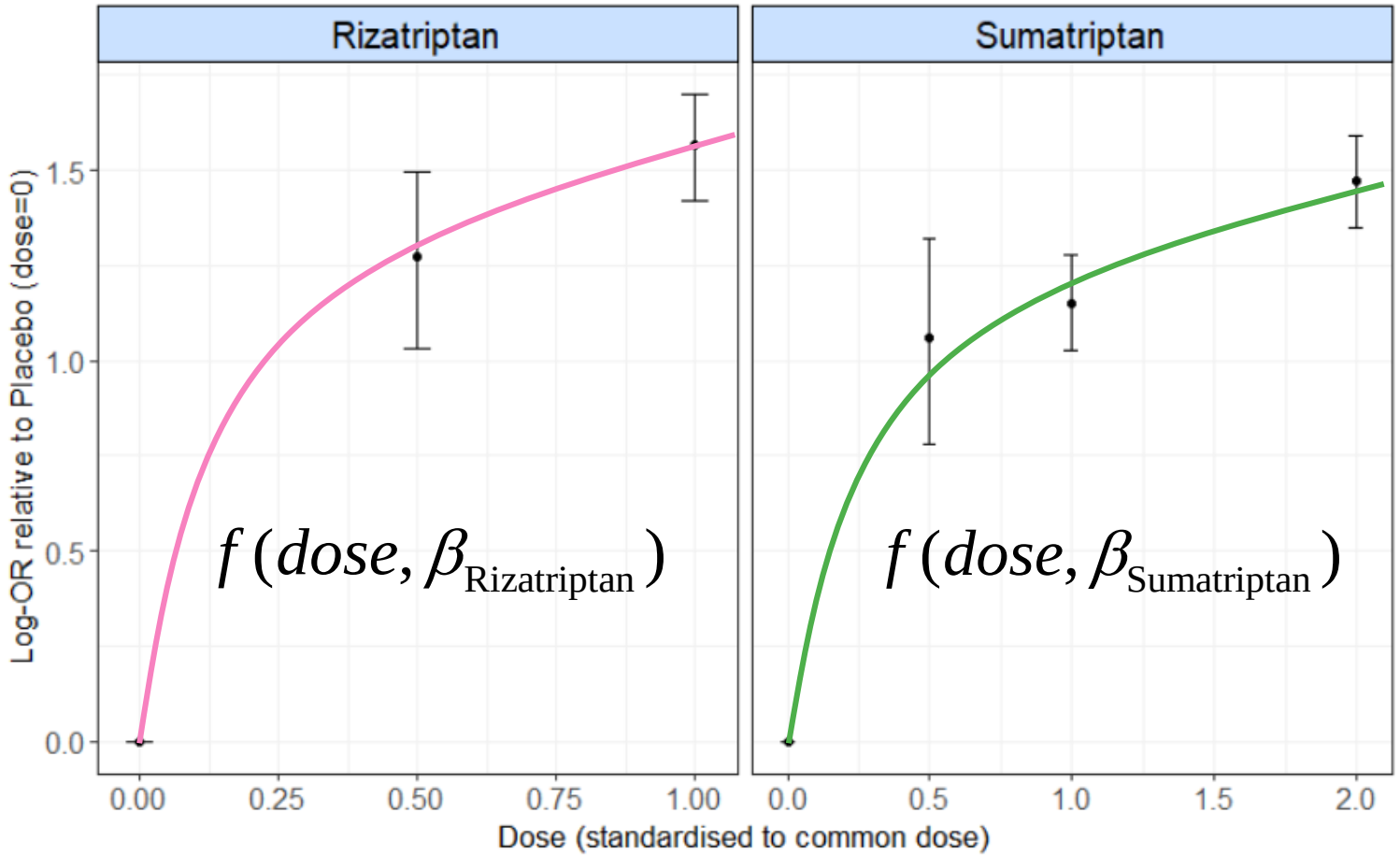
Fitting a dose-response relationship





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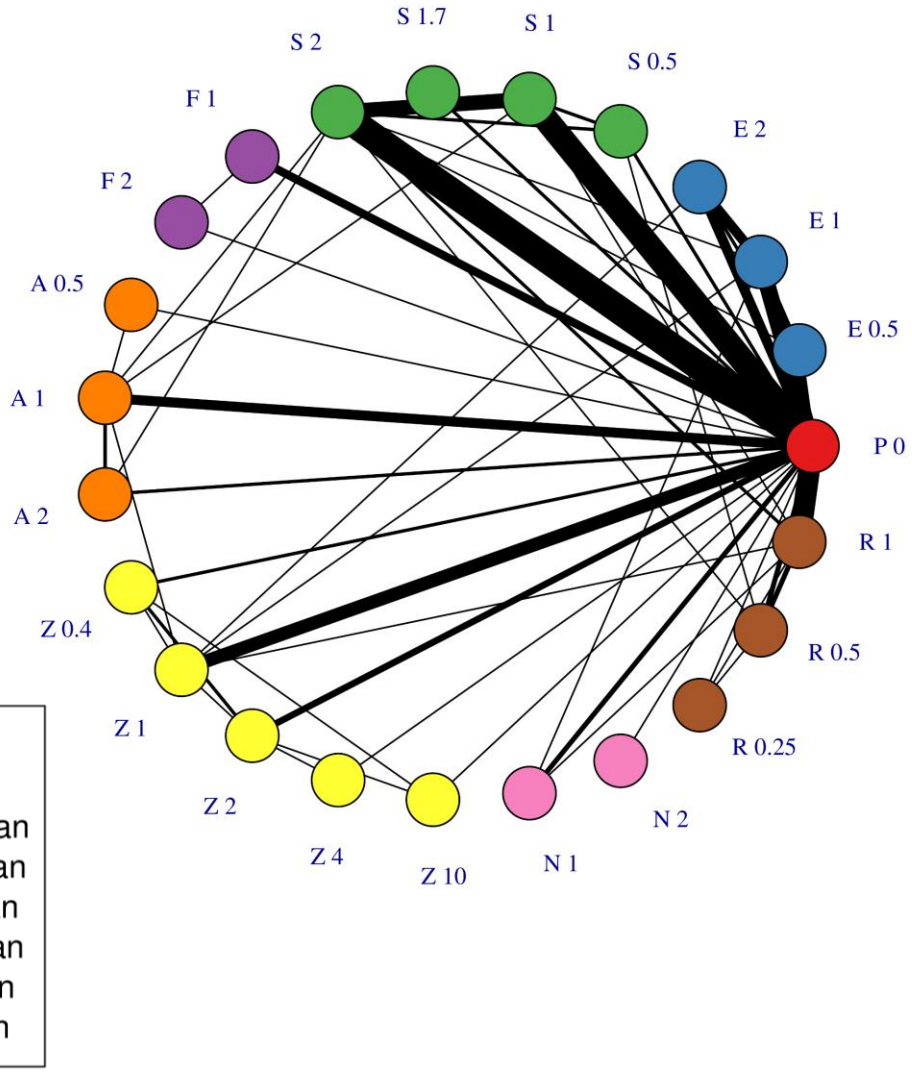
Illustrative dataset

Triptans in migraine

- 70 studies of 8 interventions compared at multiple doses
- Outcome: % patients with pain relief at 2h
- Treatment effect modelled as log-OR



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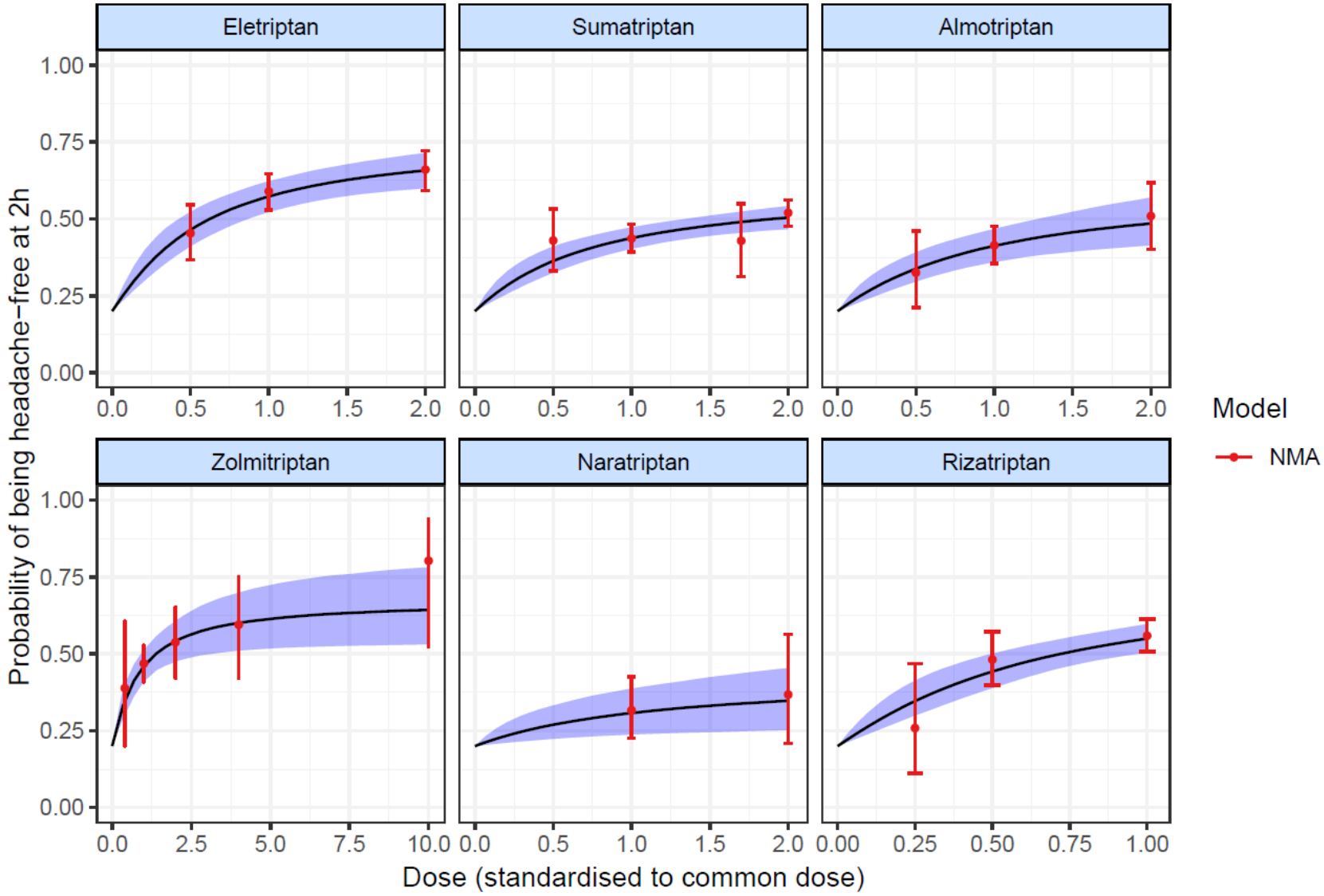
Scenario 1: Connected network

Fitting structural dose-response function increases precision versus standard “split” NMA…

…but assumes that dose-response relationship is correctly specified.



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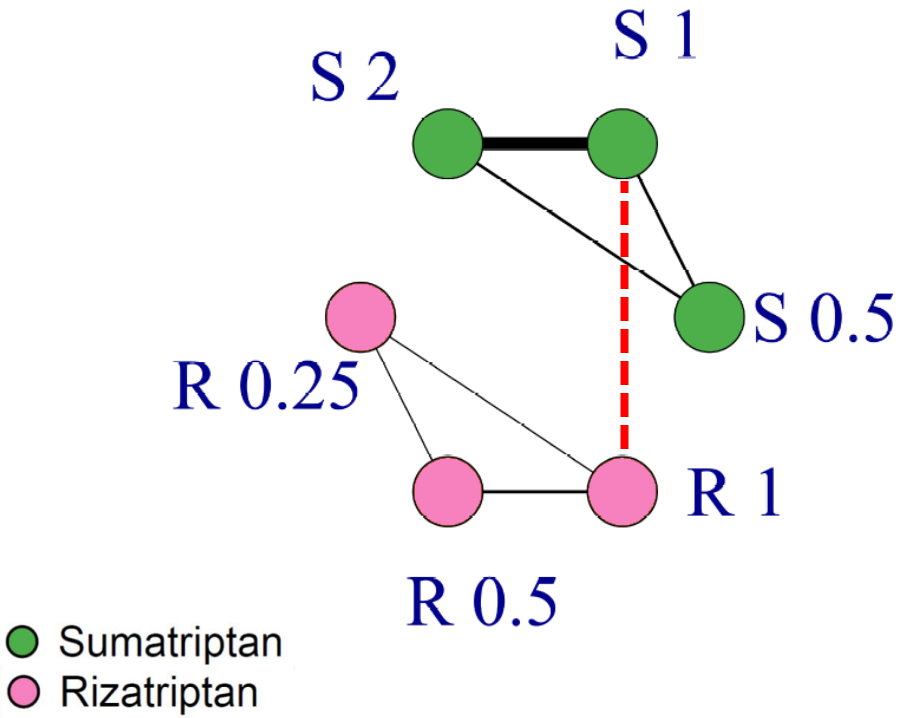
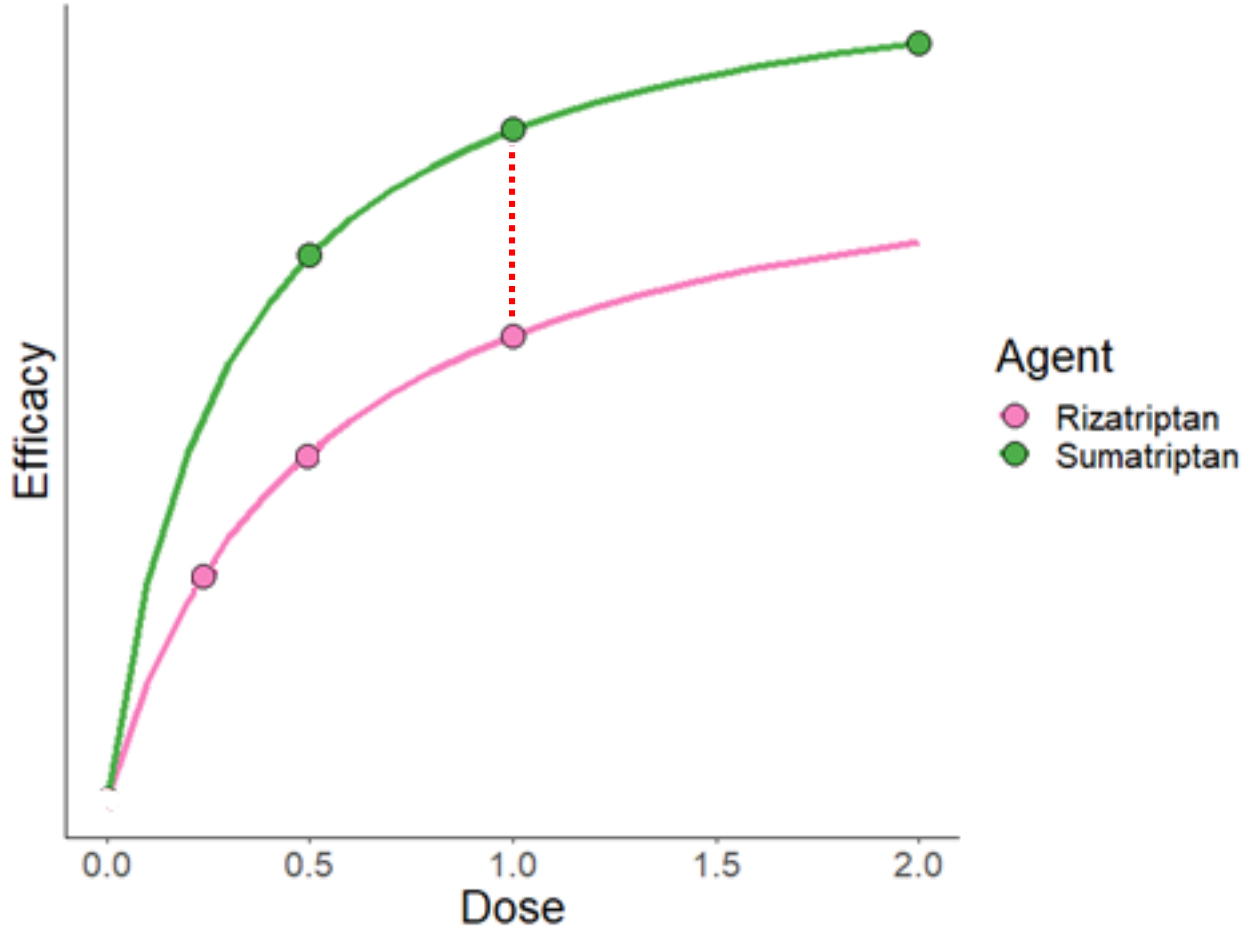
Scenario 2: Disconnected network
No common comparator





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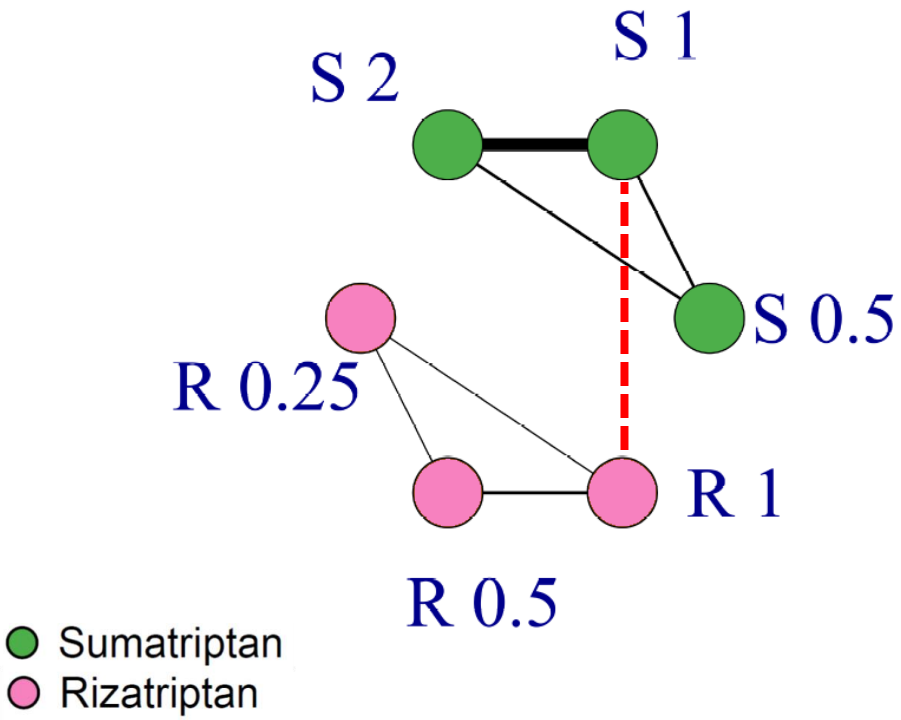

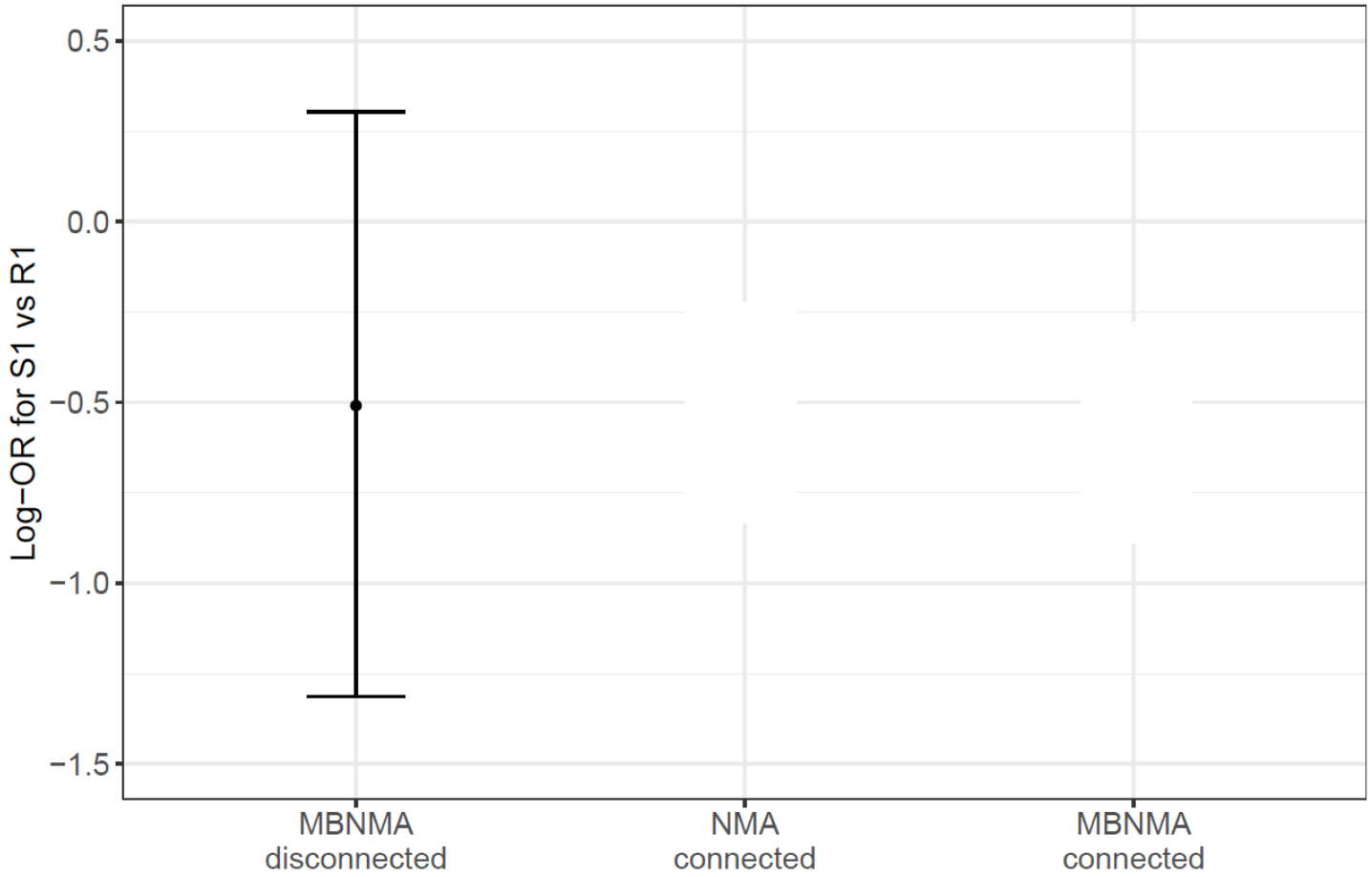

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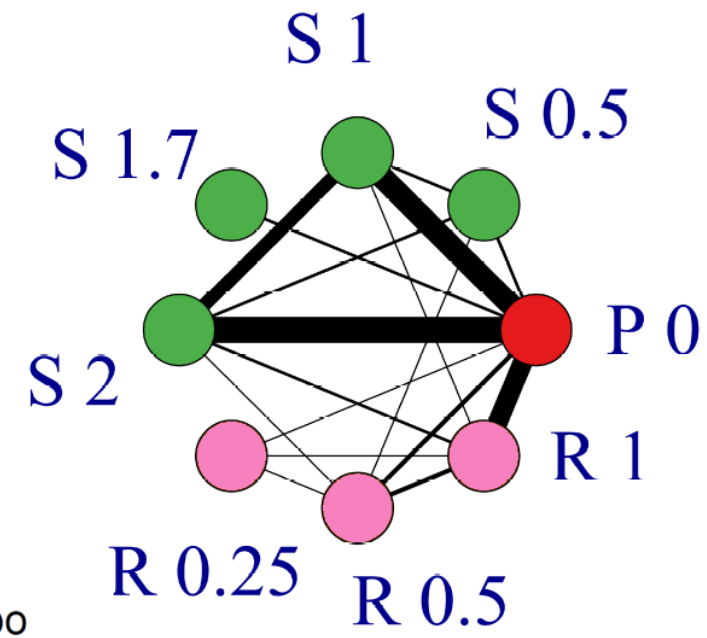

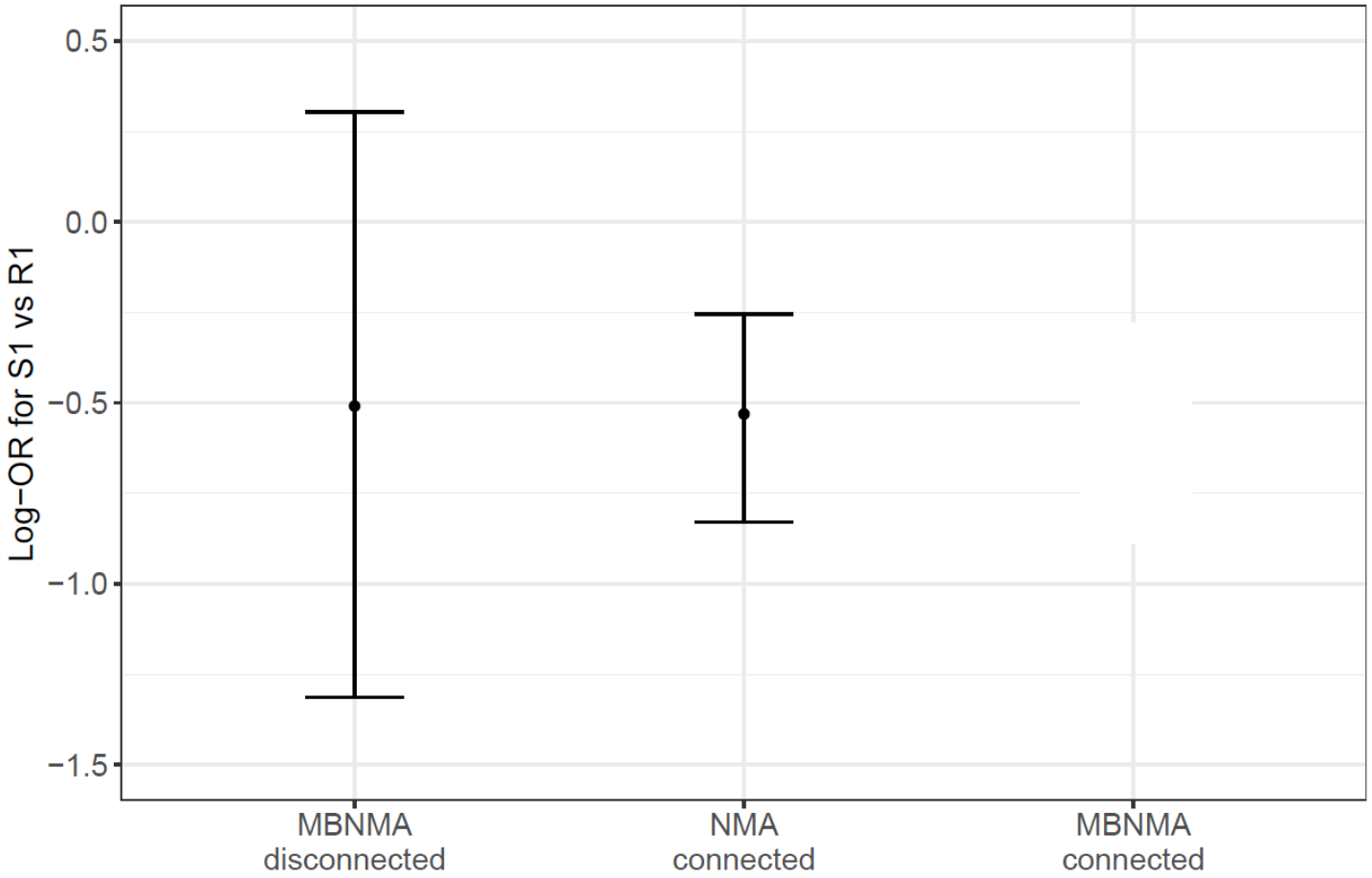

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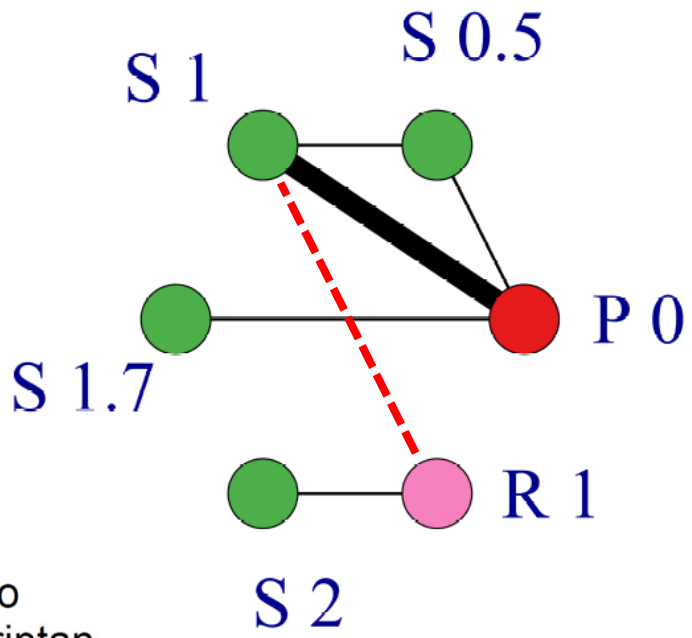
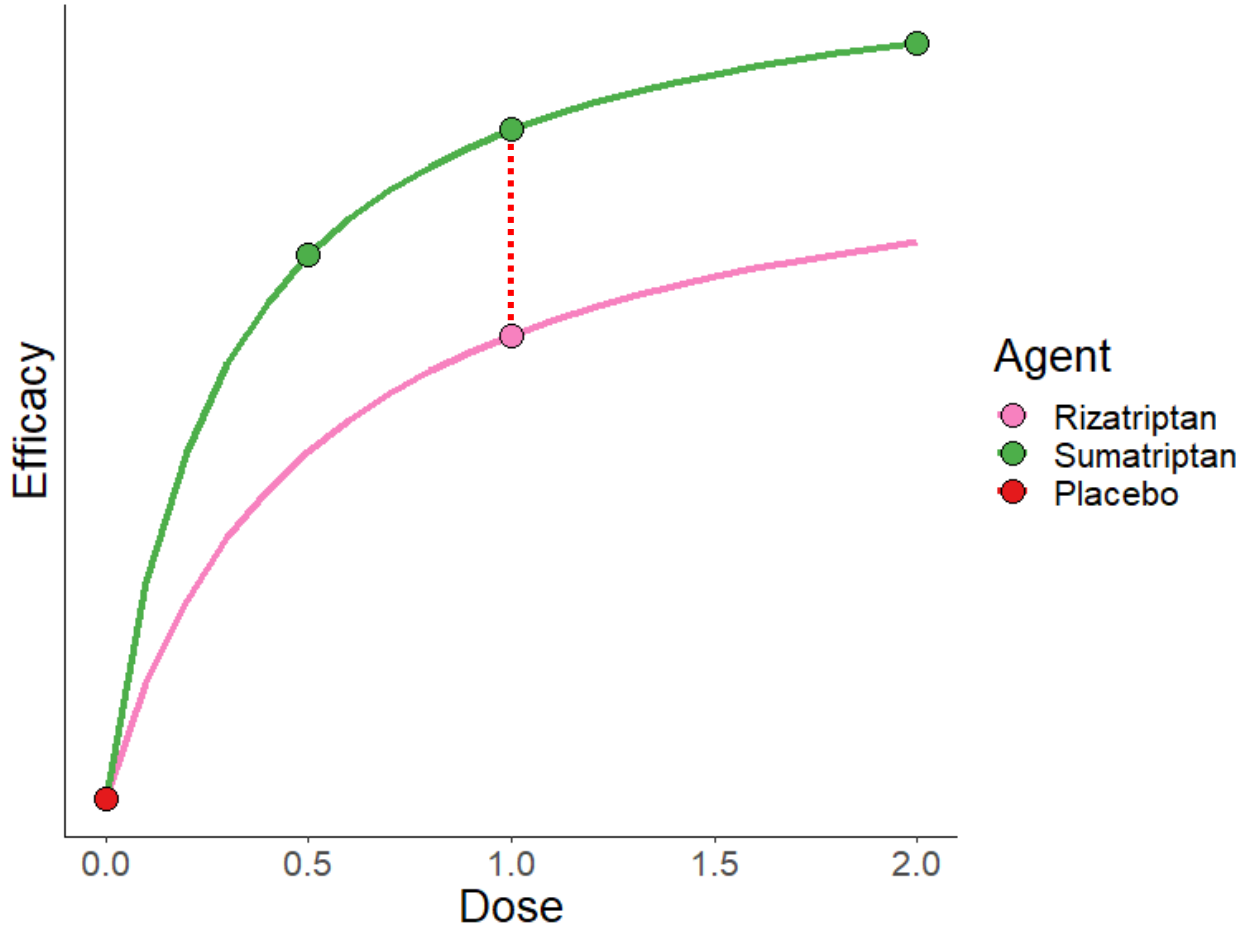
Scenario 3: Disconnected network
Interventions only compared via non-focal dose





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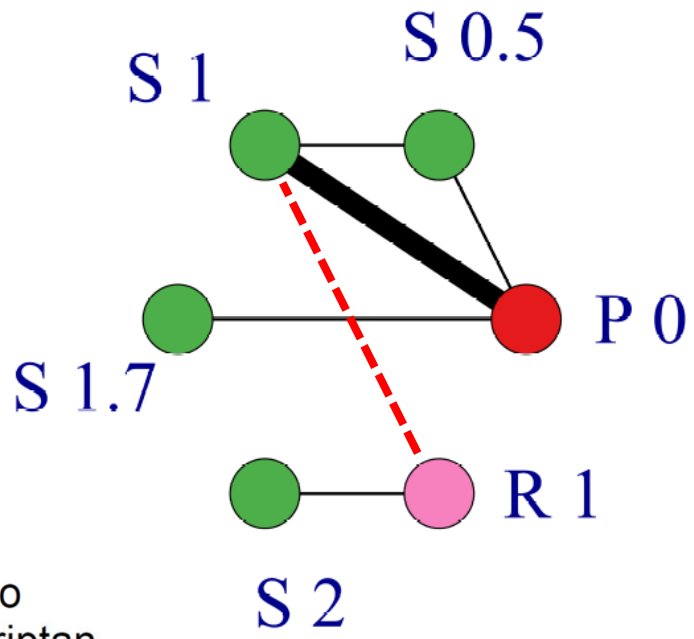

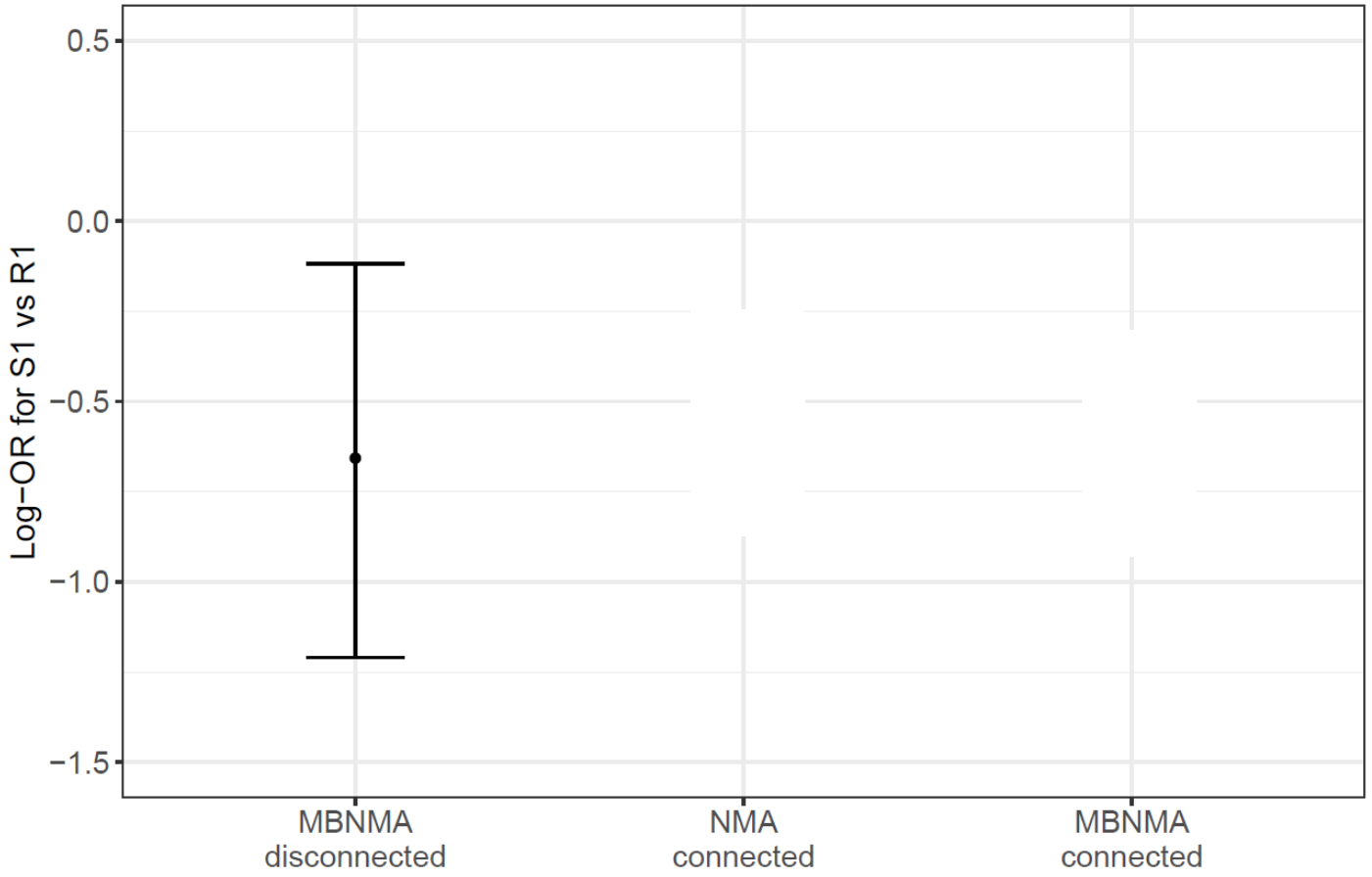

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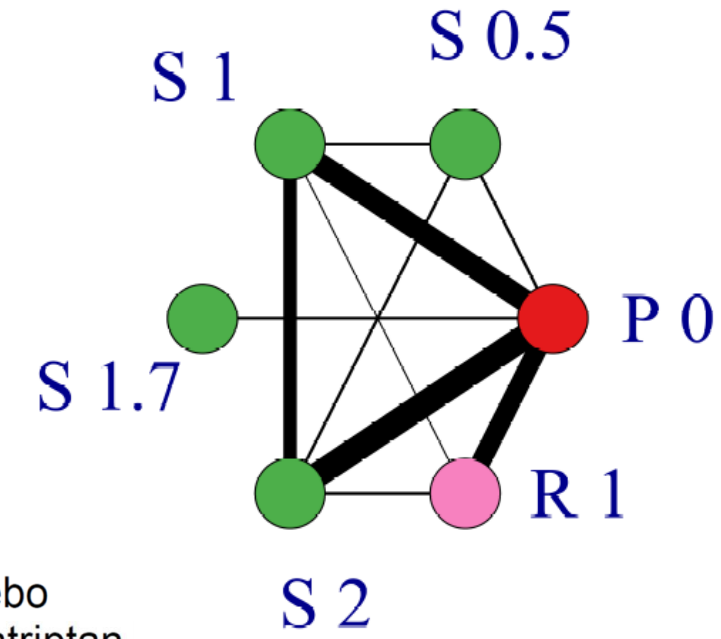

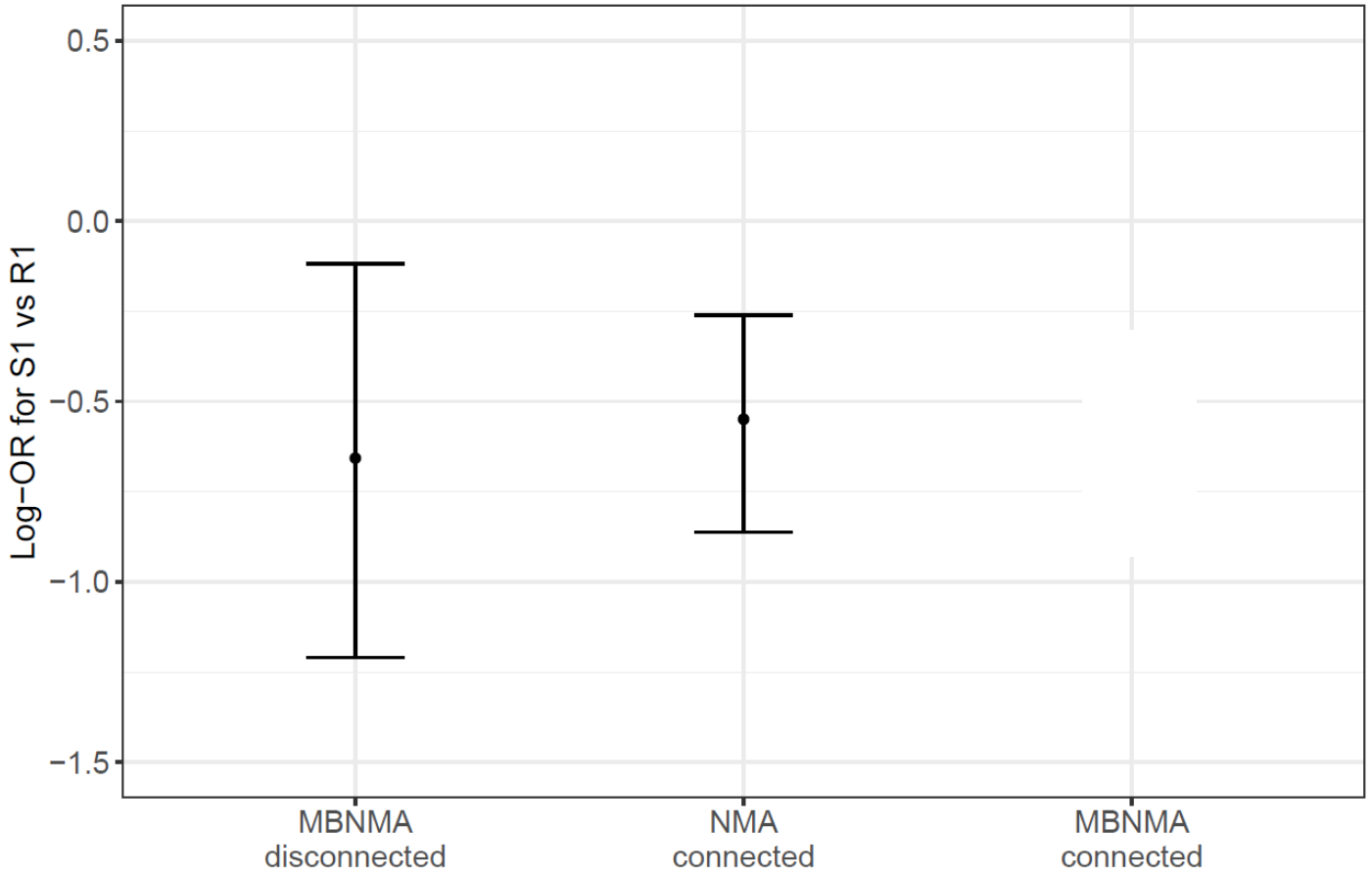

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Take Home Messages

- Sharing of information via dose-response relationship can:
  - improve precision
  - link disconnected networks of evidence
- Availability of evidence at different doses is key – Phase II studies
- Sharing dose-response parameters from different populations based on understanding of pharmacometrics
- Sharing of other structural information is also possible
  - E.g. analysis of data collected at multiple different time-points by modelling structural time-course relationship (`MBNMAtime`)

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- **MBNMAdose** R package (available on CRAN)

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Use of bivariate network meta-analysis and RWE to borrow information across lines of therapy in rheumatoid arthritis: Bayesian evidence synthesis with target trial emulation

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9 November 2022

EU

imi innovative medicines initiative

Get Real

UKRI Medical Research Council

NIHR National Institute for Health Research

Conflicts and disclosures

- I have served as a paid consultant, providing methodological advice, to NICE, Roche, RTI Health Solutions and IQVIA
- I have received research funding from European Federation of Pharmaceutical Industries & Associations (EFPIA) and Johnson & Johnson.
- I have received research funding from the Medical Research Council (MRC) , the National Institute for Health Research (NIHR) and EU Innovative Medicines Initiative (IMI).
- I have no financial or any other conflicts relating to specific products mentioned in my presentation

Outline

- Introduction and sources of data
- Use of registry data: target trial emulation
- Synthesis of RCT and registry data: bivariate NMA

Multi-parameter evidence synthesis

Bayesian statistics provides flexible framework for modelling complex data allows multiple parameters to be modelled simultaneously

- Network meta-analysis (NMA) facilitates simultaneous comparison of multiple treatments
- Multivariate meta-analysis (MVMA) allows for joint modeling of treatment effects on multiple correlated outcomes
- There are many advantages of MVMA
  - potential for reduced uncertainty
  - potential for reduced outcome reporting bias
  - inclusion of broader evidence base form relevant studies

Meta analysis and real world data

- Evidence base of meta-analysis traditionally consisted of data from randomised controlled trials (RCTs), which were considered gold standard in evaluation of health technologies.
- More recently, there have been growing interest in the use of so called real world evidence (RWE) from observational studies in health care evaluation.
- Considerable research has focussed on inclusion of real world data (RWD) in evidence synthesis with the aim of overcoming some limitations of RCT data.

Objectives

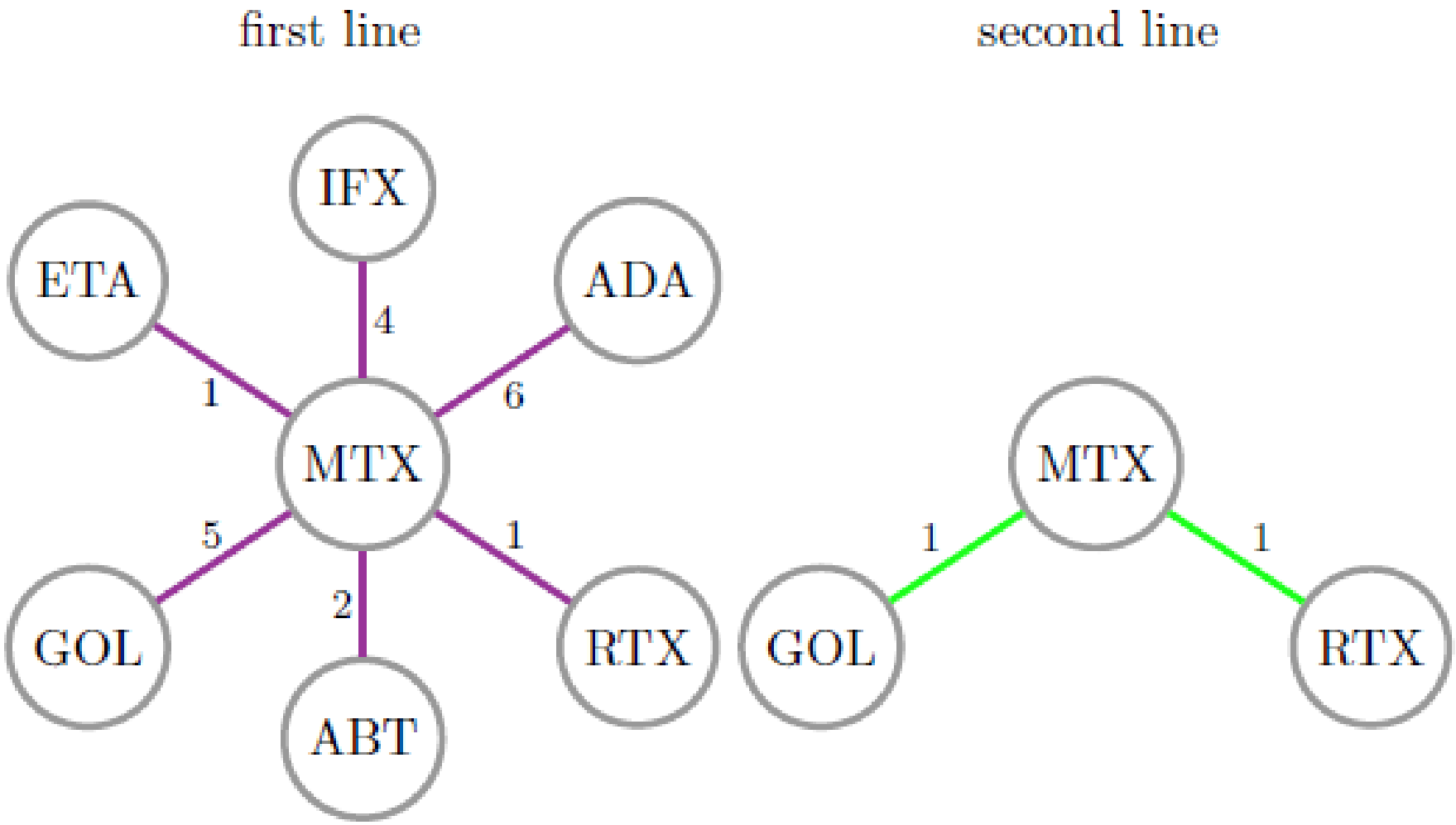
- When data from RCTs are available on effectiveness of a particular treatment, but only in the first line of therapy, a costly trial need to be carried out to also evaluate the effectiveness of the new therapy when used in patients as a second line treatment (or vice versa).
- The aim of this study was to investigate the added value of registry data in amalgamating data in a network of RCTs for first and second lines.
- It illustrates how RWD can be used to optimise an evidence base on effectiveness estimates of biologic therapies in rheumatoid arthritis (RA).

Data sources

- Randomised controlled trials (first and second line of therapy) from a literature review

- British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA; https://www.bsrbr.org/)

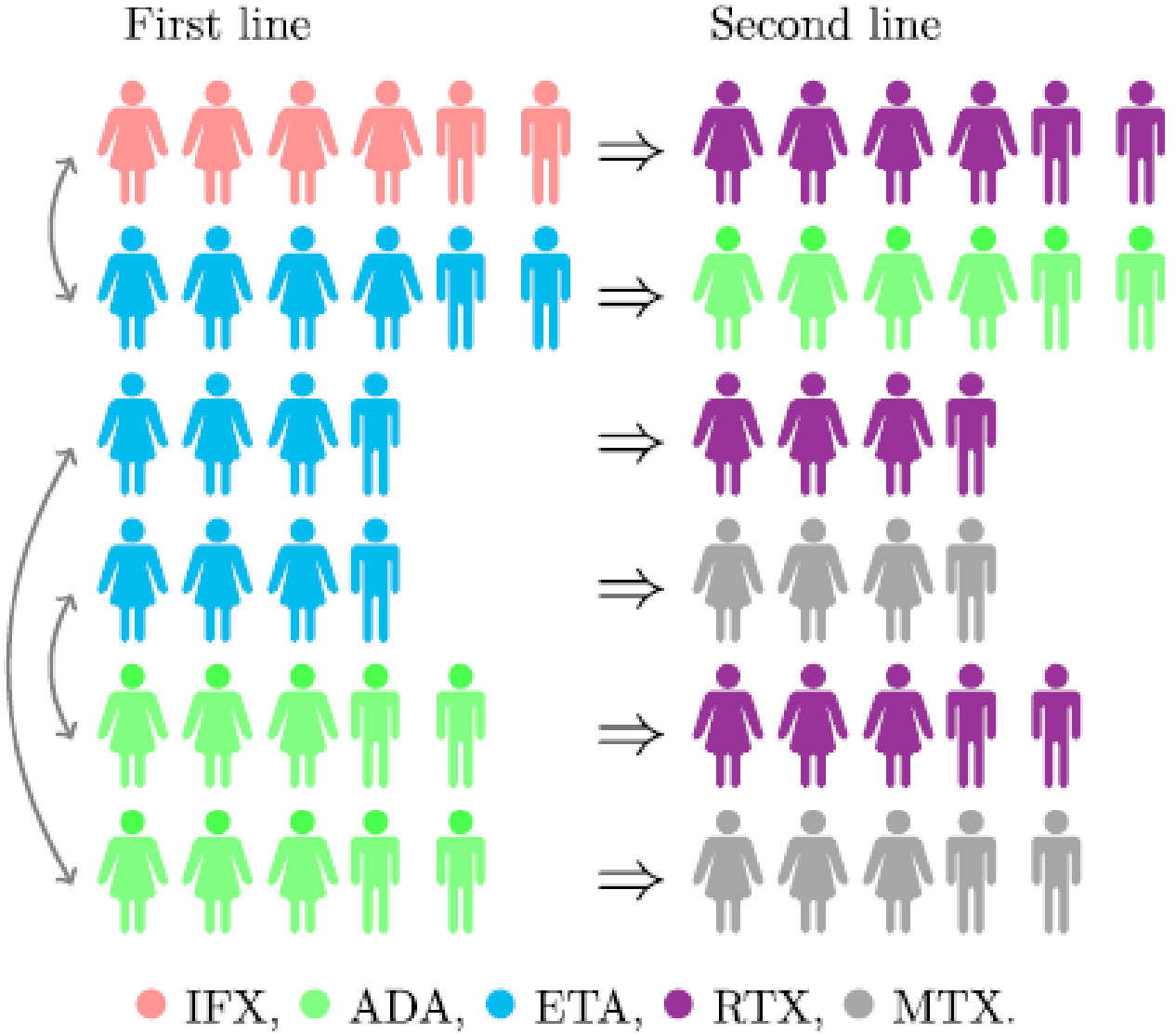
Network of RCTs



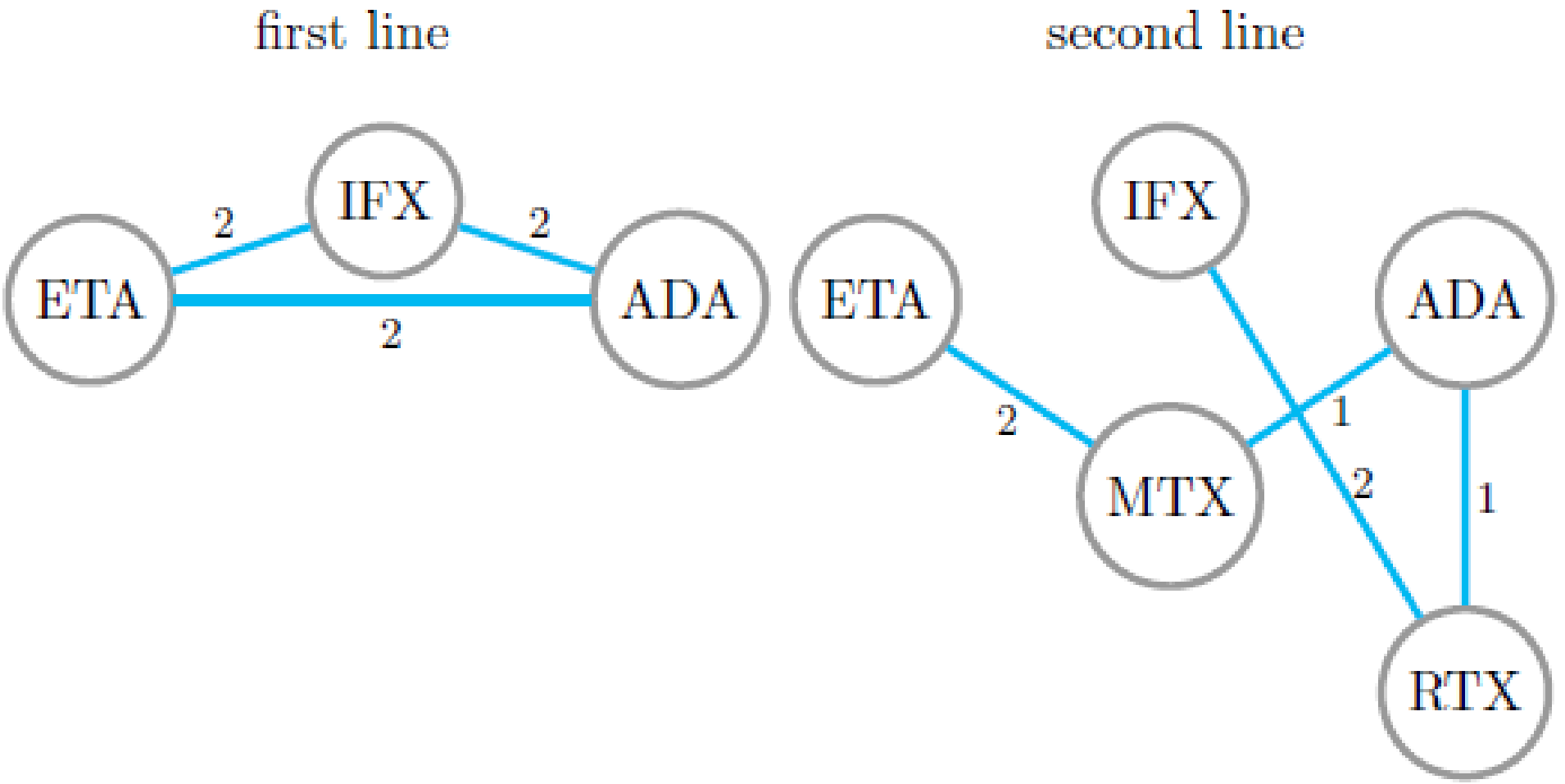
Target trial emulation: protocol in brief

- Eligibility criteria: adults with RA with previous DMARDs
- Eligibility criteria: two lines of therapy; biologic or synthetic DMARDs
- Assignment procedures:
  - groups defined by sequences of therapy matched to form experimental and control treatment groups
  - assumed no unmeasured confounding
  - prognostic factors: age, gender, duration of the disease, RF+ve, DAS-28.
- The follow-up period: minimum follow-up time had to ensure that data were collected 24 weeks after initiation of each line of therapy
- Outcome: ACR20 response criteria
- Causal contrast and statistical analysis:
  - inverse probability weighting with propensity scoring
  - per-protocol effect in all emulated trials

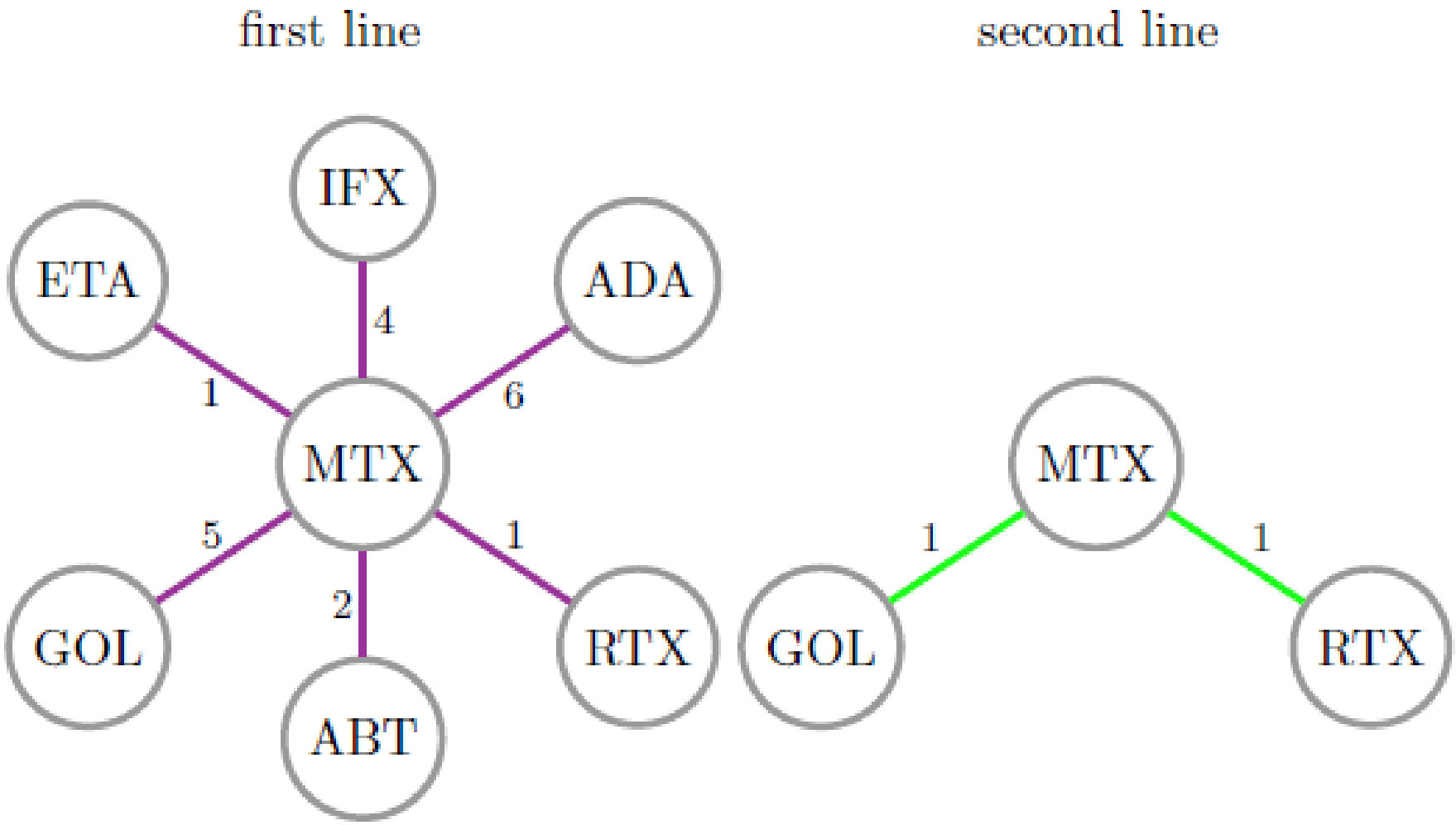
Target trial emulation: assignment procedure



Network of target trials (BSRBR-RA)

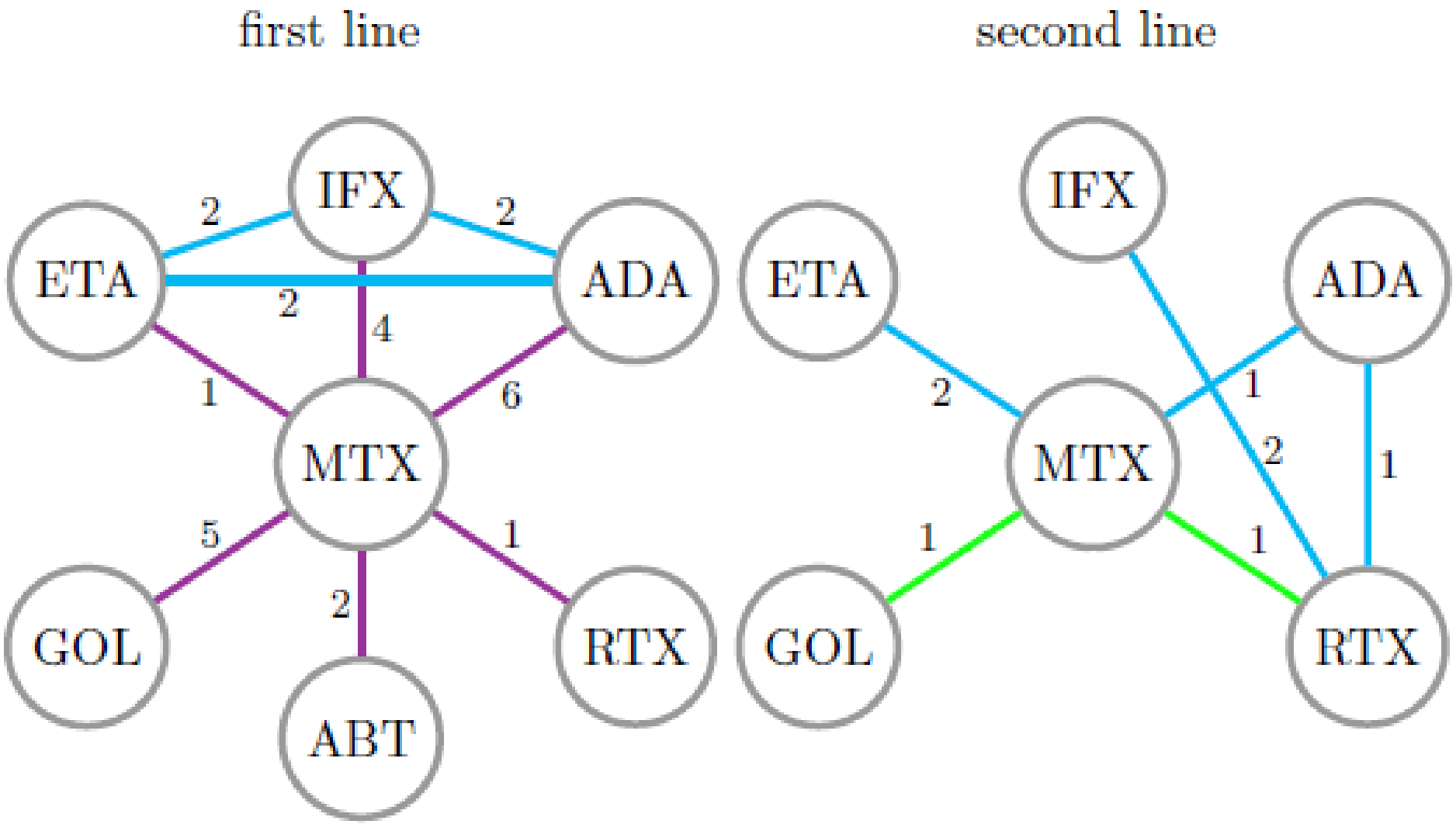


Network of RCTs



Disjoint networks/populations: no between-study correlation

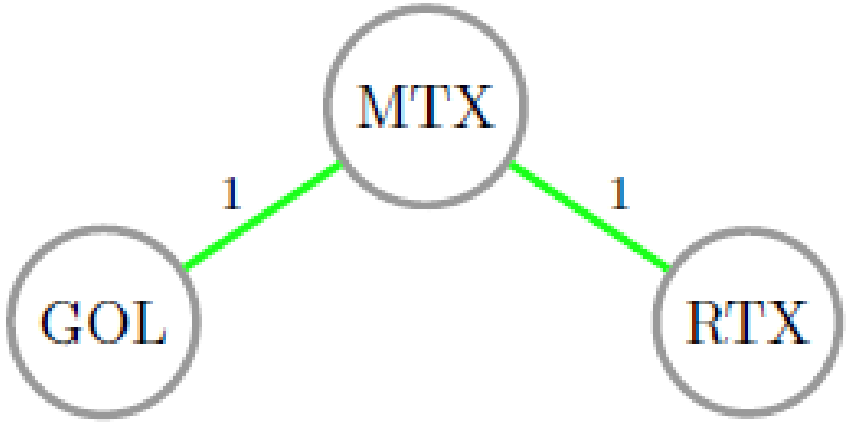
Combined networks



Target trials (blue) provide data on both lines, thus contributing to the between-study correlation

Results – second line alone; RCT data

	fixed effects			random effects		
	MTX	GOL	RTX	MTX	GOL	RTX
MTX		2.73 (1.68, 4.31)	4.84 (3.14, 7.25)		6.41 (0.21, 33.4)	11.34 (0.37, 59.4)
GOL	2.62 (1.64, 4.19)		1.88 (0.95, 3.36)			15.7 (0.05, 64.3)
RTX	4.68 (3.08, 7.1)	– –				



Results – second line alone; RCT data + BSRBR-RA

	MTX	ADA	ETA	IFX	GOL	RTX
MTX		5.03 (0.59, 19.4)	4.26 (0.71, 14.4)	10.3 (0.45, 47.1)	5.1 (0.3, 22.8)	3.86 (0.45,14.9)
ADA	4.9 (0.59, 18.7)		2.04 (0.09, 9.51)	2.99 (0.13, 13.9)	2.74 (0.05, 12.6)	1.14 (0.13, 4.37)
ETA	4.24 (0.72, 14.3)	2.06 (0.1, 9.48)		5.16 (0.09, 22.9)	2.53 (0.06, 11.5)	1.79 (0.08, 8.13)
IFX	10.6 (0.49, 48.9)	3.21 (0.15, 14.7)	5.19 (0.1, 23.7)		3.2 (0.02, 13.7	0.76 (0.12, 2.6))
GOL	5.09 (0.31, 22.7)	2.64 (0.05, 12.6)	2.66 (0.06, 11.4)	3.27 (0.02, 12.6)		3.46 (0.06, 15.8)
RTX	3.85 (0.46, 14.8)	1.16 (0.14, 4.43)	1.78 (0.08, 8.04)	0.72 (0.12, 2.44)	3.35 (0.06, 15.4)	

ORs with 95% CrIs from univariate NMA of data from RCTs and BSRBR-RA of biologic in second line of therapy

- upper triangle: adjusted using IPW-PS
- lower triangle: unadjusted

Results – all data included

	MTX	ADA	ETA	IFX	GOL	ABT	RTX
MTX		4.1 (0.57, 15.3)	3.81 (0.87, 11.1)	7.64 (0.3, 36.2)	4.92 (0.32, 21.7)	–	4.4 (0.49, 17.3)
ADA	2.96 (1.51, 5.29)		2.01 (0.13, 8.64)	2.17 (0.15, 9.48)	2.94 (0.06, 13.4)	–	1.7 (0.13, 7.43)
ETA	3.07 (1.72, 5.18)	1.1 (0.58, 2.03)		3.92 (0.07, 16.7)	2.19 (0.07, 9.96)	–	1.91 (0.1, 8.69)
IFX	3.13 (1.38, 6.31)	1.09 (0.56, 2.03)	1.05 (0.47, 2.04)		4.79 (0.03, 20.0)	–	1.65 (0.09, 7.85)
GOL	3.03 (1.38, 5.78)	1.08 (0.49, 2.12)	1.02 (0.45, 1.91)	1.06 (0.42, 2.14)		–	4.03 (0.07, 18.3)
ABT	3.37 (1.08, 7.81)	1.19 (0.41, 2.76)	1.13 (0.36, 2.55)	1.16 (0.37, 2.64)	1.2 (0.38, 2.88)		–
RTX	3.09 (1.55, 5.83)	1.09 (0.57, 2.08)	1.04 (0.51, 1.97)	1.06 (0.52, 2.0)	1.11 (0.5, 2.31)	1.17 (0.39, 2.74)	

ORs with 95% CrIs for second line treatments
from bivariate NMA of data from RCTs and BSRBR-RA of biologic in both lines of therapy

- upper triangle: using "standard" bivariate NMA model
- lower triangle: assuming exchangeability of biologic therapies *(Bujkiewicz et al Stat Med 2019)*.

Conclusions

- Registry data can be used to bridge networks of first and second lines of therapy which otherwise are disconnected
- Bivariate NMA of combined data from RCTs and RWE can be used to predict effectiveness of a treatment in second line use when the therapy is only investigated in a RCT as first line (or vice versa)
- The analysis could be improved by accounting for the differences in study design in NMA
- The approach can be applied to other settings where RCT data are available for disjoint subsets of population; for example, children and adults.

References

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Sharing information across related populations in HTA: methods and policy implications

A case-study on Intravenous Immunoglobulin for severe sepsis and septic shock

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Outline

+ Introduction to the case-study and motivation
+ The process of information-sharing
+ Measuring the *degree of information-sharing*
+ Case-study results: the impact of information-sharing
+ Concluding remarks

Using IVIG for sepsis in adults is associated with high uncertainty

Decision Research Question	
(P) Population	Adults
(I) Intervention	IVIG or IVIGAM
(C) Comparator	Albumin or Placebo
(O) Outcome	All-cause mortality
(S) Study design	RCTs

Indirect evidence
CHILDREN
IVIG or IVIGAM
Albumin or Placebo
All-cause mortality
RCTs

- There were issues with the methodological quality of the available evidence

  There was no clear best-fitting evidence synthesis model that makes clinical sense

- There was substantial heterogeneity that could not be adequately explained using the suspected effect modifiers

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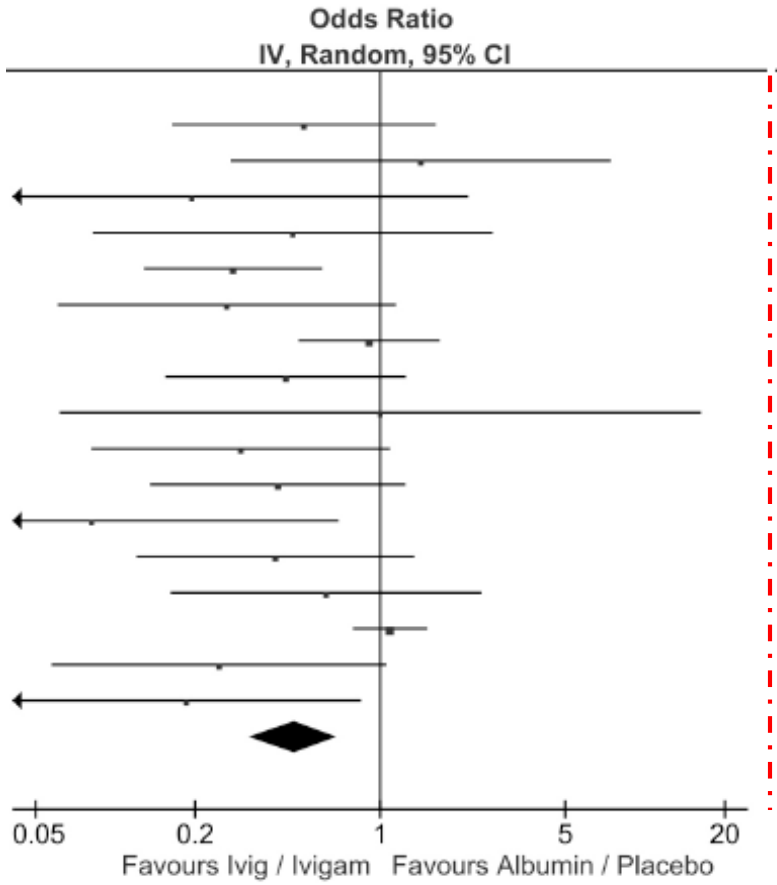
An evaluation of the feasibility, cost and value of information of a multicentre randomised controlled trial of intravenous immunoglobulin for sepsis (severe sepsis and septic shock): incorporating a systematic review, meta-analysis and value of information analysis

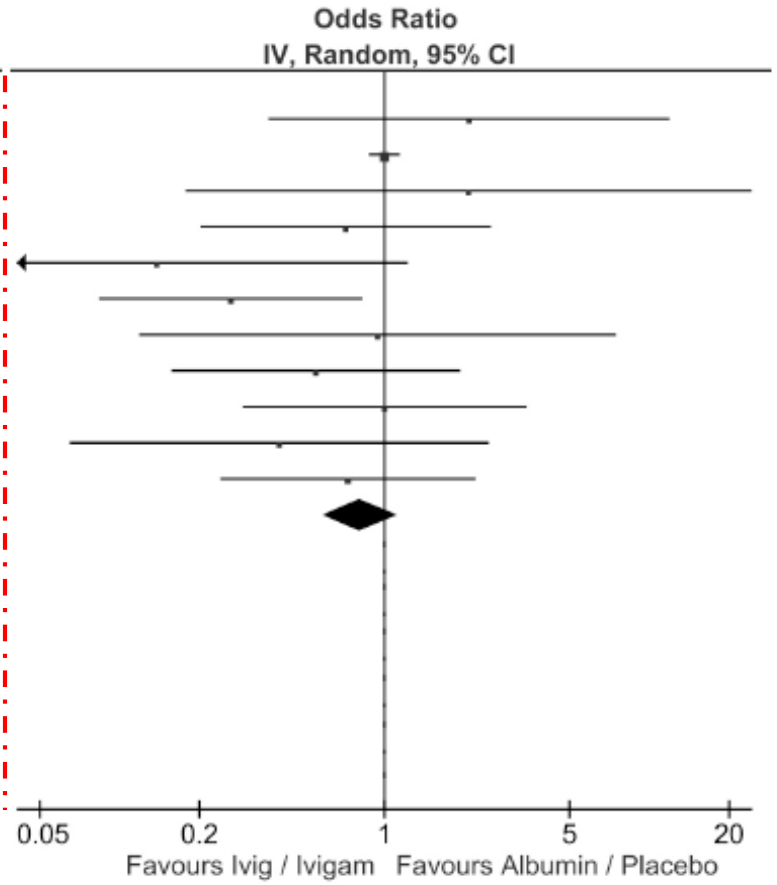
MO Soares, NJ Welton, DA Harrison, P Peura, M Shankar-Hari, SE Harvey, JJ Madan, AE Ades, SJ Palmer and KM Rowan

The indirect evidence in children is high quality and could potentially alleviate some weaknesses in the adult evidence

Direct evidence: Adults



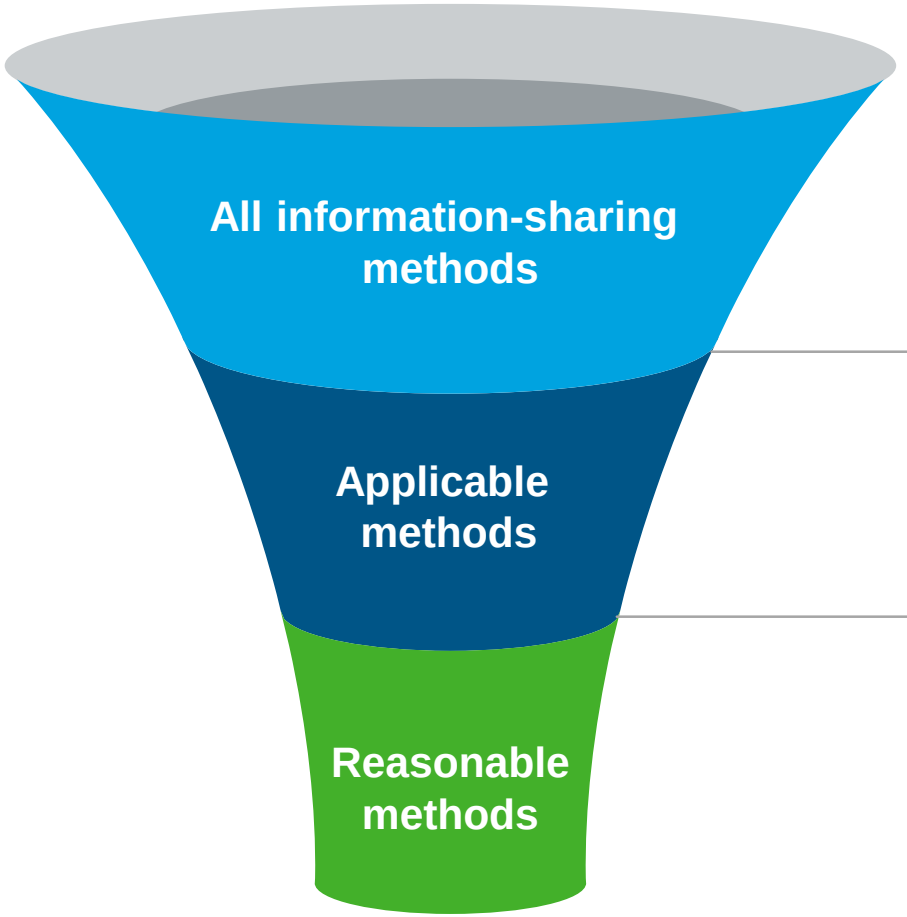
Indirect evidence: Children



Strengths of the indirect evidence

- Less between-studies heterogeneity
- Higher quality studies
- A very large publicly funded study

Choosing information-sharing methods



What are the methodological options?

- A classification of all methodological options has been previously provided in Nikolaidis et al., 2021. The ‘core’ relationships and the listed methods can serve as a starting point for deliberation.

Which methods can be applied on my data?

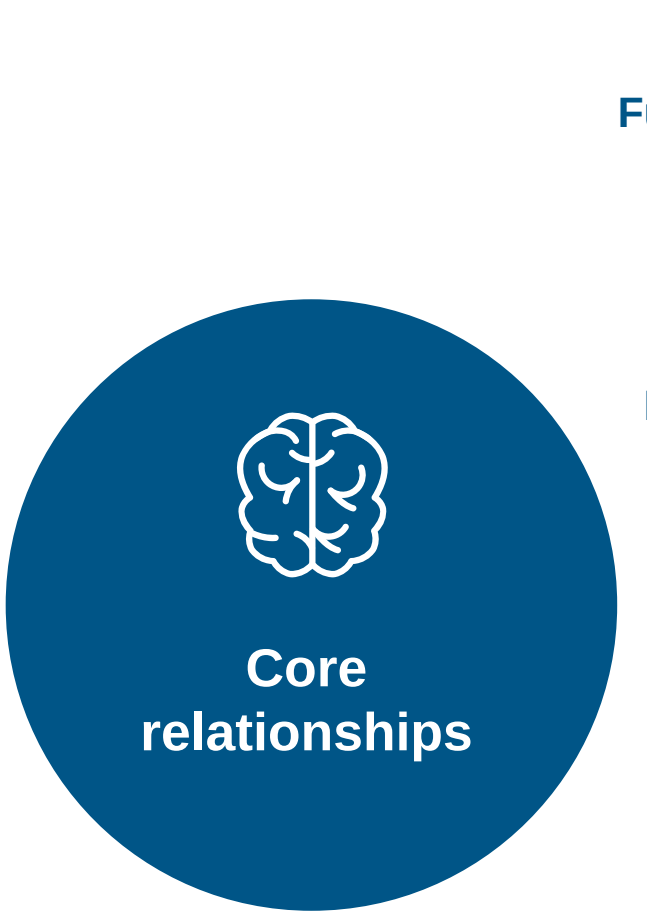
- The full list of methods should then be refined in the context of the case-study. The number of indirect evidence sets and the type of indirect data will determine the applicable methods

Which methods are expected to impose an appropriate degree of information-sharing?

- Clinical opinion should then be sought to assess the plausibility of combining the various evidence sets. This step will determine the methods that are expected to impose the most realistic degree of information-sharing

Nikolaidis, G.F., Woods, B., Palmer, S. et al. *Classifying information-sharing methods*. BMC Med Res Methodol 21, 107 (2021). https://doi.org/10.1186/s12874-021-01292-z

Several information-sharing methods were used in this case-study



Functional

- Lumping

Exchangeability-based

- Multi-level model

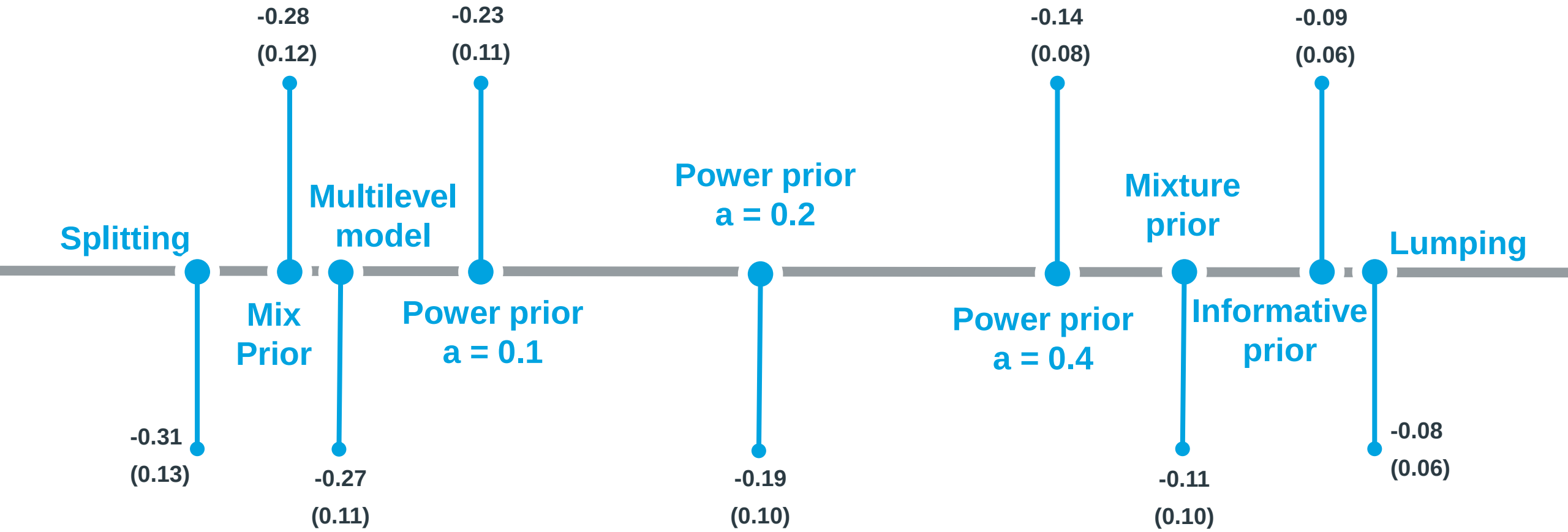
Prior-based

- Informative priors
- Mixture priors
- Commensurate priors
- Power priors

Multivariate

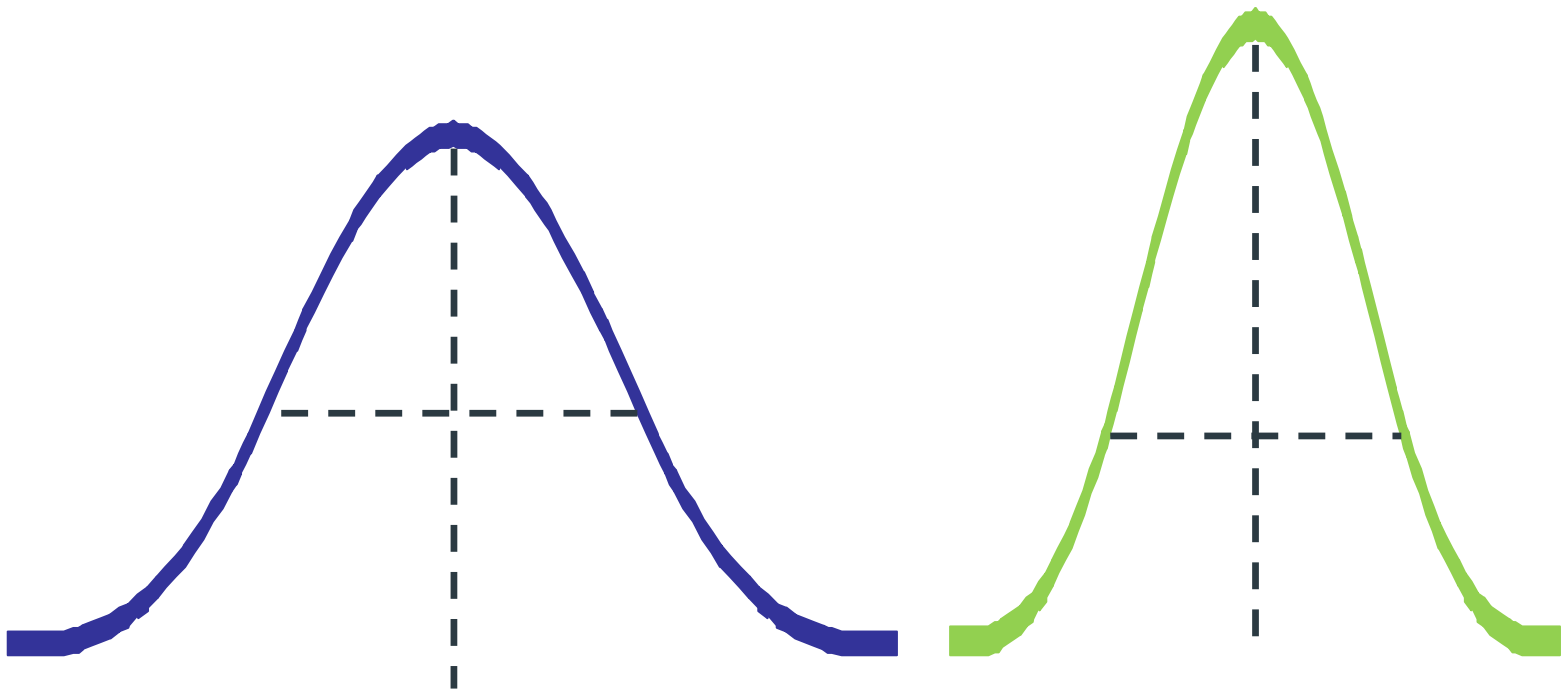
No multivariate methods were used, because no study reported for both the direct and the indirect population

The results clearly demonstrate the ‘information-sharing *spectrum*’



Numbers correspond to posterior relative effect point estimates (log odds-ratios) and their corresponding standard errors

Measuring the imposed '*degree of information-sharing*'

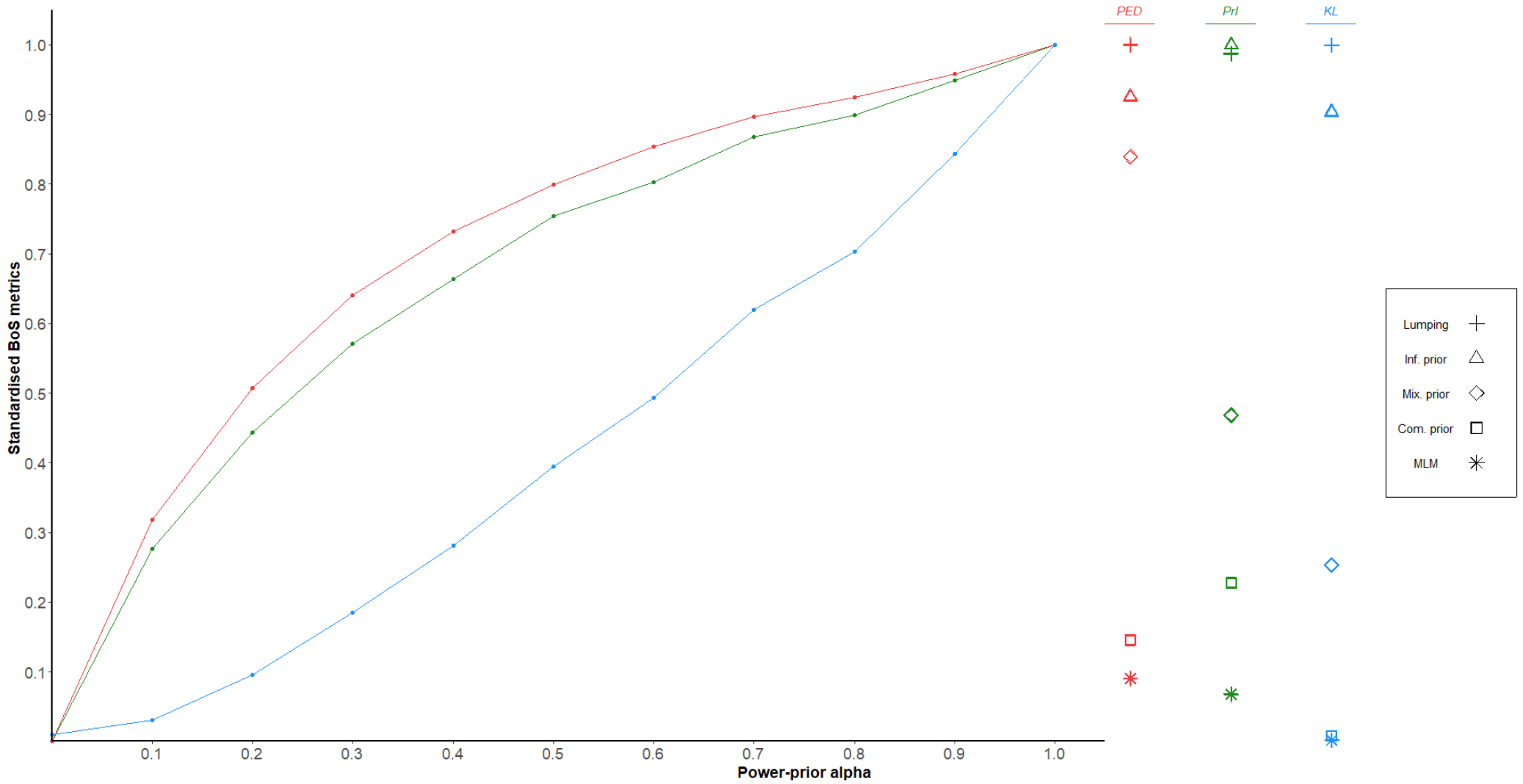


NO information-sharing

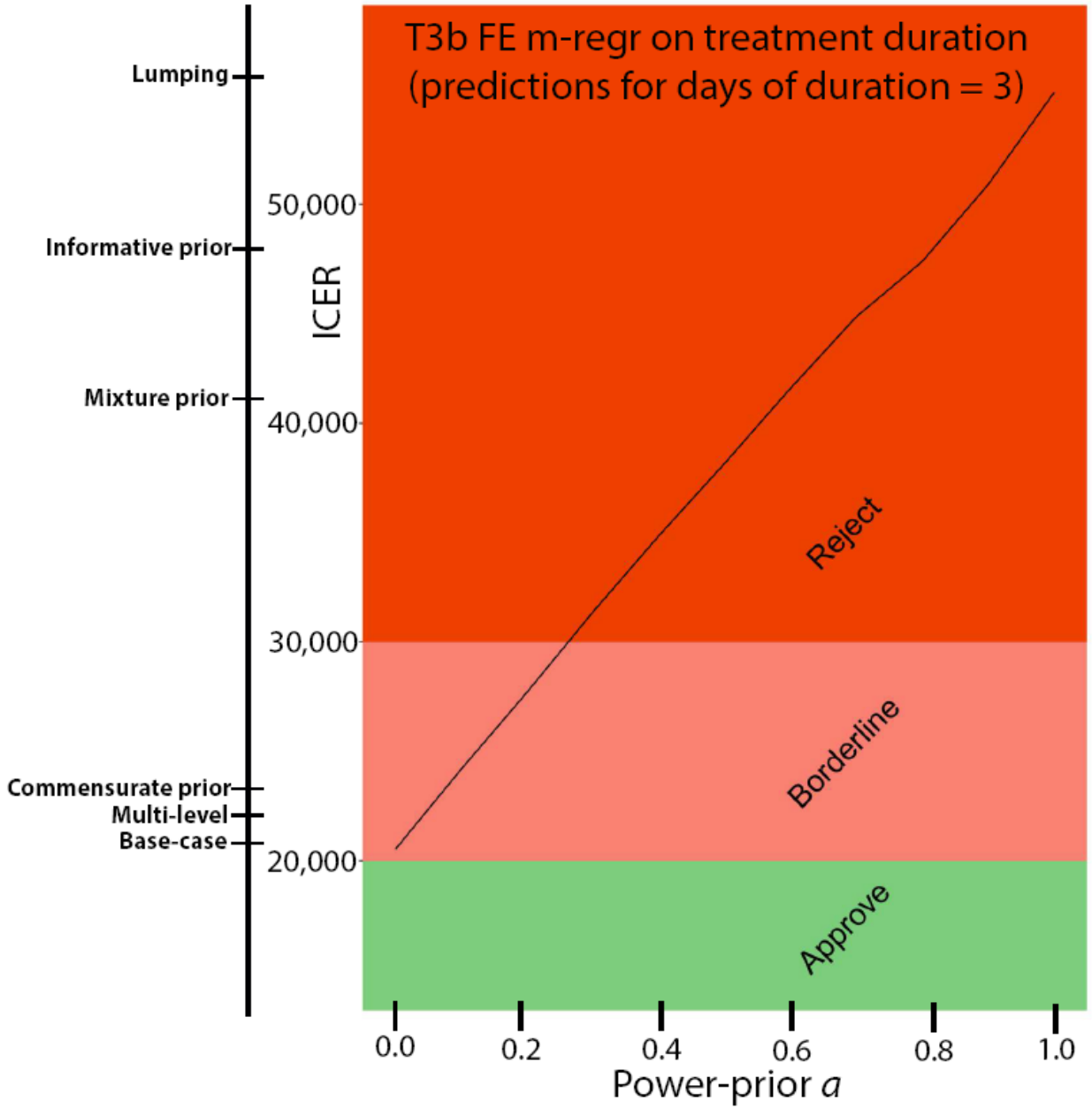
WITH information-sharing

- The use of indirect evidence can impact the point estimate, the uncertainty, or both
- Unlike in simulation experiments, in HTA it is impossible to know which method better approximates the truth
- Hence, we can only compare the estimates produced with and without information-sharing and **invite clinical input to form a judgements about appropriateness**

The strength of information-sharing may differ across metrics



The choice of method can impact adoption decisions



Concluding remarks

1

Use of information-sharing

- Information-sharing is commonplace in HTA. It just mostly happen implicitly using crude methods

2

Methods of information-sharing

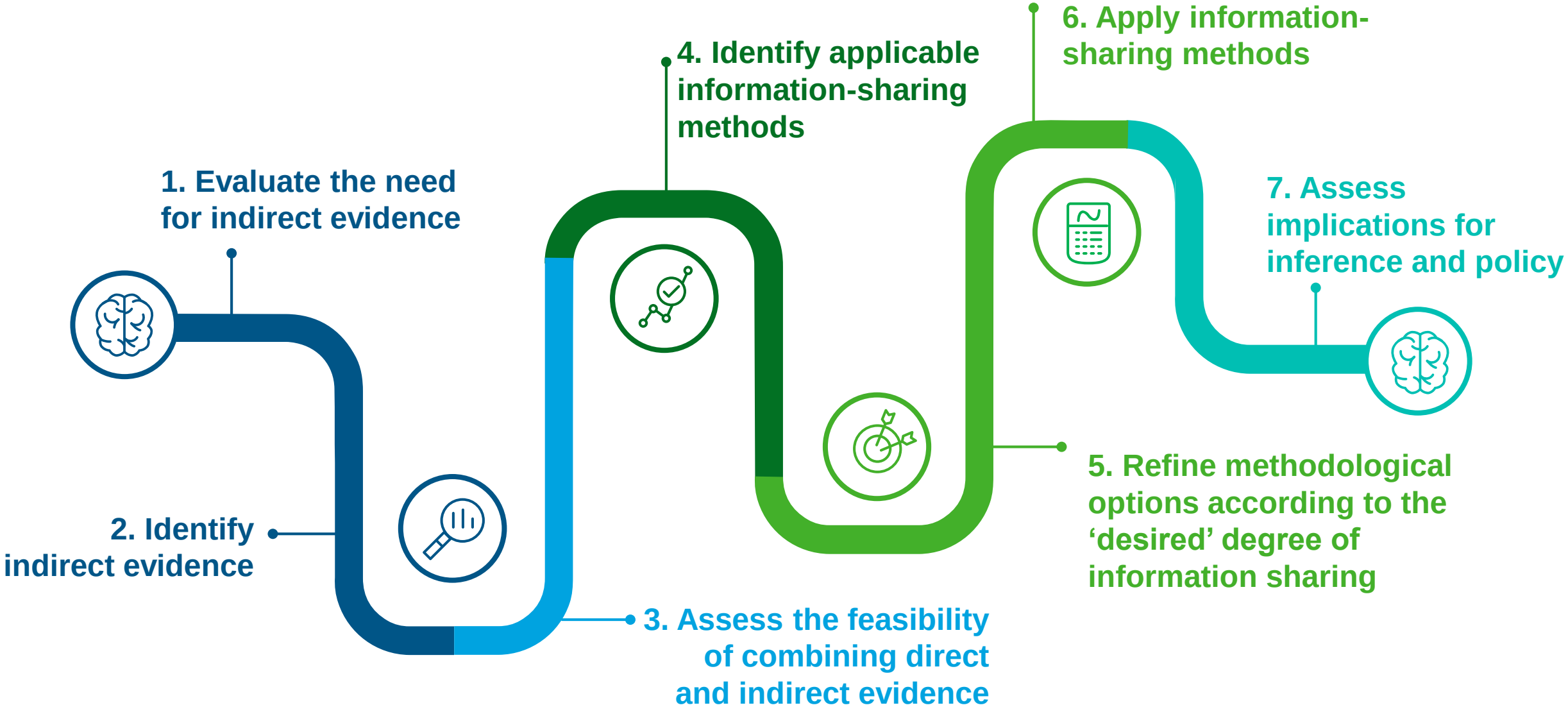
- Lumping vs splitting is a false dilemma. More sophisticated methods can impose more moderate and potentially more appropriate degrees of information-sharing.
- Clinical judgement is required to determine the most appropriate information-sharing method(s)

3

Need for information-sharing in HTA

- HTA requires a transparent and thorough process of information-sharing that incorporates clinical judgements
- Further research should expedite this process to enable fast and easy application in HTA

Information-sharing process



Discussion/polling

About you [Multiple Choice]

Q1: Do you work in HTA, or with HTA evidence?

Yes, No

Q2: Is the HTA evidence you work with appraised by a decision making body?

Yes , No

Q3: Do you work for:

- A company whose products are subject to HTA appraisals
- Decision making body
- Academia
- Consultancy
- None of the above

Q4: In your HTA work, what are the most common evidence problems you encounter? [Multiple Choice]

- relative effectiveness cannot be determined without strong judgements, e.g. disconnected networks
- evidence is sparse and further research is not possible (or is less likely), e.g. orphan drugs, paediatric indications
- evidence on final outcomes is sparse/immature but there is evidence on surrogate/intermediate outcomes
- direct evidence is uncertain and ‘indirect’ evidence could reduce it (e.g. multi-indication products, product in a common class)
- Other

Q5: What are the greatest challenges in using sharing of information? [Numerical average]

Rank from most to least important

- Lack of methodological guidance on how to conduct these analyses
- Potential reluctance of policy makers in accepting such an approach
- Lack of analytical skills in my team to implement/appraise such analyses

Important developments that would support the use of sharing of information methods in your work…

Q6: What is the most important piece of **methodological** guidance?

- How to identify the most impactful and relevant source of indirect evidence
- How to choose the most appropriate quantitative method of sharing
- How to identify, present and validate (with clinical experts) the strength of sharing imposed

Q7: What is the most important **policy** development?

- Decision makers to define explicit criteria on the use of information sharing in evidence submissions
- Decision makers to define the impact of the use of information sharing for reimbursement/pricing (e.g. managed access agreements and/or request for price reductions)