Get Real

Real-Life Data in Drug Development

Bridging efficacy to effectiveness: The IMI GetReal project

Meta-analyses, outcome prediction, evidence synthesis and modelling

WP4 Webinar 10 May 2016

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115303], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

Get Real

Real-Life Data in Drug Development

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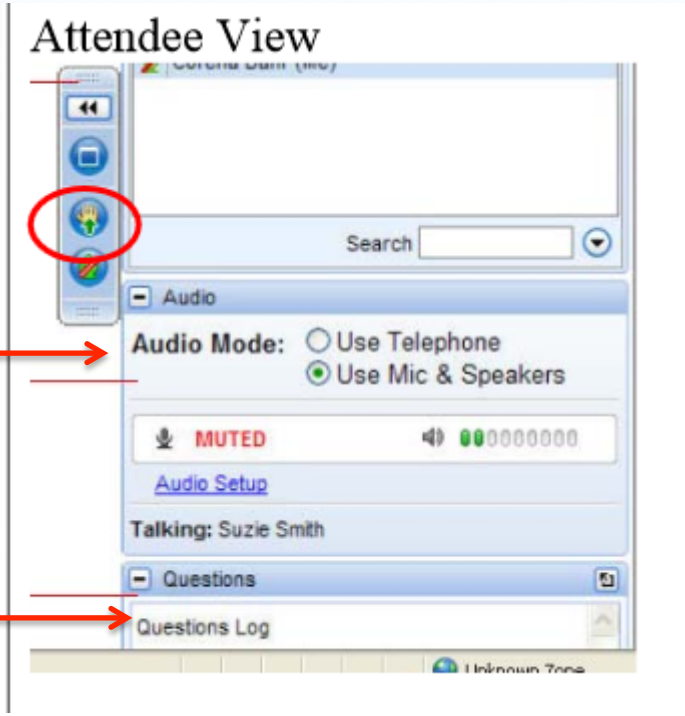
How to Use the Webinar Tools

Raise your hand

Dial in or headphones

Ask a question



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Save the date!

- **CONFERENCE: 17 June 2016 - London**: GetReal Putting Real World Healthcare Data to Work (Upon invitation only)
- **www.imi-getreal.eu or vitaltransformation.com**

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Get Real

Real-Life Data in Drug Development

An introduction to WP4 and Get Real

Matthias Egger
Director of the Institute of Social and Preventive Medicine (ISPM),
University of Berne, Switzerland

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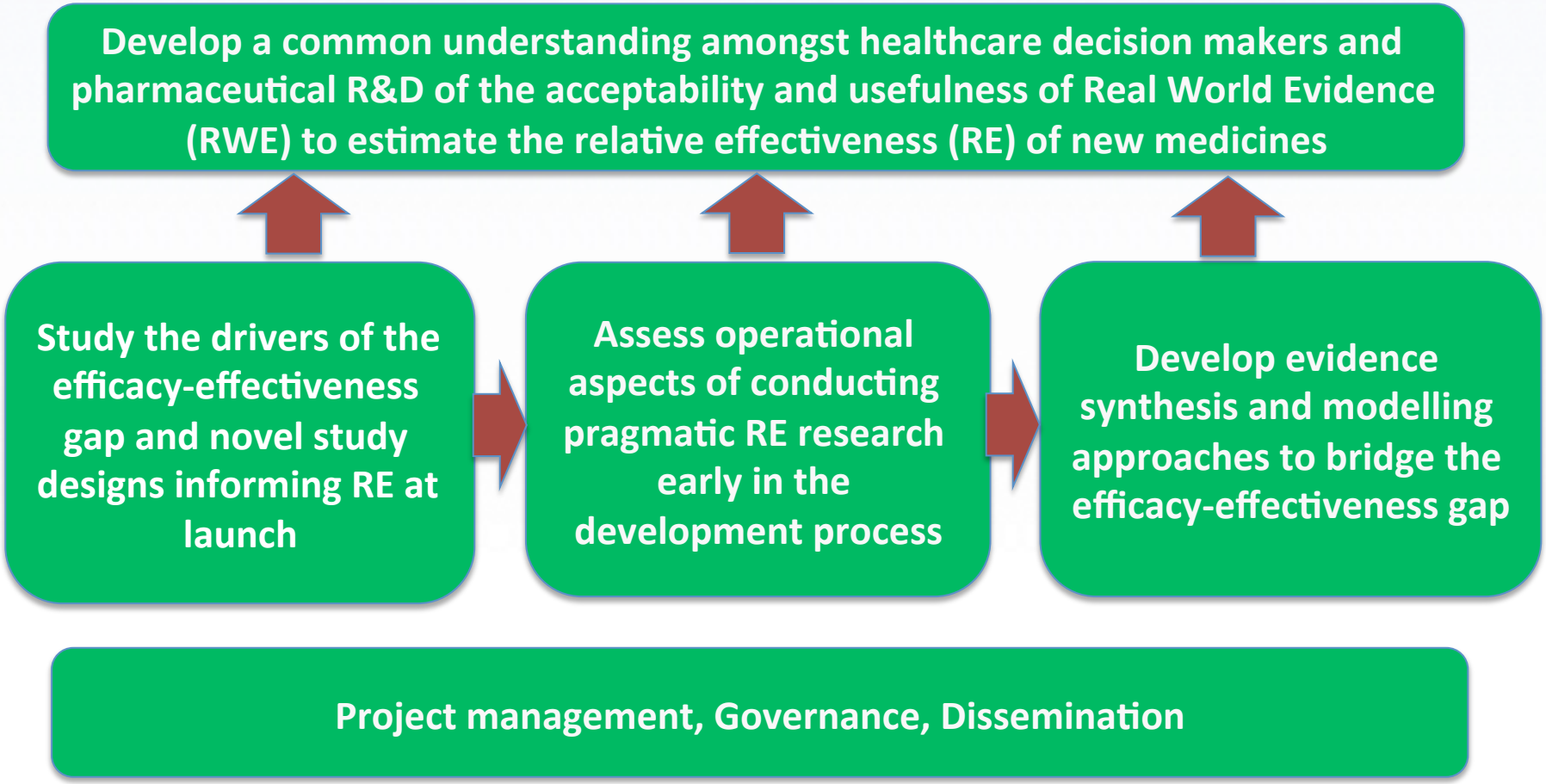
Architecture of GetReal



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Key questions in evidence synthesis and modelling

- How well can relative effectiveness be estimated from phase II and III RCT efficacy studies alone?
- How should RCTs, additional relative effectiveness studies and observational data best be integrated to address specific decision making needs of regulatory and HTA bodies at launch?
- How can relative effectiveness be predicted from available efficacy and observational data?

Egger, Fletcher, Moons. JRSM 2016

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Key questions

Questions	Outcomes	Applicability	Data sources	Evidence synthesis	Conditions
1) How efficacious and safe is this drug?	Efficacy, safety	Typical patients included in clinical trials	Phase II/III randomised clinical trials	Clinical trials, standard meta-analysis	Study conditions
2) How efficacious and safe is this drug compared to alternative therapies?	Relative efficacy, relative safety	Typical patients included in clinical trials	Phase II/III randomised clinical trials	Network meta-analysis	Study conditions
3) How effective and safe is this drug compared to alternative therapies, in the patients who will likely receive it post-launch?	Relative effectiveness, relative safety in predicted study populations	Patients predicted to receive the drug post-launch	Phase II/III randomised clinical trials, clinical databases and registries	Individual patient data (IPD) network meta-analysis and meta-regression	Study conditions
4) How effective and safe is this drug compared to alternative therapies, in the patients who will likely receive it in the real world of a health care system?	Relative effectiveness, relative safety in predicted real world populations	Patients predicted to receive the drug post-launch in a given health care system	Phase II/III randomised clinical trials, clinical databases and registries, expert opinion, patient preferences	Mathematical modelling	Real world conditions

Egger, Fletcher, Moons. JRSM 2016

Get Real

Real-Life Data in Drug Development

Estimating and appraising treatment effects using randomized and real-world evidence

A case study on schizophrenia

Georgia Salanti
School of Medicine, University of Ioannina, Greece

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Case study

Comparing 15 antipsychotics in schizophrenia

Aripiprazole, Amisulpride, Asenapine, Chlorpromazine, Clozapine, Flupentixol, Iloperidone, Lurasidone, Quetiapine, Olanzapine, Paliperidone, Risperidone, Sertindole, Ziprasidone, Zotepine

RCTs (Randomized Controlled Trials): 168 trials with study-level data (active and placebo)

RWE (Real World Evidence): A large cohort study (SOHO) with 11.000 patients (*Patient-level data*)

Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis.
Leucht S et al. Lancet. 2013

efpia

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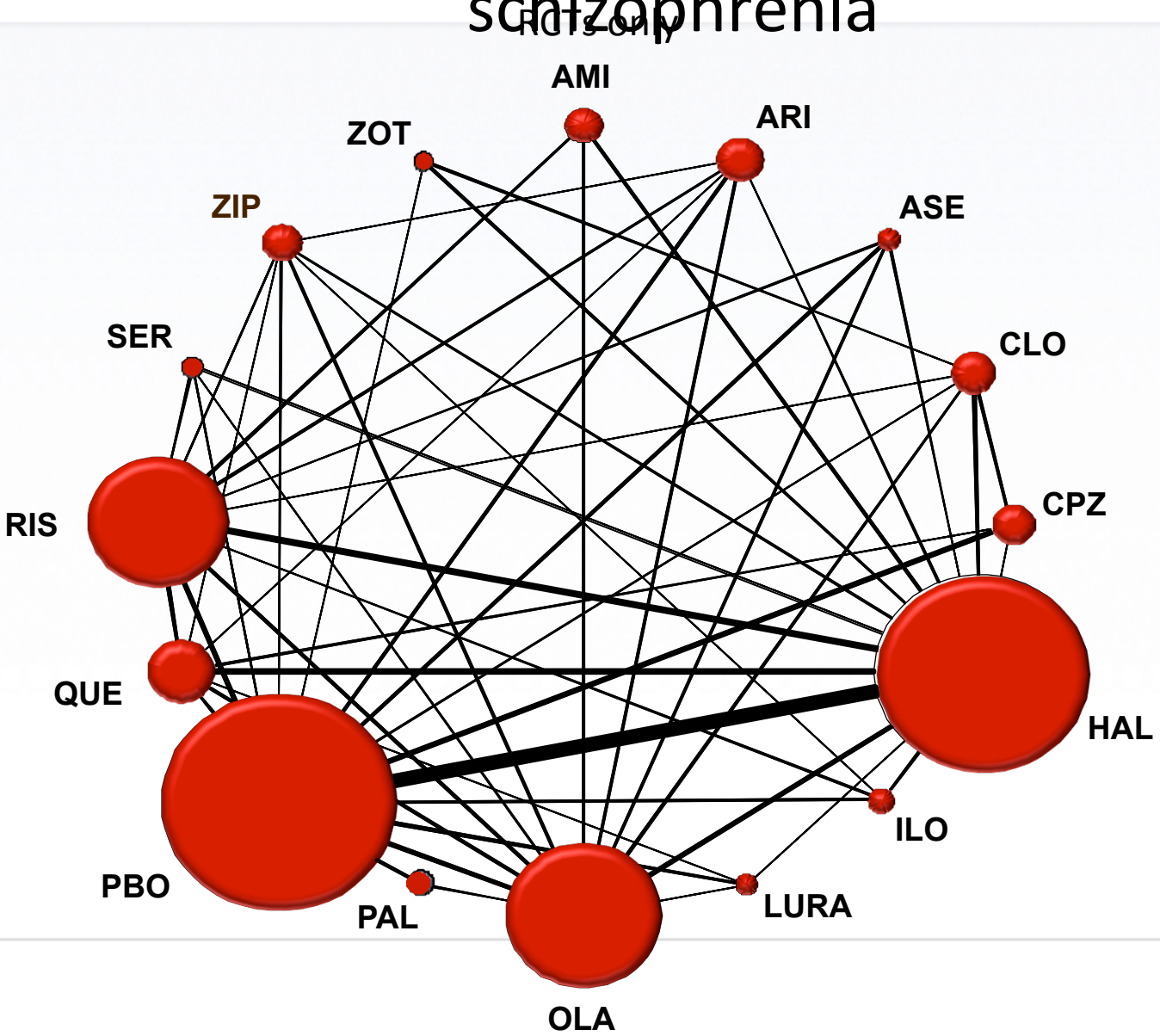
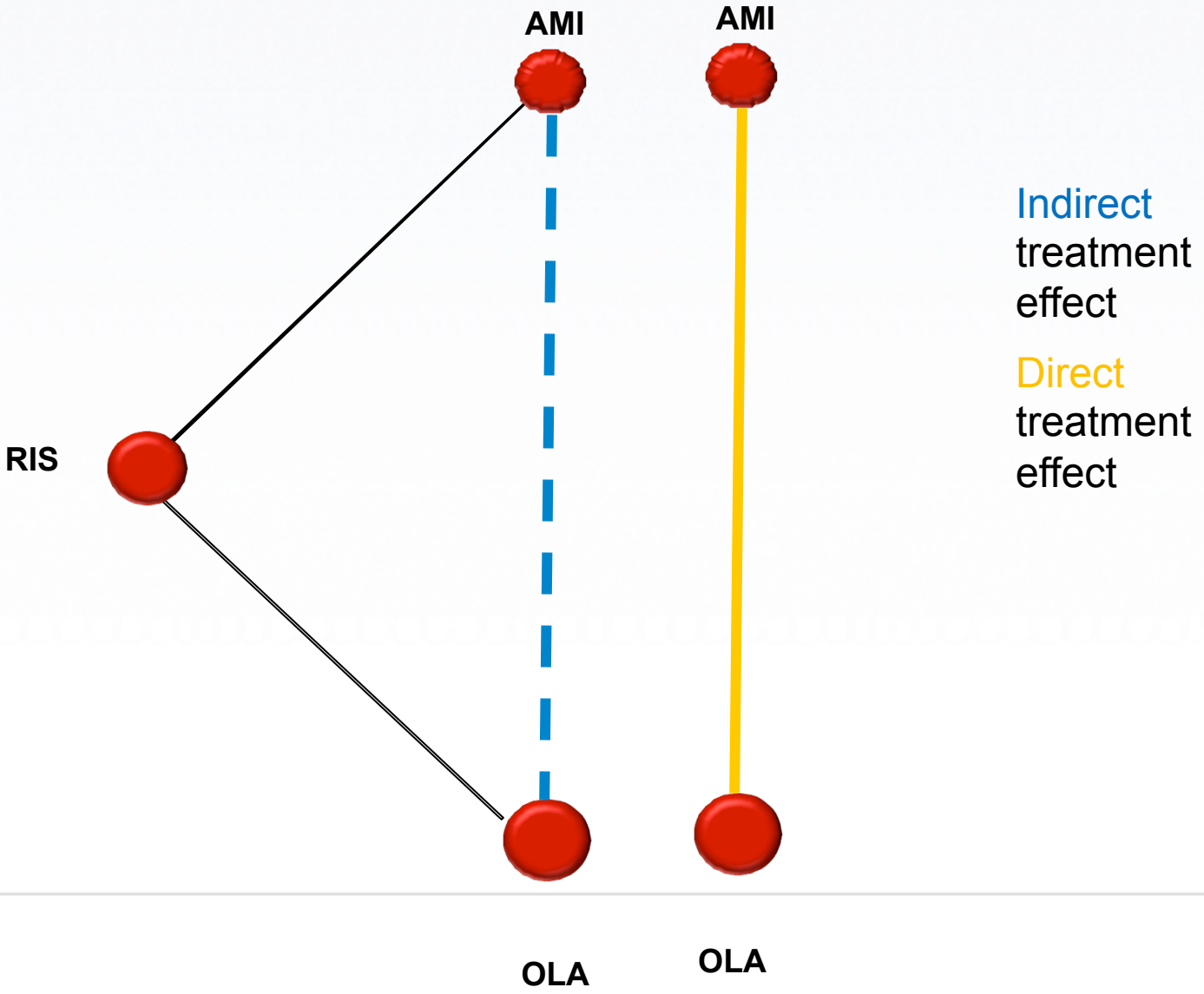
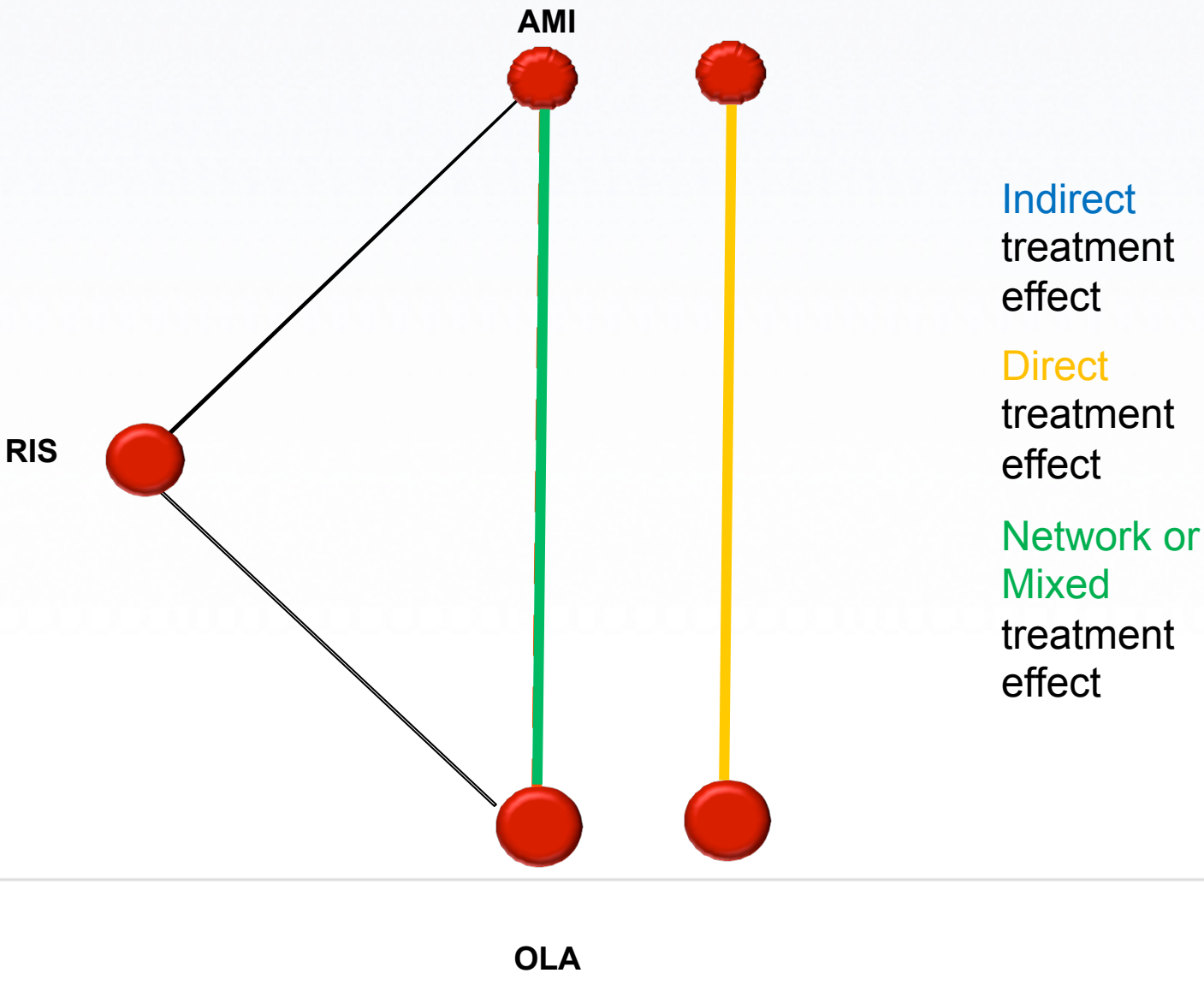
Network of 15 antipsychotic drugs in schizophrenia



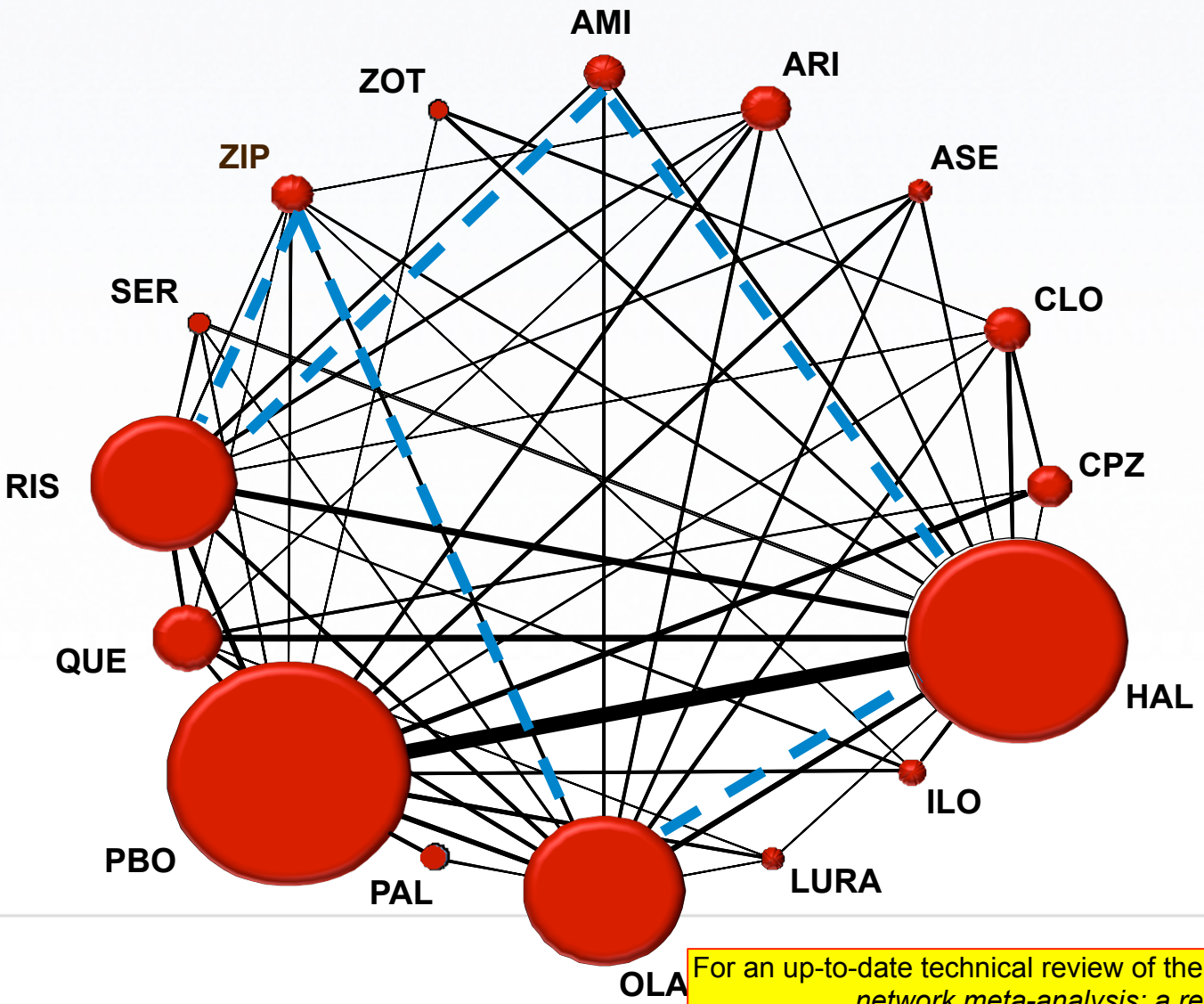
Network of 15 antipsychotic drugs in schizophrenia



Network of 15 antipsychotic drugs in schizophrenia



Network of 15 antipsychotic drugs in schizophrenia



For an up-to-date technical review of the methods see *GetReal in network meta-analysis: a review of the methodology.* Efthimiou O et al. Res Synth Methods. 2016

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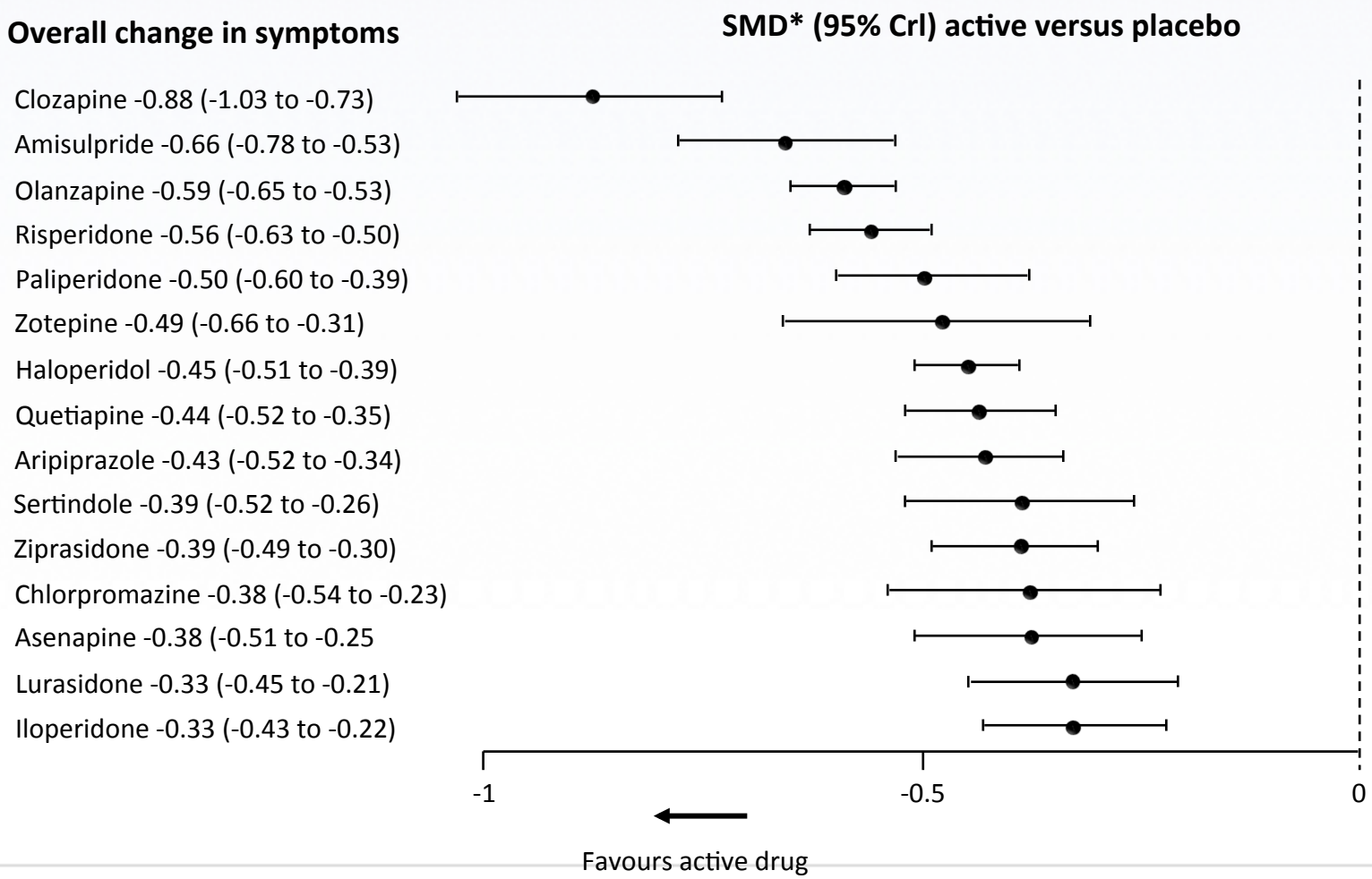
Efficacy and acceptability of 15 antipsychotic drugs in schizophrenia

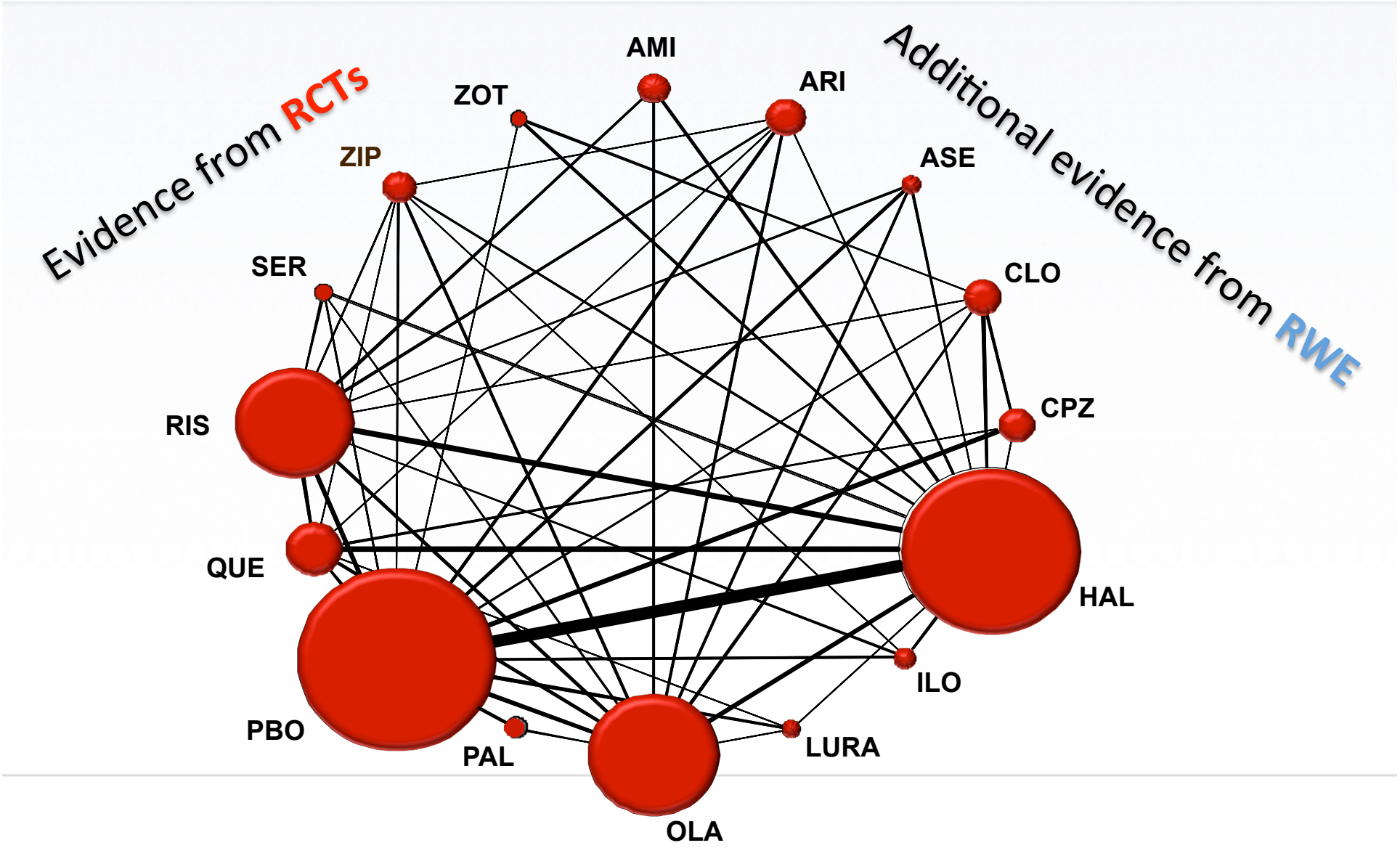
CLO	1·10 (0·69 to 1·69)	1·00 (0·68 to 1·43)	0·87 (0·59 to 1·22)	0·97 (0·63 to 1·42)	0·70 (0·39 to 1·16)	0·57 (0·40 to 0·82)	0·76 (0·50 to 1·10)	0·76 (0·51 to 1·09)	0·60 (0·38 to 0·89)	0·65 (0·43 to 0·95)	0·71 (0·48 to 1·01)	0·68 (0·43 to 1·01)	0·61 (0·39 to 0·90)	0·67 (0·45 to 0·99)	0·46 (0·32 to 0·65)
−0·22 (−0·41 to −0·04)	AMI	0·93 (0·69 to 1·22)	0·81 (0·60 to 1·08)	0·90 (0·62 to 1·24)	0·66 (0·37 to 1·10)	0·53 (0·40 to 0·70)	0·70 (0·51 to 0·95)	0·71 (0·51 to 0·96)	0·56 (0·38 to 0·78)	0·60 (0·43 to 0·83)	0·67 (0·44 to 0·95)	0·63 (0·43 to 0·89)	0·56 (0·39 to 0·79)	0·63 (0·44 to 0·87)	0·43 (0·32 to 0·57)
−0·29 (−0·44 to −0·14)	−0·07 (−0·19 to 0·05)	OLA	0·87 (0·76 to 1·01)	0·97 (0·78 to 1·20)	0·71 (0·43 to 1·13)	0·58 (0·50 to 0·66)	0·76 (0·63 to 0·91)	0·76 (0·64 to 0·90)	0·60 (0·47 to 0·76)	0·65 (0·53 to 0·79)	0·72 (0·54 to 0·94)	0·68 (0·53 to 0·86)	0·61 (0·47 to 0·77)	0·68 (0·54 to 0·84)	0·46 (0·41 to 0·52)
−0·32 (−0·47 to −0·16)	−0·09 (−0·21 to 0·03)	−0·03 (−0·10 to 0·04)	RIS	1·12 (0·88 to 1·40)	0·82 (0·49 to 1·29)	0·66 (0·58 to 0·76)	0·87 (0·73 to 1·04)	0·88 (0·72 to 1·06)	0·69 (0·53 to 0·88)	0·75 (0·61 to 0·91)	0·83 (0·61 to 1·08)	0·78 (0·60 to 1·01)	0·70 (0·53 to 0·89)	0·78 (0·62 to 0·96)	0·53 (0·46 to 0·60)
−0·38 (−0·57 to −0·20)	−0·16 (−0·32 to −0·00)	−0·09 (−0·21 to 0·02)	−0·07 (−0·19 to 0·06)	PAL	0·74 (0·43 to 1·20)	0·60 (0·48 to 0·75)	0·79 (0·61 to 1·01)	0·79 (0·61 to 1·02)	0·63 (0·46 to 0·85)	0·68 (0·52 to 0·88)	0·75 (0·53 to 1·02)	0·71 (0·52 to 0·95)	0·63 (0·47 to 0·85)	0·70 (0·53 to 0·93)	0·48 (0·39 to 0·58)
−0·39 (−0·60 to −0·19)	−0·17 (−0·38 to 0·04)	−0·10 (−0·29 to 0·08)	−0·08 (−0·26 to 0·11)	0·01 (−0·22 to 0·20)	ZOT	0·86 (0·51 to 1·32)	1·13 (0·66 to 1·78)	1·14 (0·67 to 1·81)	0·90 (0·51 to 1·46)	0·97 (0·56 to 1·55)	1·07 (0·61 to 1·71)	1·02 (0·58 to 1·65)	0·91 (0·51 to 1·47)	1·01 (0·58 to 1·61)	0·69 (0·41 to 1·07)
−0·43 (−0·58 to −0·28)	−0·21 (−0·32 to −0·09)	−0·14 (−0·21 to −0·08)	−0·11 (−0·18 to −0·05)	−0·05 (−0·16 to 0·08)	−0·04 (−0·21 to 0·14)	HAL	1·32 (1·11 to 1·57)	1·33 (1·11 to 1·57)	1·05 (0·82 to 1·31)	1·13 (0·93 to 1·35)	1·25 (0·93 to 1·63)	1·19 (0·92 to 1·50)	1·06 (0·82 to 1·34)	1·17 (0·95 to 1·43)	0·80 (0·71 to 0·90)
−0·44 (−0·61 to −0·28)	−0·22 (−0·36 to −0·08)	−0·15 (−0·25 to −0·06)	−0·13 (−0·22 to −0·03)	−0·06 (−0·19 to 0·08)	−0·05 (−0·24 to 0·14)	−0·01 (−0·10 to 0·08)	QUE	1·01 (0·80 to 1·25)	0·80 (0·60 to 1·04)	0·86 (0·68 to 1·07)	0·95 (0·69 to 1·26)	0·90 (0·68 to 1·19)	0·81 (0·61 to 1·03)	0·89 (0·70 to 1·13)	0·61 (0·52 to 0·71)
−0·45 (−0·62 to −0·28)	−0·23 (−0·37 to −0·08)	−0·16 (−0·25 to −0·07)	−0·13 (−0·23 to −0·03)	−0·07 (−0·20 to 0·08)	−0·06 (−0·25 to 0·14)	−0·02 (−0·12 to 0·08)	−0·01 (−0·12 to 0·11)	ARI	0·80 (0·59 to 1·04)	0·86 (0·68 to 1·07)	0·95 (0·69 to 1·27)	0·90 (0·68 to 1·18)	0·80 (0·6 to 1·05)	0·89 (0·69 to 1·14)	0·61 (0·51 to 0·72)
−0·49 (−0·68 to −0·30)	−0·27 (−0·43 to −0·10)	−0·20 (−0·33 to −0·06)	−0·17 (−0·31 to −0·04)	−0·10 (−0·27 to 0·07)	−0·09 (−0·31 to 0·12)	−0·06 (−0·19 to 0·07)	−0·04 (−0·19 to 0·10)	−0·04 (−0·19 to 0·11)	SER	1·09 (0·81 to 1·45)	1·21 (0·84 to 1·69)	1·14 (0·81 to 1·56)	1·02 (0·73 to 1·39)	1·13 (0·83 to 1·52)	0·78 (0·61 to 0·98)
−0·49 (−0·66 to −0·31)	−0·26 (−0·41 to −0·12)	−0·20 (−0·29 to −0·10)	−0·17 (−0·27 to 0·07)	−0·10 (−0·24 to 0·04)	−0·09 (−0·29 to 0·11)	−0·05 (−0·15 to 0·04)	−0·04 (−0·16 to 0·08)	−0·04 (−0·16 to 0·09)	0·00 (−0·15 to 0·16)	ZIP	1·11 (0·80 to 1·50)	1·06 (0·78 to 1·41)	0·94 (0·70 to 1·24)	1·05 (0·81 to 1·33)	0·72 (0·59 to 0·86)
−0·50 (−0·67 to −0·33)	−0·27 (−0·47 to −0·08)	−0·21 (−0·37 to −0·05)	−0·18 (−0·34 to −0·02)	−0·11 (−0·30 to 0·08)	−0·10 (−0·32 to 0·11)	−0·07 (−0·22 to 0·09)	−0·05 (−0·22 to 0·11)	−0·05 (−0·22 to 0·13)	−0·01 (−0·21 to 0·19)	−0·01 (−0·19 to 0·16)	CPZ	0·96 (0·66 to 1·34)	0·86 (0·61 to 1·19)	0·96 (0·68 to 1·32)	0·65 (0·50 to 0·84)
−0·50 (−0·69 to −0·30)	−0·27 (−0·45 to −0·10)	−0·21 (−0·34 to −0·08)	−0·18 (−0·32 to −0·04)	−0·11 (−0·28 to 0·05)	−0·10 (−0·32 to 0·11)	−0·07 (−0·20 to 0·07)	−0·05 (−0·20 to 0·09)	−0·05 (−0·20 to 0·10)	−0·01 (−0·19 to 0·17)	−0·01 (−0·17 to 0·14)	0·00 (−0·20 to 0·20)	ASE	0·91 (0·64 to 1·22)	1·01 (0·73 to 1·36)	0·69 (0·54 to 0·86)
−0·55 (−0·74 to −0·36)	−0·33 (−0·50 to −0·16)	−0·26 (−0·39 to −0·13)	−0·23 (−0·37 to −0·10)	−0·17 (−0·33 to −0·00)	−0·16 (−0·37 to 0·06)	−0·12 (−0·25 to 0·01)	−0·11 (−0·25 to 0·03)	−0·10 (−0·25 to 0·05)	−0·06 (−0·24 to 0·11)	−0·07 (−0·22 to 0·09)	−0·05 (−0·25 to 0·14)	−0·05 (−0·23 to 0·12)	LUR	1·12 (0·83 to 1·50)	0·77 (0·61 to 0·96)
−0·55 (−0·73 to −0·38)	−0·33 (−0·48 to −0·18)	−0·26 (−0·38 to −0·15)	−0·24 (−0·35 to −0·12)	−0·17 (−0·32 to −0·02)	−0·16 (−0·36 to 0·04)	−0·12 (−0·23 to −0·02)	−0·11 (−0·24 to 0·02)	−0·10 (−0·24 to 0·03)	−0·07 (−0·23 to 0·10)	−0·07 (−0·20 to 0·06)	−0·06 (−0·24 to 0·13)	−0·06 (−0·22 to 0·11)	0·00 (−0·16 to 0·16)	ILO	0·69 (0·56 to 0·84)
−0·88 (−1·03 to −0·73)	−0·66 (−0·78 to −0·53)	−0·59 (−0·65 to −0·53)	−0·56 (−0·63 to −0·50)	−0·50 (−0·60 to −0·39)	−0·49 (−0·66 to −0·31)	−0·45 (−0·51 to −0·39)	−0·44 (−0·52 to −0·35)	−0·43 (−0·52 to −0·34)	−0·39 (−0·52 to −0·26)	−0·39 (−0·49 to −0·30)	−0·38 (−0·54 to −0·23)	−0·38 (−0·51 to −0·25)	−0·33 (−0·45 to −0·21)	−0·33 (−0·43 to −0·22)	PBO

Overall efficacy and ranking of antipsychotic drugs



* SMD: Standardized Mean Difference

Network of 15 antipsychotic drugs in schizophrenia



Estimating the agreement between different sources of evidence

- **Transitivity**: effect modifiers are evenly distributed accross the various comparisons
- The assumption of transitivity might be **difficult to defend** in the presence of both RWE and RCTs
- Studies have differences in *inclusion criteria, settings, methods etc*
- There might be discrepancies
  - Between direct and indirect evidence (statistical: inconsistency)
  - Between RWE and RCTs

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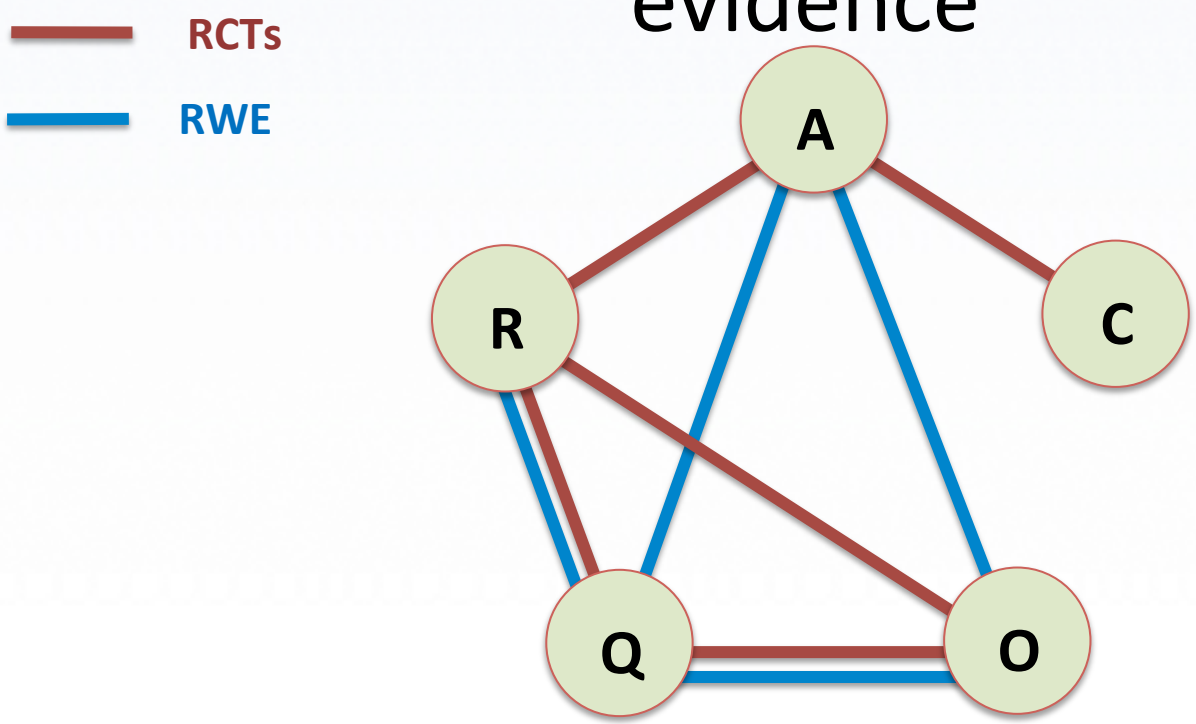
Estimating agreement between sources of evidence



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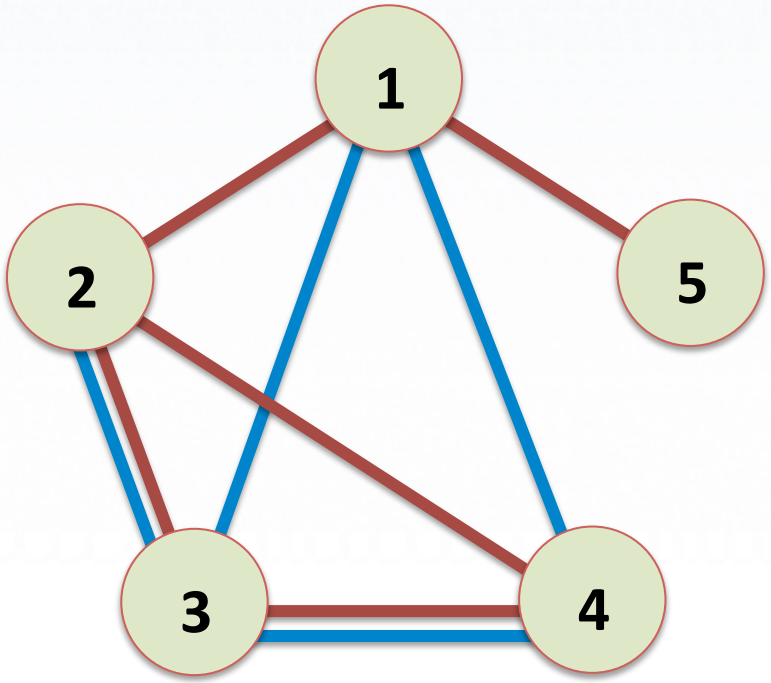
Estimating agreement between sources of evidence

RCTs

RWE



From now on drugs will be anonymized

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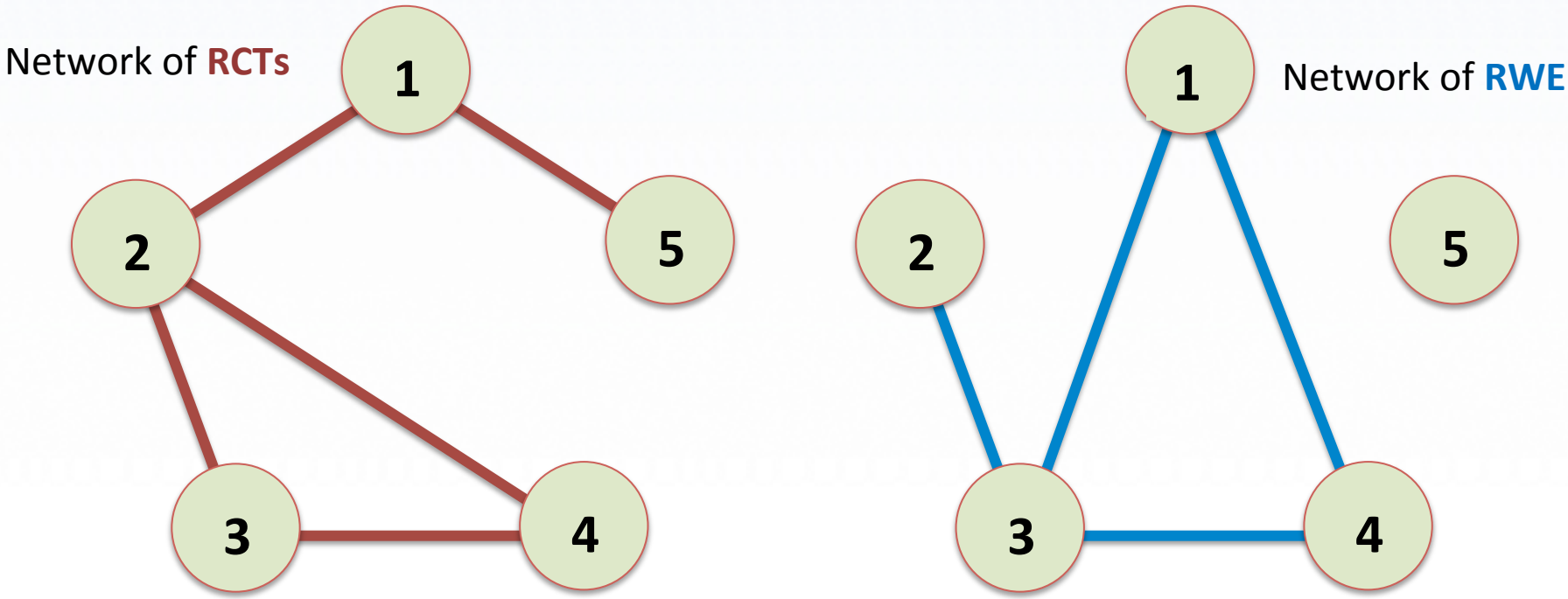
Estimating agreement between sources of evidence



- Direct randomized
- Indirect randomized (via drug 2)

- Direct non-randomized
- Indirect non-randomized (via drug 1)

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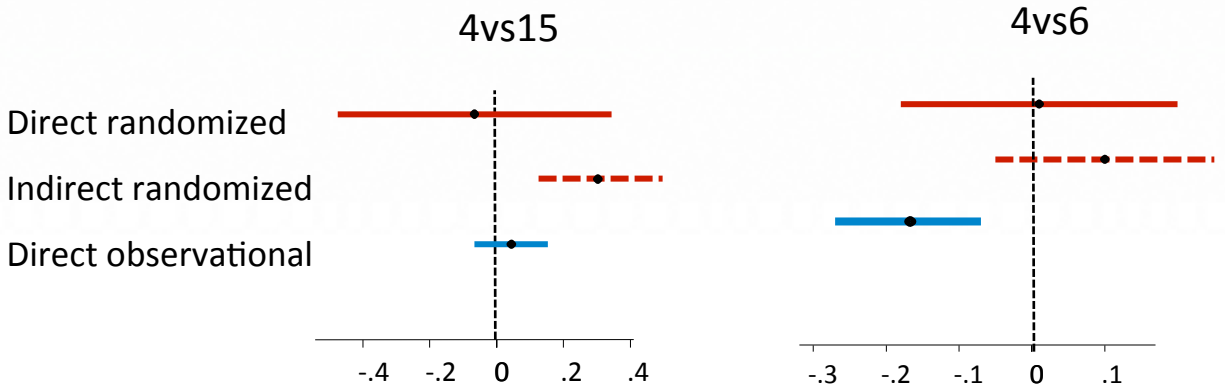
Estimating agreement between sources of evidence

For each treatment comparison there may be up to 4 different types of evidence

- Direct randomized
- Indirect randomized
- Direct observational
- Indirect observational



Direct ≠ Indirect

RCT ≠ RWE

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Choosing evidence versus an all-inclusive approach

- **If differences are found, we try to explain them**
  - Check the effect modifiers, differences in included populations and settings
  - *IPD network meta-regression* for patient-level covariates

  See GetReal in individual participant data (IPD) meta-analysis: a review of the methodology. Debray TP et al. Res Synth Methods. 2015
- **Residual disagreement: should we discard RWE?**
  - Better to include it and explore the impact of various degrees of credibility attached to the RWE

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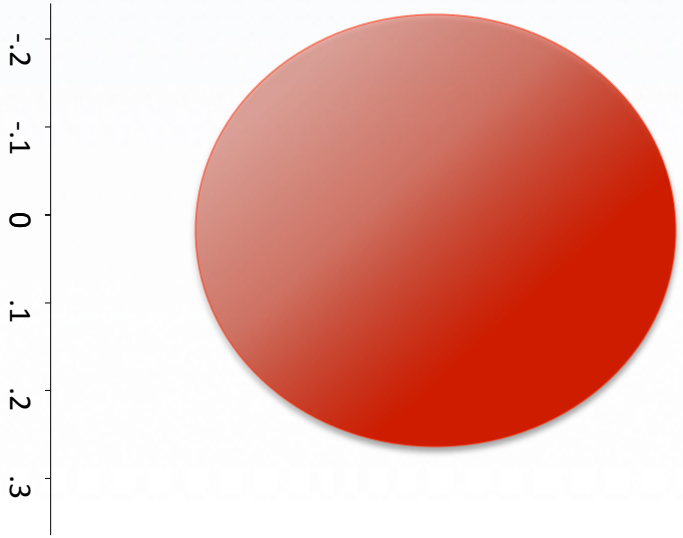
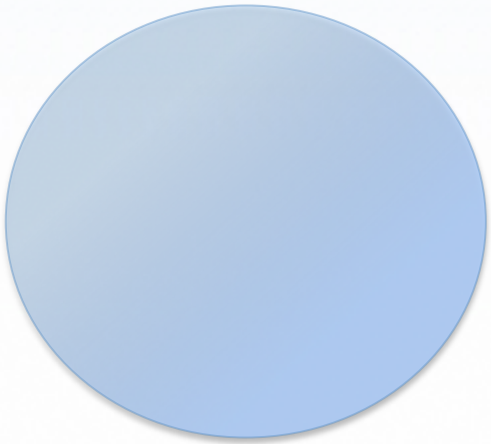
Synthesis of RCTs and RWE

RCTs: higher credibility



RWE: higher relevance



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Synthesis of RCTs and RWE

Different assumptions about the credibility of RWE can be encompassed in

1. **Design-adjusted analysis**
2. **Informative priors from RWE**
3. **A three-level hierarchical model**

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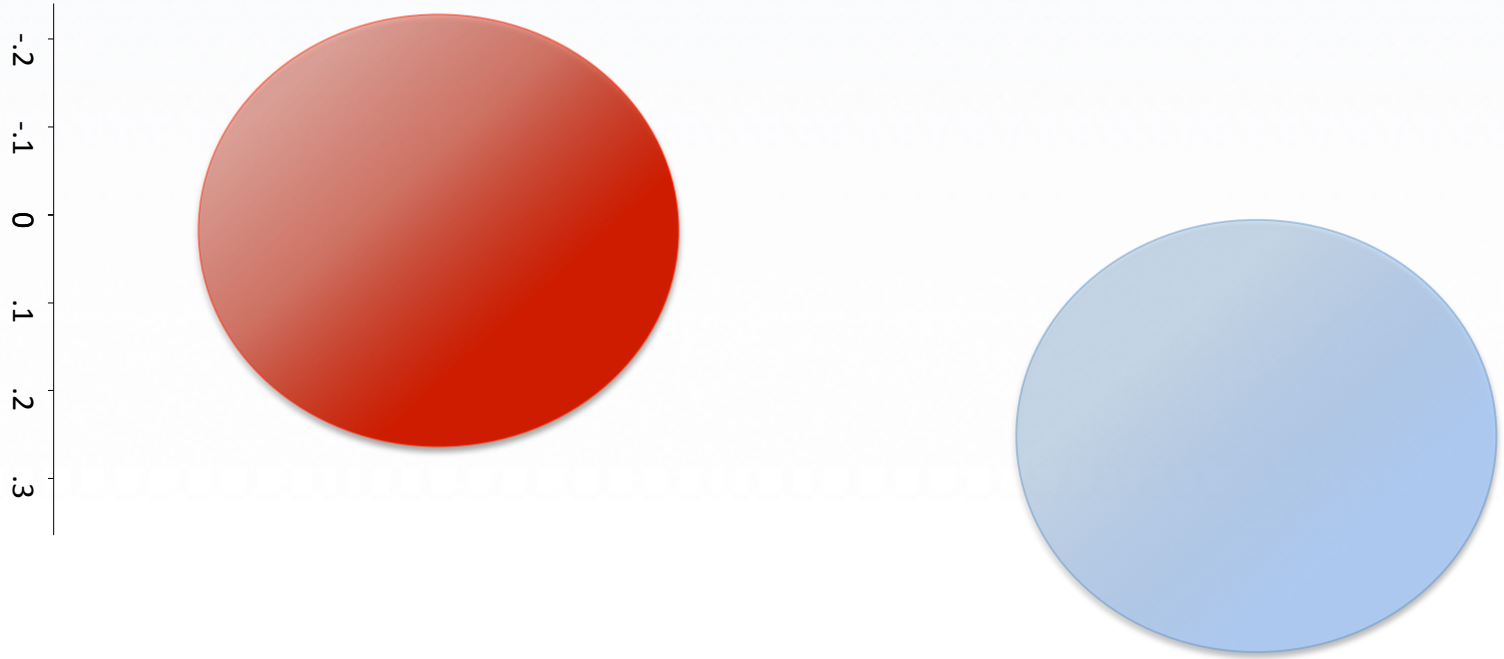
Synthesis of RCTs and RWE

Higher risk of bias and large precision?



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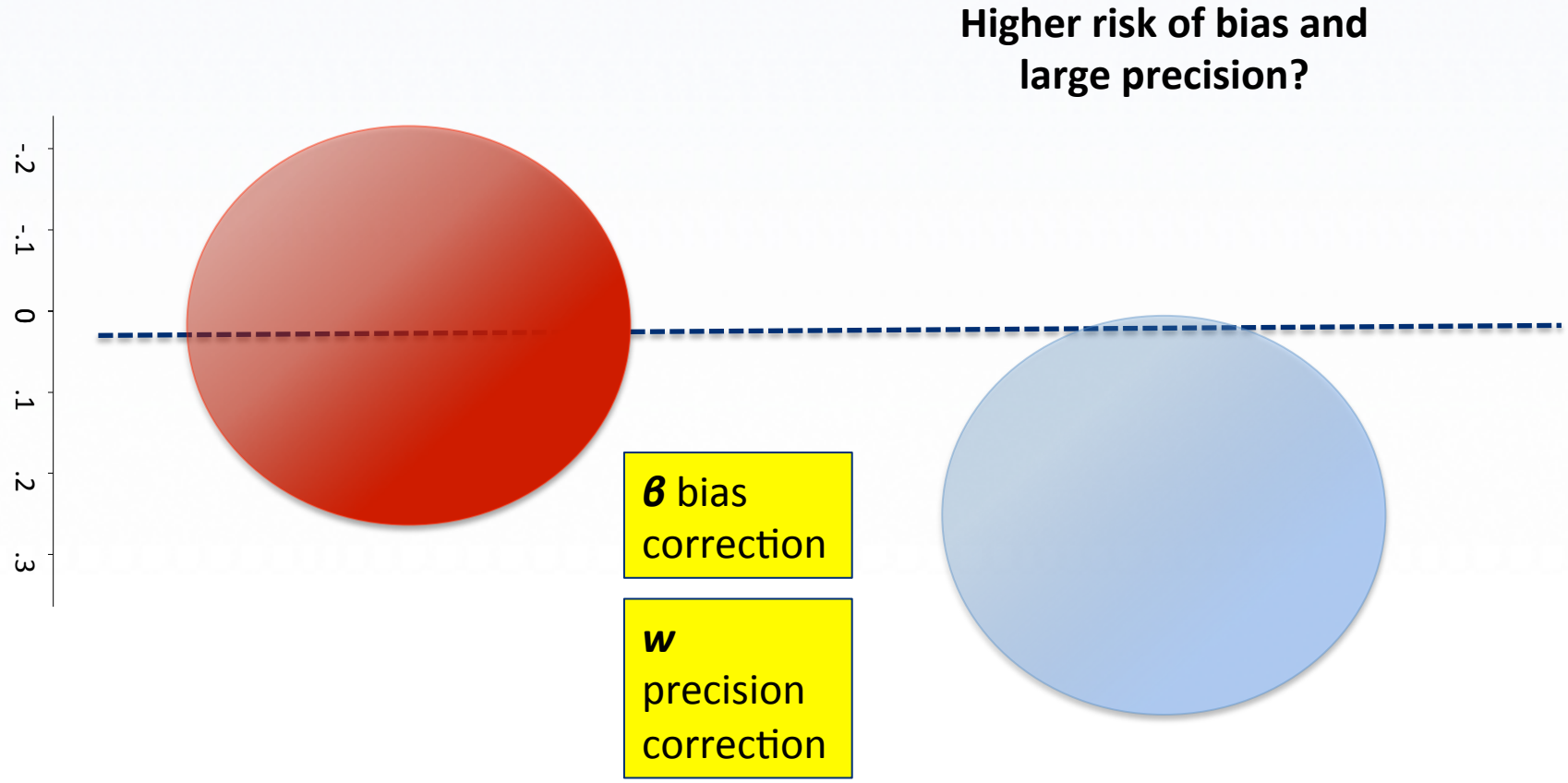

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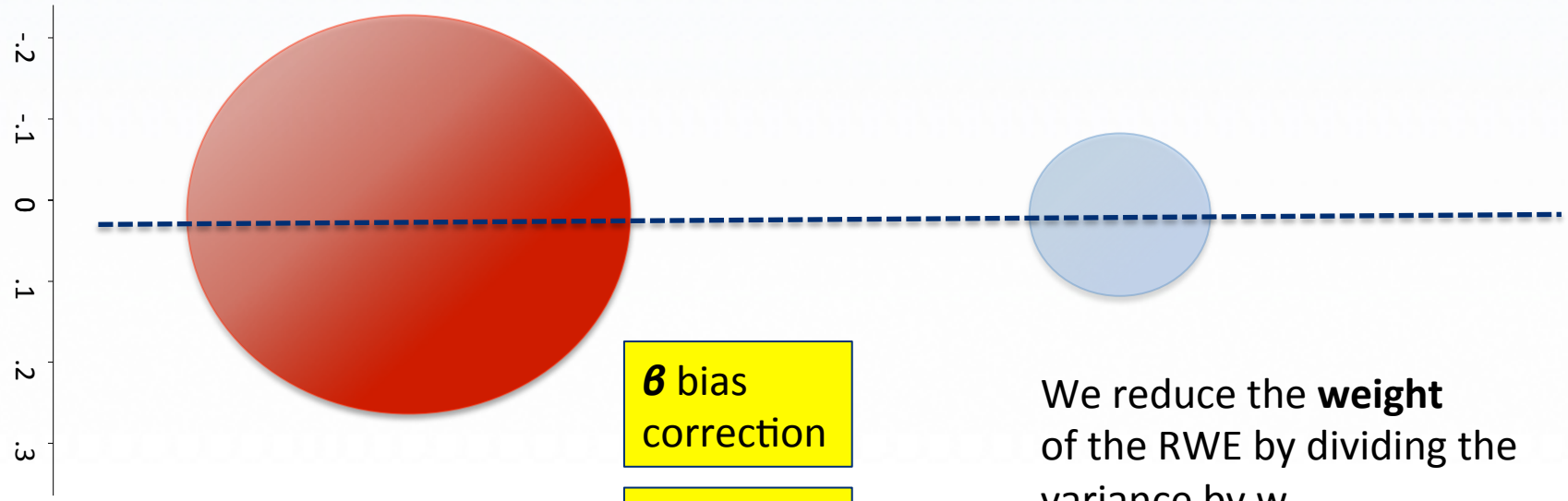

β bias correction

w precision correction

We reduce the **weight** of the RWE by dividing the variance by w

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Design-adjusted analysis

- Adjust each study separately
  - For bias we add ***b*** to the summary effect
  - Decrease the weight it carries in the summary effect by **w**
    - ***w = 1 :*** RWE taken at face value
    - ***w = 0*** : ignore RWE
- Pinpointing exact values for ***b*** and ***w*** may be a difficult task
  - Needs expert opinion
  - Sensitivity analyses are necessary

By changing the value of *w* researchers can control the amount of confidence they want to place to the RWE

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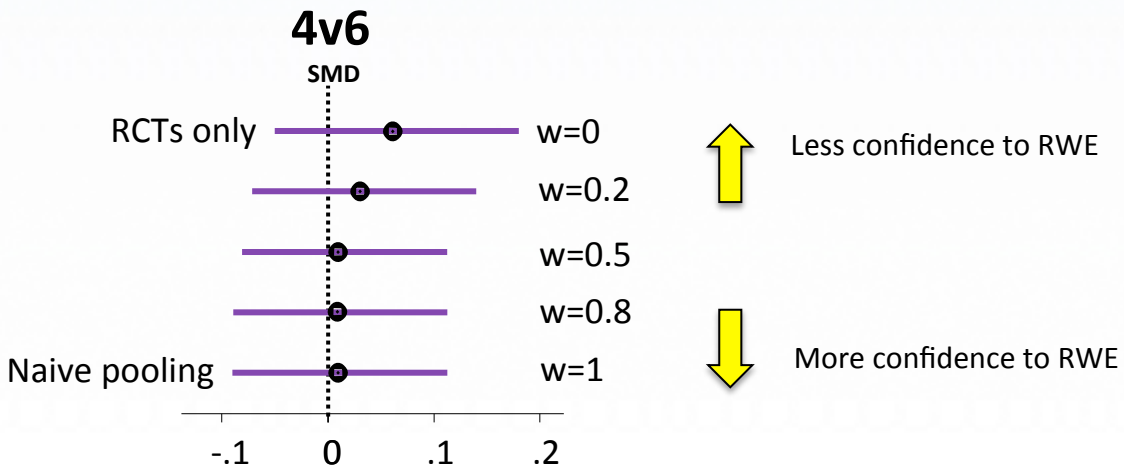
Design-adjusted analysis: Results

No bias adjustment (*β=0*), a single *w* parameter (only one non-randomized study)



Results for the other comparisons are even less sensitive to the amount of confidence placed in RWE

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Using non-randomized evidence as prior information

- Observational studies can be viewed as «prior-knowledge» which when combined with the «observed data» gives a posterior summary effect
- *Adjust for bias* and *downweight* the prior distribution to address concerns of bias and over-precision

Dividing the variance of the prior distribution by ***w***

≈

raising the likelihood function to power ***α***

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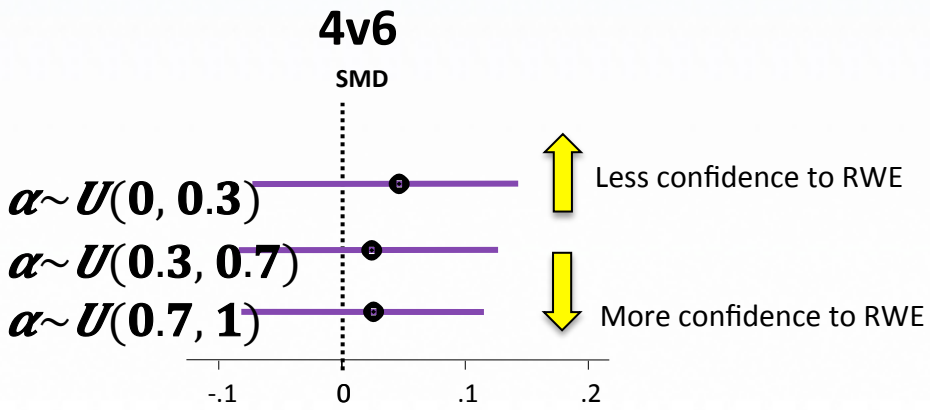
RWE as prior: Results

No bias adjustment ($\beta=0$), a single α parameter in the normal likelihood to be used as prior



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What is the risk of bias in the overall result?

- In the NMA results
  - there is still **some impact** from RWE
  - there are some RTCs of high risk of bias
  - evidence from studies flows directly and indirectly
- Crack the problem using **the contribution matrix: It estimates how much information (%) is contributed by each study**
  - In the naïve analysis (*w=1*) RWE accounted for **5.8%** of the information in the network
  - The sample size of the observational study is about 20% of the total sample size in the network
  - For the design-adjusted analysis with w= 0.5 RWE contributed **5 %** of the information
- Consequently the risk of bias the NMA results is largely dictated by the risk of bias in the included RCTs

- Evaluating the quality of evidence from a network meta-analysis. Salanti G PLoS One 2014
- Graphical tools for network meta-analysis in STATA. Chaimani A et al PLoS One. 2013
- Visualizing assumptions and results in network meta-analysis: The network graphs package Chaimani and Salanti. Stata Journal 2015.

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Take home message

- If you are concerned about residual differences between RCTs and RWE, or if you think that RWE is less trustworthy than RCTs **decrease the influence of the RWE** in your estimates by dividing the variance by w
- It is **difficult to predict** the magnitude or direction of possible biases introduced by including RWE in an NMA
  - We thus advise to explore the effect of **placing different levels of confidence** in the observational evidence before they draw final conclusions in a sensitivity analysis
- We also recommend that the risk of bias in the results is evaluated after considering the relative contribution of each source of evidence in the pooled estimates
- Extend the NMA with mathematical modelling **to make predictions in a real-world setting**

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Prediction of Real-World Treatment Effect based on RCT and RW Evidence:

A case study on rheumatoid arthritis

Eva-Maria Didden

Institute of Social and Preventive Medicine (ISPM), University of Berne

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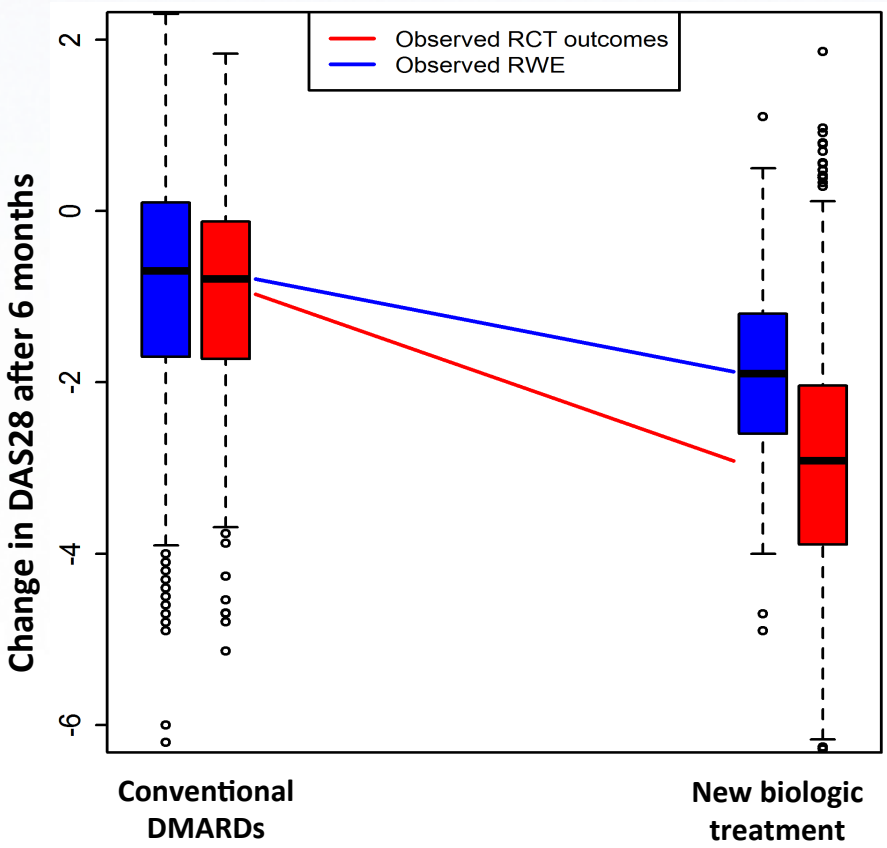
Motivation



- Obvious gap in treatment oucome

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Research Question

Set up a mathematical model that allows to predict the real-world effect of a new biologic treatment in patients with *Rheumatoid Arthritis* (RA) if…

- **only RCT data on the new treatment and …**
- **no observational data on the new treatment, but …**
- **observational data on an existing similar treatment …**

are available?

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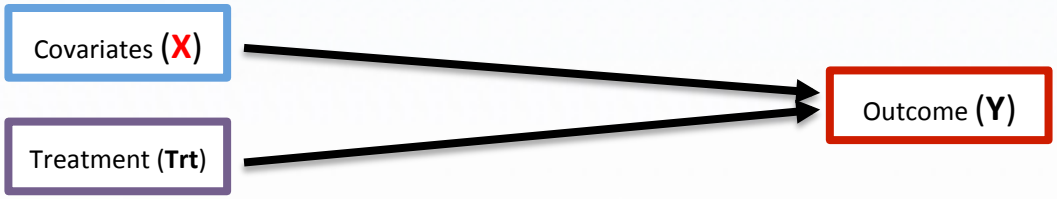
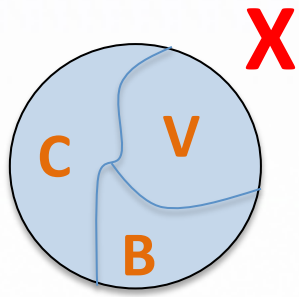
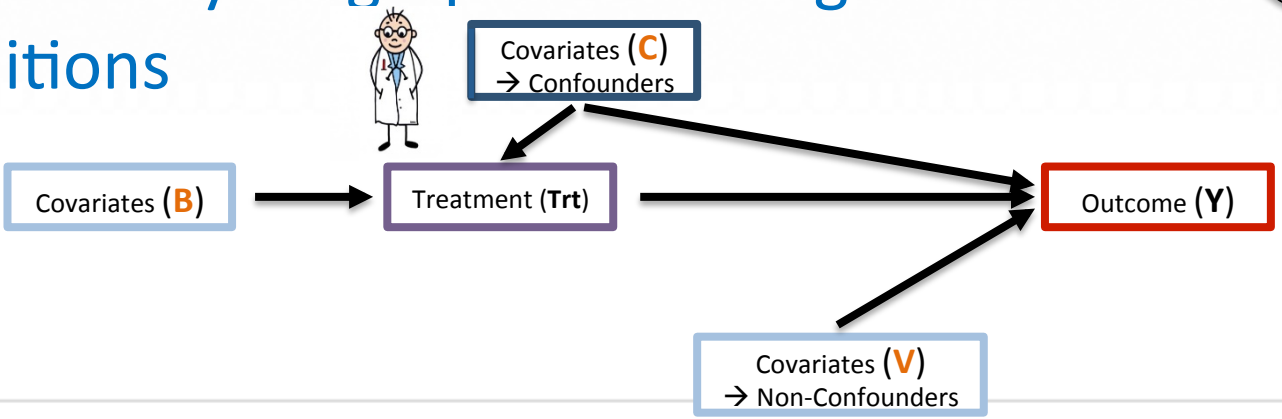
Graphical Model Representation

- Directed acyclic graph visualizing RCT conditions





- Directed acyclic graph visualizing real-world conditions



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Formal Model Representation (side note)

α: Intercept, β: Treatment effect
γ: (non-confounding) Covariate effect

- Linear model for RCT data:

$$Y_{rct} \sim N(\alpha_{rct} + \beta_{rct} Trt + \gamma_{rct} X_{rct}, \sigma^2_{rct} I)$$

$$Trt = \begin{cases} 1, & \text{biological agent} \\ 0, & \text{control treatment} \end{cases}$$

- Marginal structural model (MSM) for observational data:

→ inverse-probability-of-treatment weighting

$$Y_{obs} \sim N(\alpha_{obs} + \beta_{obs} Trt + \gamma_{obs} V_{obs}, \sigma^2 W^{-1}), \quad W \propto \frac{1}{f(Trt|C_{obs})},$$

$$\text{or} \quad W \propto \frac{1}{f(Trt|C_{obs}, B_{obs})}$$

J. M. Robins et al. (2000), "Marginal structural models and causal inference in epidemiology." *Epidemiology,* Volume 11 (5): pp. 550-560

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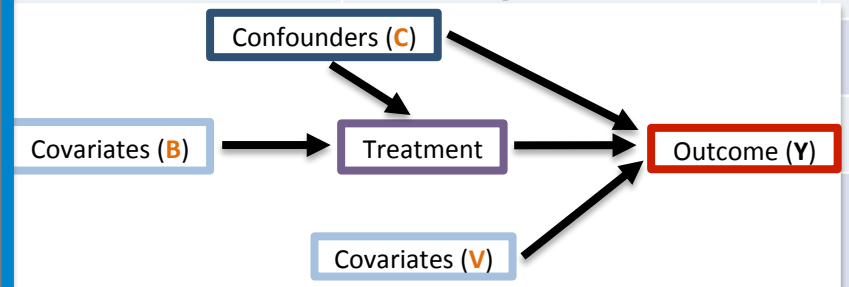
Variable Classification and Selection

Outcome: Change in	RCT DATA Covariates	RWE Covariates B	RWE Covariates V	RWE Confounders C	E
DAS28	**age**	calendar year	**BMI/obesity**	**age**	x
HAQ	**disease duration**	hospital (y/n)	gender	**disease duration**	p
EQ5D	**BMI/obesity**	socio-economics	steroid intake	**seropositivity**	
ACR	**seropositivity**	.....	# [concomitant DMARDs]	baseline DAS28	(RA) e
CDAI	gender		baseline HAQ	# [previous anti-TNF agents]	Stats r (Cross-valid.)
RADAI	# [previous anti-TNF agents]		type of concomitant DMARDs	# [previous DMARDs]	t
.....	.....			smoking	Not selec-ted
				comorbidities	
				.....	



DAS28 – Disease activity score (28 joints)
HAQ – Health assessment questionnaire
DMARD – Disease modifying anti-rheumatic drug
TNF – Tumor necrosis factor
BMI – Body mass index

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Modelling Concept

1. Develop a mathematical model, informed by …
   - observational evidence on treatment decision
   - RCT(s) on the efficacy of the new treatment, and on all significant effect modifiers and prognostic factors

2. Predict real-world treatment effect for the RCT population(s)
   - Predict treatment decision based on RWE
   - Predict treatment outcome, using evidence from the available RCT(s)

3. Predict treatment effect for a real-world patient population, using evidence from the available RCT(s)

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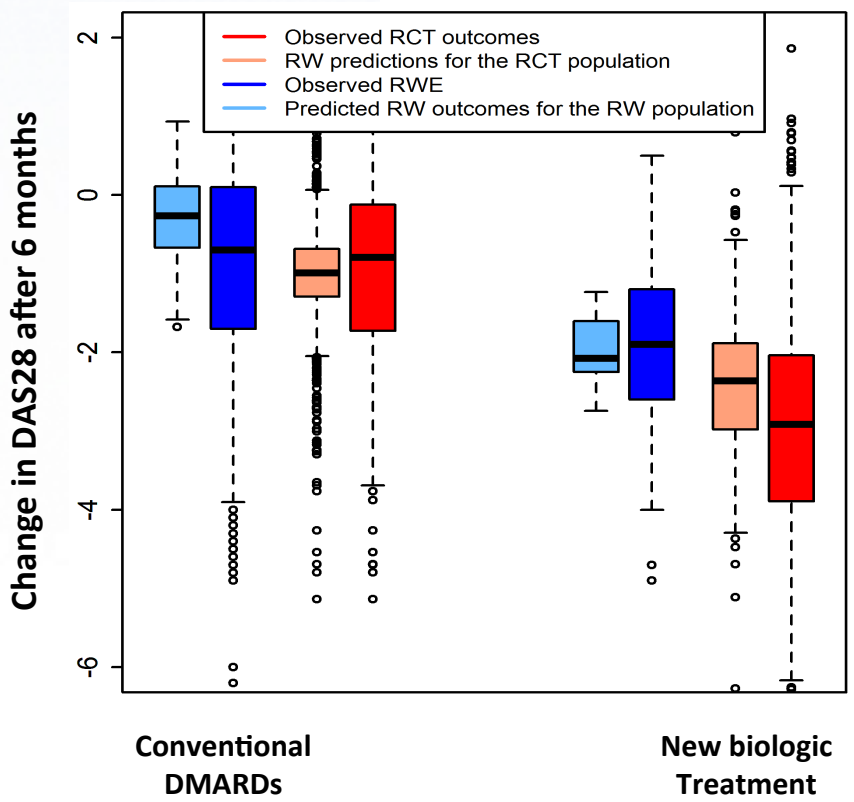
Predicted Effectiveness vs. Observed Efficacy/ Effectiveness

Findings – RCT population:

- Predicted effectiveness is lower than observed efficacy
- Predicted effectiveness is higher than effectiveness observed in real-world

Findings – real-world population:

- Predicted and observed effects of the new biologic agent are similar
- Predicted and observed effects of the conventional DMARDs differ notably



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Additional Question

Predict real-world treatment outcome for any new RA patient population, assuming that

- **all patients receive the biologic treatment**
- **all patients take conventional DMARDs**

What are the main conclusions?

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Predicted Effectiveness

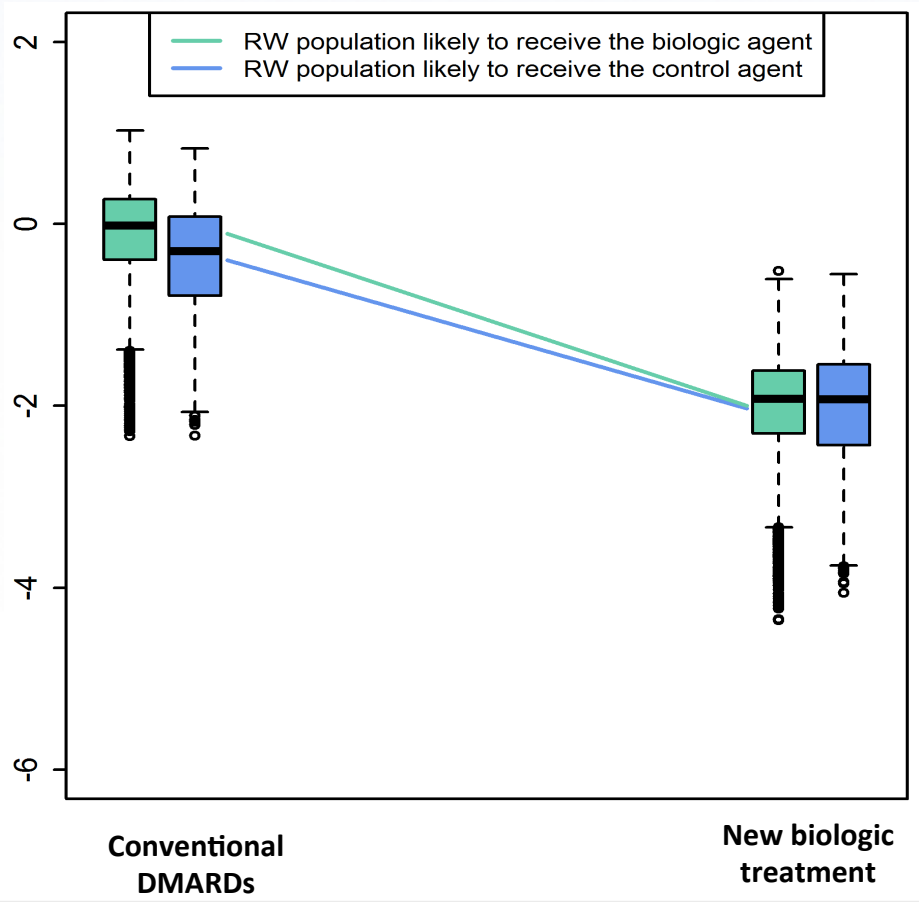
Remark:

Patient classification into two groups

- → those who are more likely to receive the new biologic treatment
- → those who are more likely to receive conventional DMARDs

Findings:

- Predicted benefit from the new biol. treatment is similar in both groups
- Patients likely to receive the control agent are expected to benefit more from the control agent



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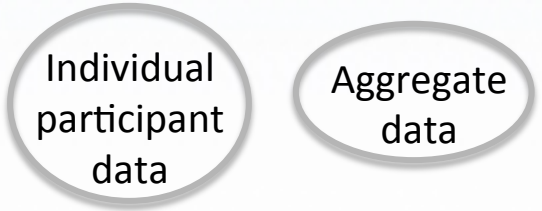
Discussion

Deliverable

Bayesian inference framework to connect information from various sources



- Prediction of real-world treatment effect
- Assessment of the efficacy-effectiveness gap

- **Main concerns: Predictive and external validity**

- **Work in progress:**
  - Inclusion of results from network meta-analyses to predict relative drug effectiveness
  - Consideration of dynamic treatment regimes with time-varying confounders and censoring information

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Conclusions

Chrissie Fletcher

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Bridging efficacy to effectiveness

- Relative effectiveness can be estimated from RCTs
  - Key assumptions are required and should be evaluated
  - Follow good scientific principles to achieve a high quality analysis
- New evidence synthesis methods enable RWE to be integrated with RCT evidence to aid decision making at product launch
  - Consider the relative contribution of each source of evidence
  - Use sensitivity analyses assessing different levels of confidence
- (Relative) effectiveness can be predicted from RCT and RWE using mathematical models and allow the efficacy to effectiveness gap to be assessed
  - Regard RCT and observational data as complementary sources of evidence
  - Model validation is key to increase accuracy of predictions

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- Other collaborators
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