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NHS National Institute for Health Research

Combining Observational & Clinical Trial Evidence for Health Technology Assessment (HTA)

Keith R Abrams, PhD CStat

Professor of Medical Statistics &

NIHR Senior Investigator Emeritus,

Department of Health Sciences

Acknowledgements

- Sylwia Bujkiewicz, Nicola Cooper, Suzanne Freeman, Stephanie Hubbard, Rhiannon Owen & Alex Sutton*, Department of Health Sciences, University of Leicester, UK*
- Pascale Dequen, *Visible Analytics*, Oxford, UK.
- Reynaldo Martina*, Department of Biostatistics, University of Liverpool, UK*
- David Jenkins*, Health Informatics, University of Manchester, UK*
- Chris Chin*, Sanofi, UK*

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Introduction & Outline

- Issues with RWE & Network Meta-Analysis (NMA)
- IMI GetReal Project
- NMA incl. Real World Evidence (RWE)
- Allowing for both rigour & relevance in RWE
- Use of RWE in Multivariate MA
- Discussion & Current/Future Areas of Research

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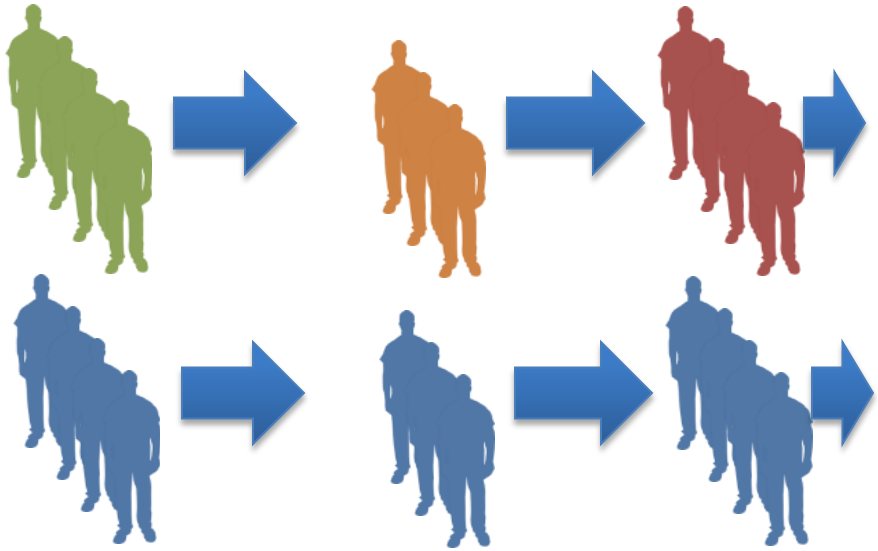
Use of RCTs & RWE in estimating RE

(Relative) Clinical Effectiveness – RCTs

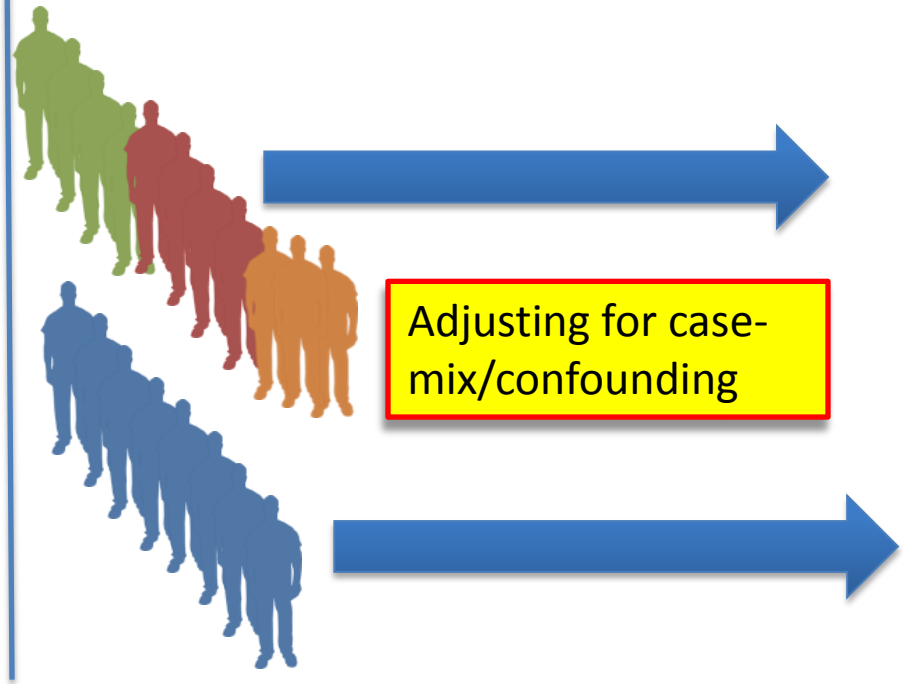
RCT_1 (A v P) RCT_2 (B v P) RCT_3 (C v P)



Common comparator + variable follow-up

Real World Evidence

Registry/Obs (A v B v C v P)



IPD available – Propensity score/IV methods

Early thrombolysis for AMI (Caldwell & Higgins *BMJ* 2005)**:**

NMA considers the network of *all* relevant evidence to a decision problem

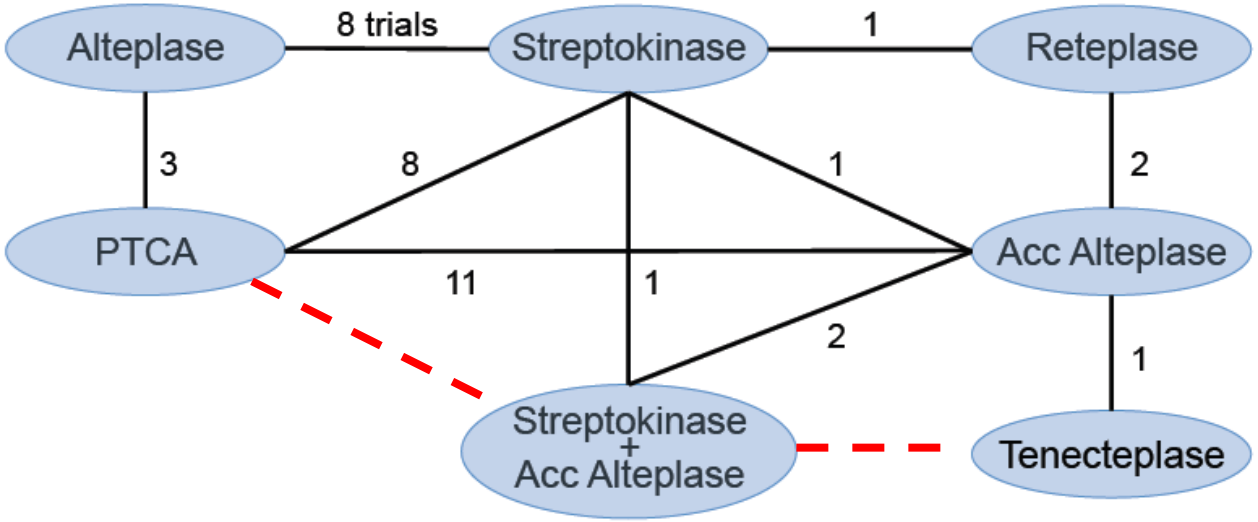


Table 3 Percentage mortality at 35 days and the probability that each treatment is best (lowest mortality) in multiple treatment comparison analysis*

	Fixed effect model		Random effects model	
	35 day Mortality %	Probability best	35 day Mortality %	Probability best
Streptokinase	6.7	0	6.8	0
Alteplase	6.7	0	6.5	0.003
Accelerated alteplase	5.8	0	5.8	0.001
Streptokinase + alteplase	6.5	0	6.6	0.002
Reteplase	6.1	0	6.0	0.01
Tenecteplase	5.8	0.004	5.8	0.03
Percutaneous transluminal coronary angioplasty	4.4	0.995	4.3	0.95

NMA methods allow comparison/effect estimates for all interventions & associated uncertainty

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Innovative Medicines Initiative (IMI)

Real-Life Data in Drug Development

- Europe's largest public-private initiative
- Joint undertaking between European Union and European pharmaceutical industry association EFPIA.
- **GetReal project**
- Understanding how real-world data can contribute to decision-making in drug development
  - October 2013 to December 2016 (39 months)
  - 29 partners
  - Total budget: €18 million
    - 50% staff from the 15 participating pharma companies
    - 50% cash contribution from the EU to fund 'public' sector

Focus of GetReal

Real-Life Data in Drug Development

RWE intensifying across product lifecycle, but **RCTs are getting shorter** with conditional licencing by FDA & EMA -> HTA/reimbursement agencies face ***challenge*** of making decisions with **less RCT evidence**

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

WP3

Overcoming practical barriers to the design of real-world studies

WP2

Understanding the efficacy-effectiveness gap

simulation of trials to improve design

WP4

Identifying best practice and creating new methods for evidence synthesis and predictive modelling

WP1

Frameworks

Processes

Policies

- Standardising terminology
- Interviews to understand and the perspectives and policies of different stakeholders
- Designing a framework for decision-making during development

- 5 Case studies using drugs that had difficulty at regulation and HTA
  - 360 degree reviews
  - Re-designing development pathways to include real-world data
  - Simulation
  - Ascertaining impact on decision makers

WP1 – Case Studies

- **Multiple Sclerosis (MS)** – RWE in NMA (**UoL**, NICE & Novartis)
- **Rheumatoid Arthritis (RA)** – Lines of therapy & NMA including RWE (**UoL**, UoBern, Amgen & Roche)
- **NSCLC** – Generalisability of RCTs (**UoL** & Lilly)
- **Malignant Melanoma (MM)** – extrapolation using RWE (**UoL**, ZIN & BMS)
- **COPD** – Pragmatic RCTs (NICE & GSK)

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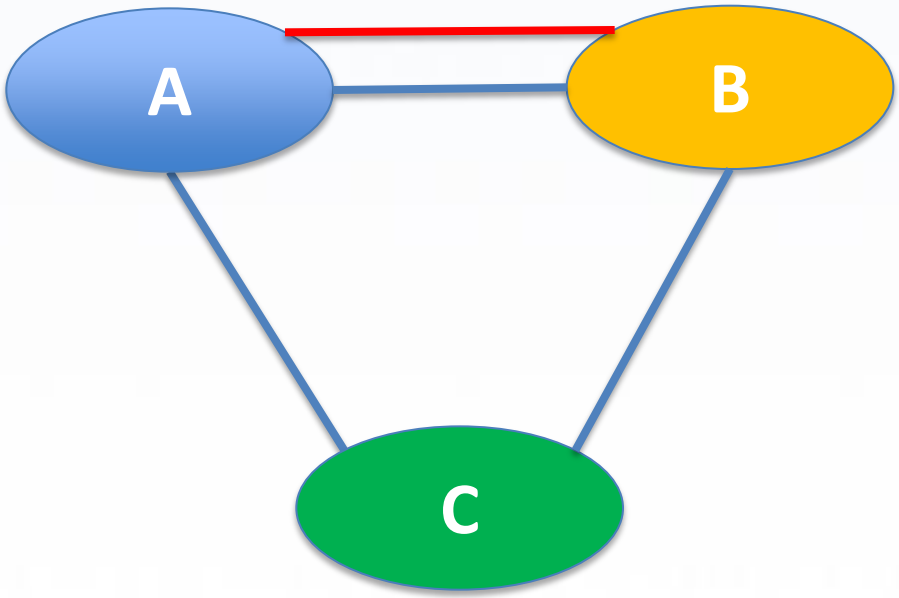
Adding RWE to NMA of RCTs



- Allow for heterogeneity using study-level covariates
- Adjust for potential biases in RWE (power transform prior & hierarchical modelling approaches)

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Power Transform Prior Approach

- RWE is weighted by term γ, i.e. likelihood is raised to the power of γ (Ibrahim & Chen, 2000);

$$P(\theta|RCT, Obs) = L(\theta|RCT)[L(\theta|Obs]^{\gamma} P(\theta)$$

- $0 \leq \gamma \leq 1$ is degree of weighting
- $\gamma = 0 \Rightarrow$ total discounting of NRSs
- $\gamma = 1 \Rightarrow$ accept at NRSs 'face value'
- Evaluate for a range of values of γ

Ibrahim JG, Chen M. Power prior distributions for regression models. *Statistical Science*. 2000 15(1):46-60.

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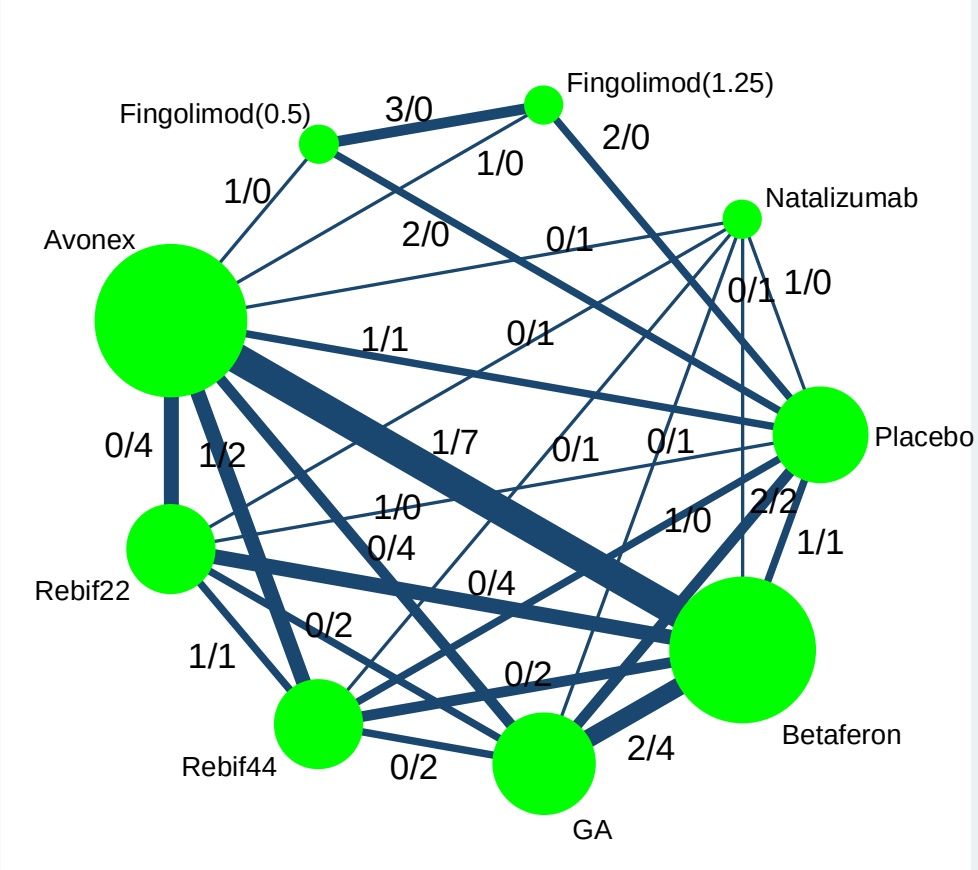
RCT + RWE network diagram



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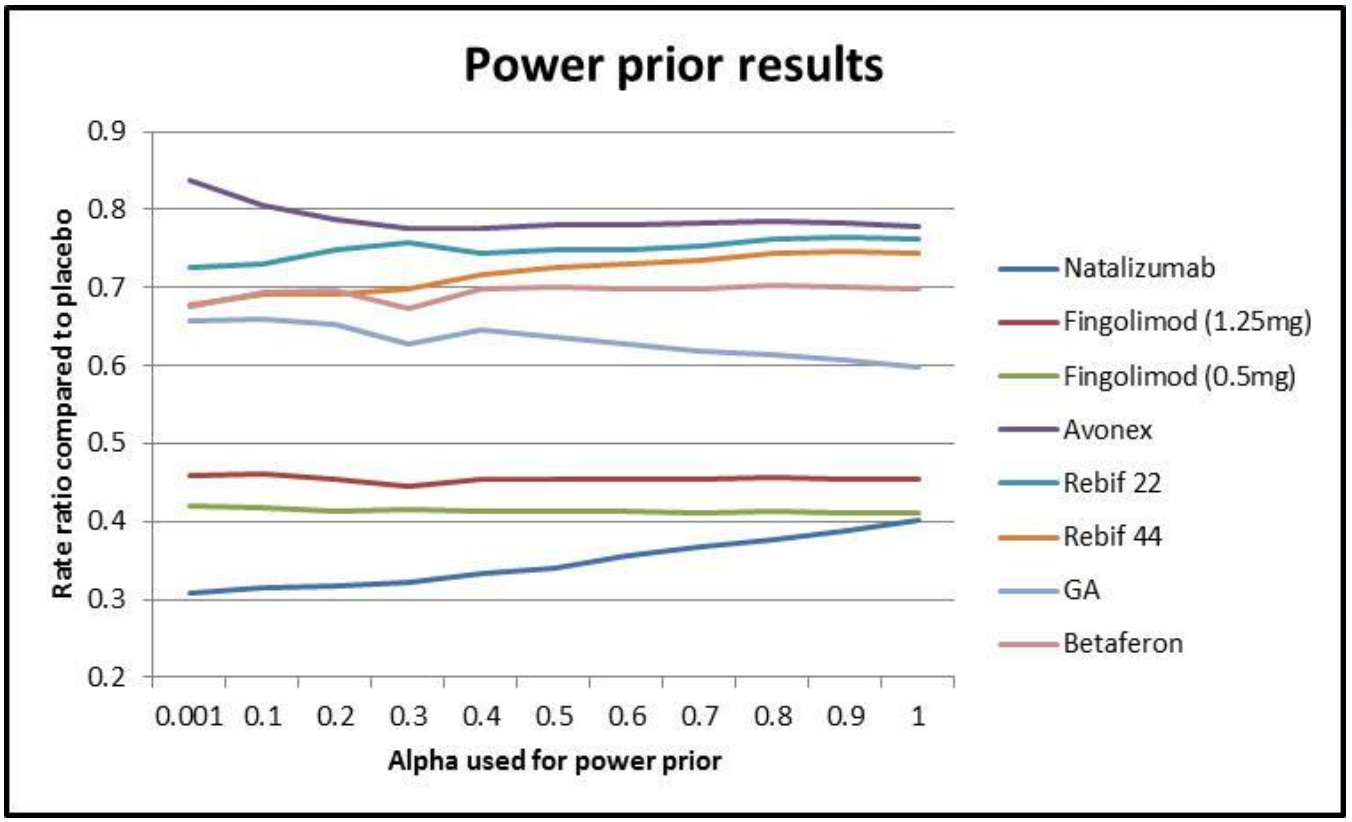
Power prior - results



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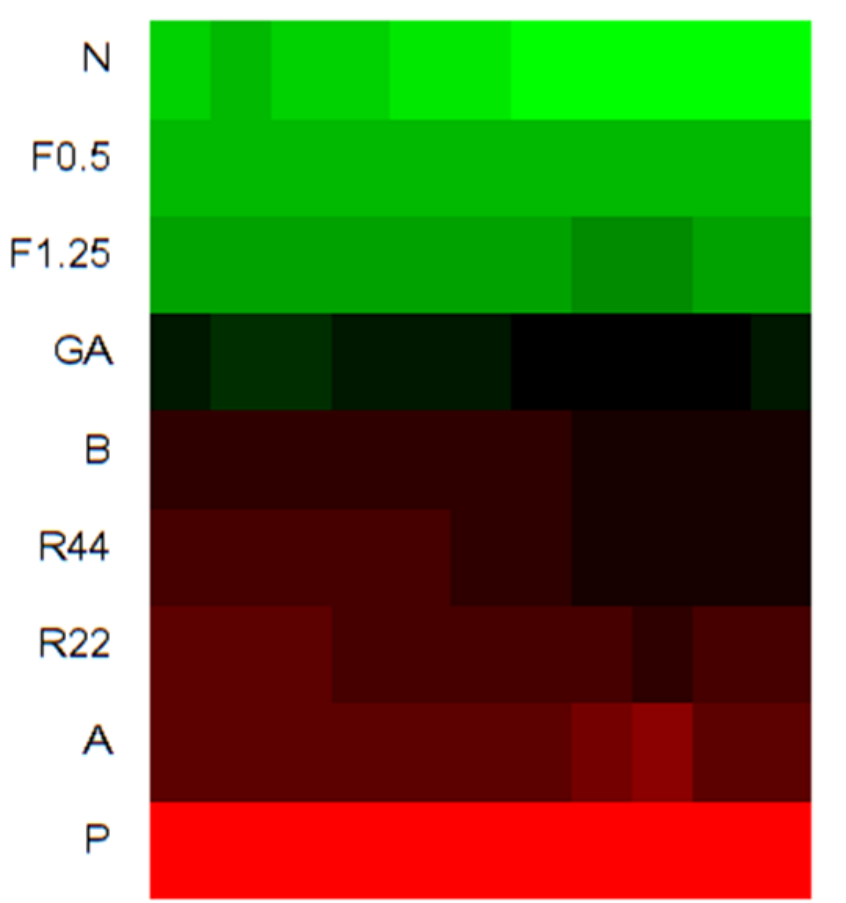
Power prior – results, ranking



0 <- γ -> 1

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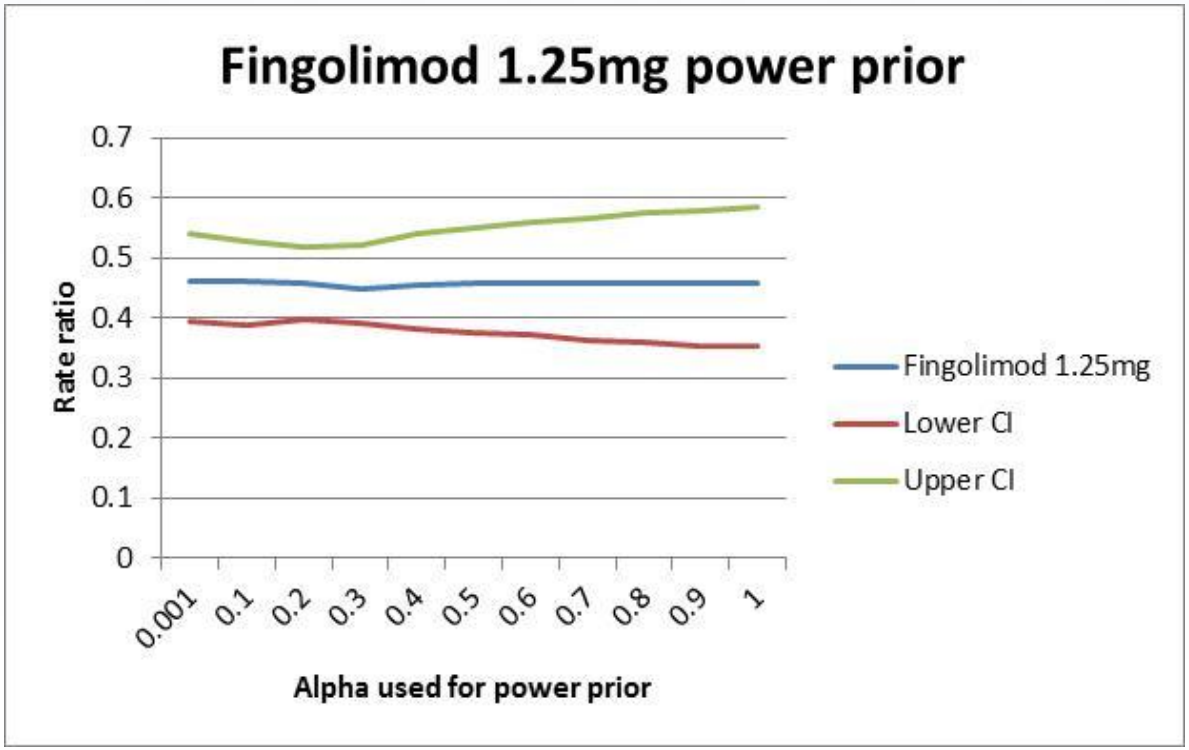
Power prior - results



Abrams KR *et al*. Multiple Sclerosis Case Study report. IMI GetReal www.imi-getreal.eu

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Benefits & Limitations

- Benefits:
  - Adjustment of IPD RWE can allow for ***known*** confounders
  - Further adjustment can allow for potential ***unknown*** confounders
  - Provides a sensitivity analysis for Decision Makers
  - Can provide revised inputs into cost-effectiveness models
- Limitations:
  - Does not give a specific answer
  - Some methods rely on meta-epidemiology to provide an estimate of bias

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Discussion of IMI GetReal

- Numerous methods are available for inclusion of RWE in R+D/regulatory/HTA process/pathway, BUT ...
  - They make various **assumptions** which my be untestable/subjective
  - Rely on **availability** of RWE(!)
  - There maybe differing levels of **acceptance** by different HTA bodies
  - Need for assessment of impact on **cost-effectiveness**
- Therefore ...
  - Further **case studies** are required & elicitation of **stakeholder views**
  - More **research on methods** for inclusion *and* adjustment of RWE (especially in form of IPD & AD)
  - Greater use of **simulation** to evaluate different methods
  - Support for initiatives to **share RWE IPD** or at least relevant **summary AD**, e.g. Conditional covariate distributions, subgroup estimates, etc.
  - **MRC/NICE**-funded Methods Project (Bristol, Leicester & York)

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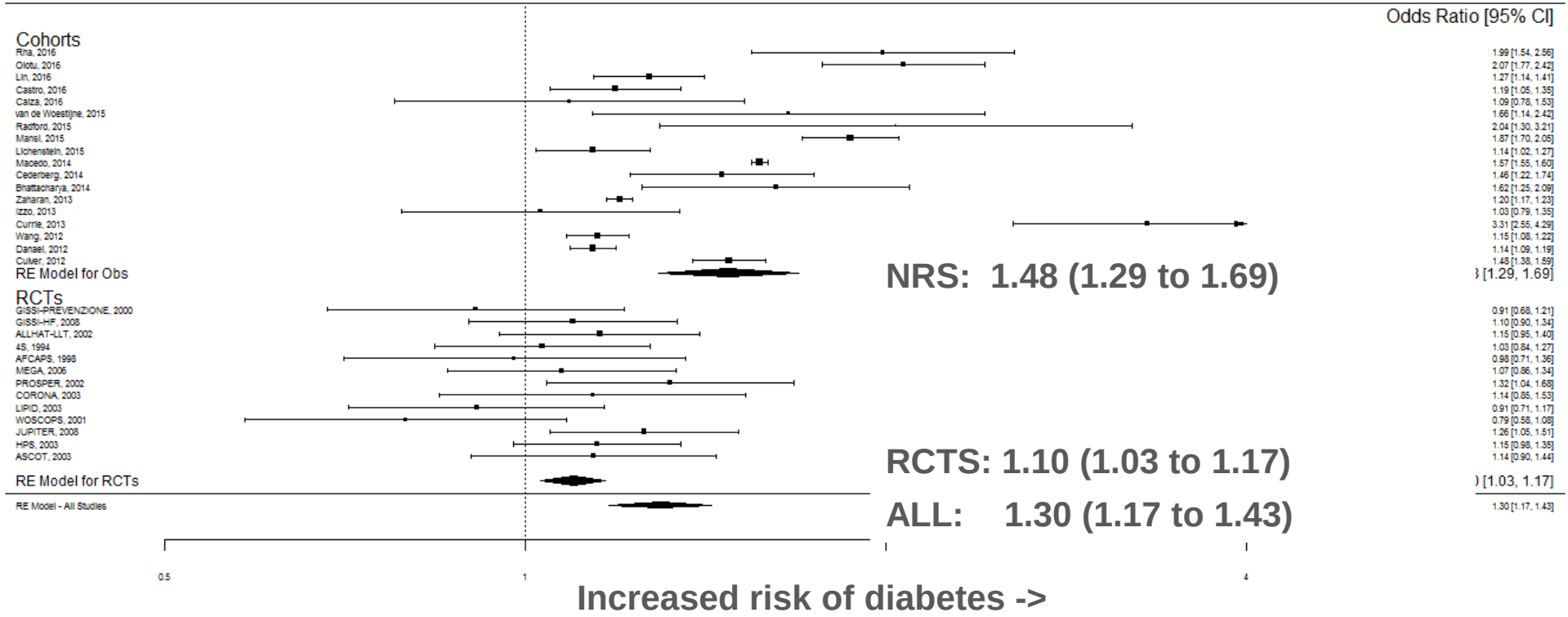
Background

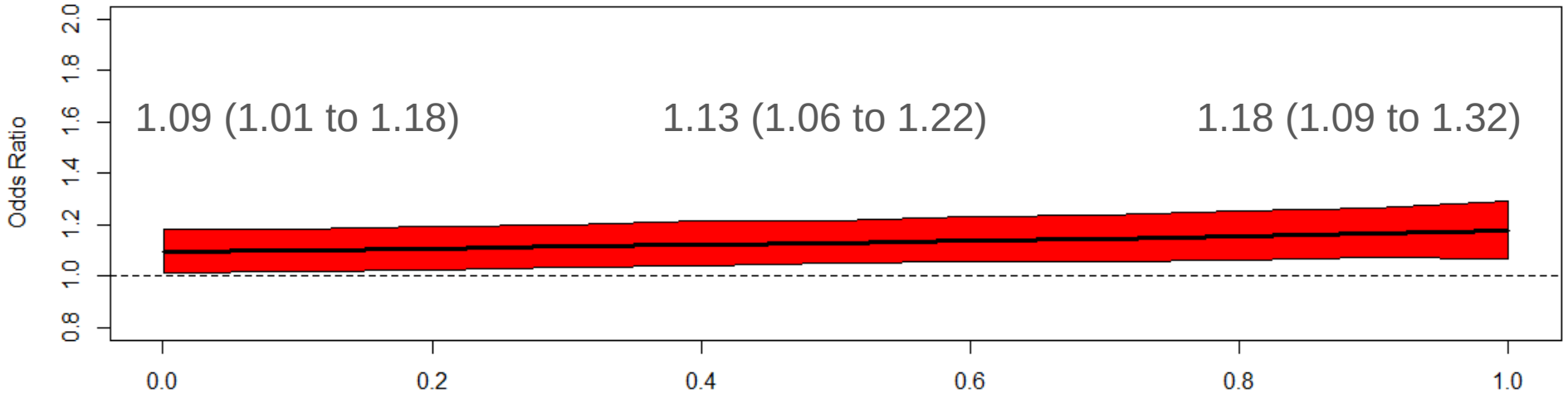
- Key question – How could decision makers proceed faced with both RCTs and Non-randomised [comparative] evidence in order to make decisions for their target population or future trial?
- Useful to think of both rigour *and* relevance
- **Rigour** – quality and risk of bias of studies – here consider mainly rigour with respect to NRS
- **Relevance** – how closely do studies match (or are aligned with) the target population?
- How can we consider **importance** of both dimensions when assessing and appraising an evidence base which contains both RCTs and NRS to help make decisions for a **target population**?

Motivating Example – Statin Therapy & Diabetes

- Sattar *et al* (2010) reported **13 RCTs** which had reported on incident cases of diabetes.
- Casula *et al* (2017) reported **18 cohort studies** which had reported on incident cases of diabetes.
- 17 out of the 18 cohort studies assessed **quality/bias** using Newcastle-Ottawa Scale (NOS).
- All studies had study-level covariate information on mean **age**, length of **follow-up** and **percentage of non-diabetics** at baseline.



Standard/Univariate Power Prior – Results



NRS totally discounted

NRS at 'face value'

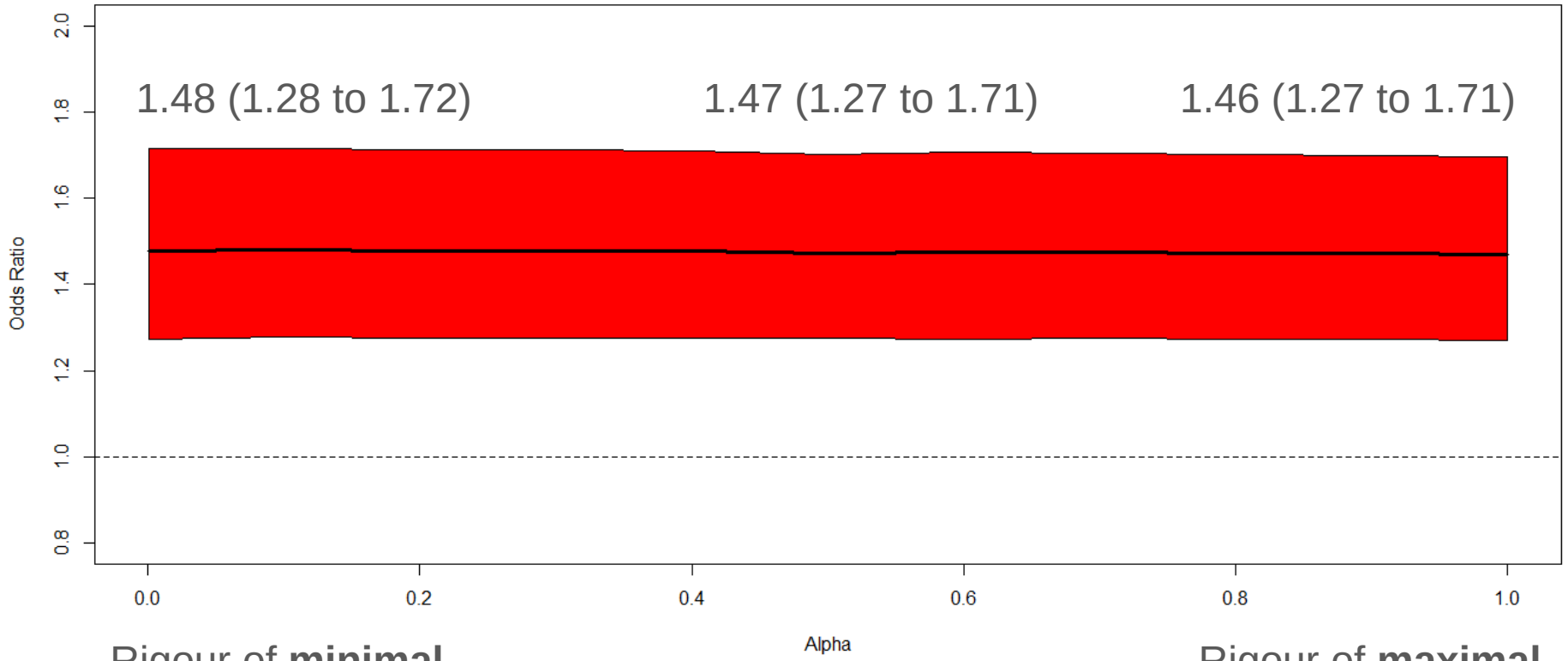
Univariate *supra* Power Prior – Methods

- Univariate power prior assumes that all NRSs get downweighted by *same* degree/factor/power γ
- Assume for each study a measure of **quality/bias/rigour** had been obtained (Newcastle-Ottawa Scale etc) and this was converted to 0-1 scale and denoted W_{Bi} (***Rigour weights***) [1 indicating the highest weight, i.e. least bias, most rigour]

$$P(\theta|RCT, Obs) = \prod_{i=1}^{n} L(\theta|RCT_i) \quad \prod_{j=1}^{m} L(\theta|OBS_j)^{\alpha^*_j} P(\theta)$$

- Where $\boldsymbol{\alpha^*_j = W^{\alpha}_{Bj}}$ and so α gives an overall measure of the ***importance of rigour*** (again $0 \leq \alpha \leq 1$)
- In statins-diabetes example, all RCTs are assumed to have rigour weight of 1, i.e. perfect quality.

Univariate *supra* Power Prior – Results



Rigour of **minimal importance** (all at 'face value')

Rigour of **maximal importance** (fully quality weighting)

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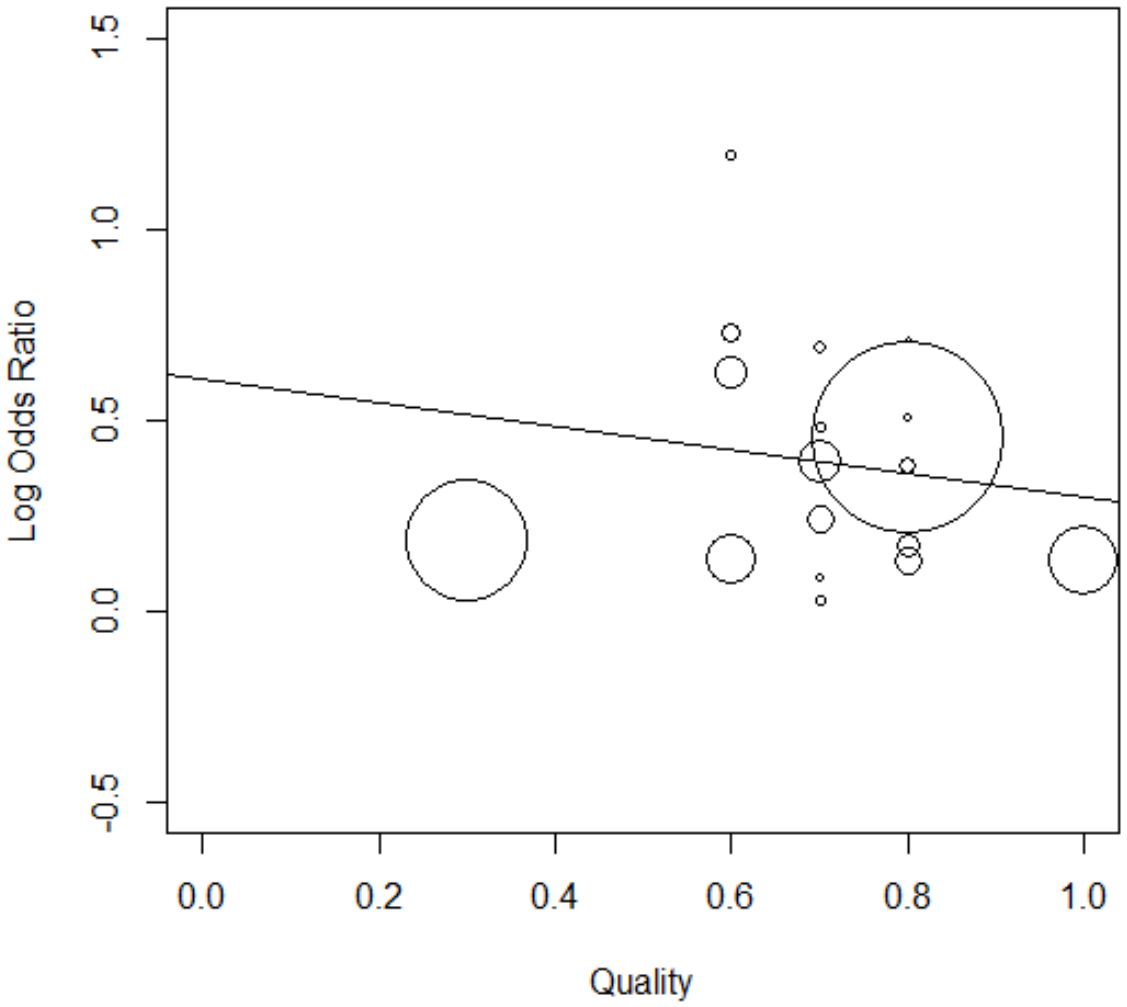
NRS – Meta-Regression for Quality (NOS)



Slope:

-0.31 (1.25 to 0.64)

P=0.52

Bivariate *supra* Power Prior – Methods

- Assume that there are 3 covariates which can be used to define **relevance**,X_1, X_2, X_3such that the **target population** is defined by X_1^* , X_2^* , X_3^* (in example, age=55, follow-up=5 years & non-diabetic=100%)
- Calculate the standardised Euclidean distance;

$$Z_i = \sqrt{(X_{1i} - X_1^*)^2 + (X_{2i} - X_2^*)^2 + (X_{3i} - X_3^*)^2}$$

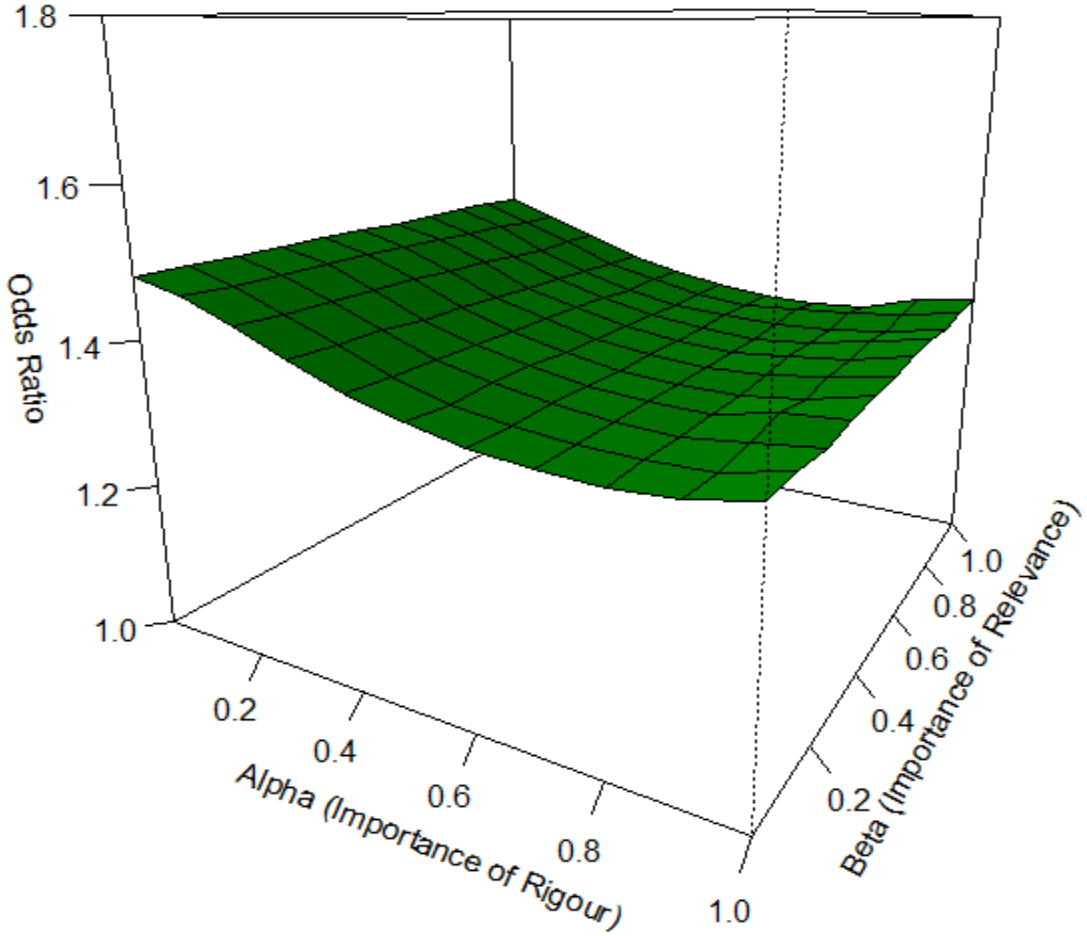
$$Z_i^* = Z_i / max(Z_i)$$

- Power Prior posterior distribution becomes;

$$P(\theta|RCTS, OBS) = \prod_{i=1}^{n} L(\theta|RCT)^{\beta_i^* \alpha_i^*} \prod_{j=1} L(\theta|OBS)^{\beta_j^* \alpha_j^*} P(\theta)$$

Where $\alpha_i^* = W_{Bi}^{\alpha}$ and $\beta_i^* = Z_i^{*\beta}$

Bivariate *supra* Power Prior – Results



Discussion of BSPP Approach

- Why not use Meta-Regression with the covariates?
  - Low power (Lambert *et al*, 2002)
- Meta-Regression + Bayesian Model Averaging (BMA)
  - Allows subjective assessment of importance of covariates
- Predicting effects in target populations?
  - Hierarchical model (accounting for sources of evidence)
- Other approaches …
  - Multi-Criteria Decision Analysis (MCDA)
  - Response surface approach
  - **Extension to NMA**
- Power prior approaches …
  - Allow decision makers to explore ***potential impact*** of non-randomised evidence on effect estimates & decisions for ***their*** target population

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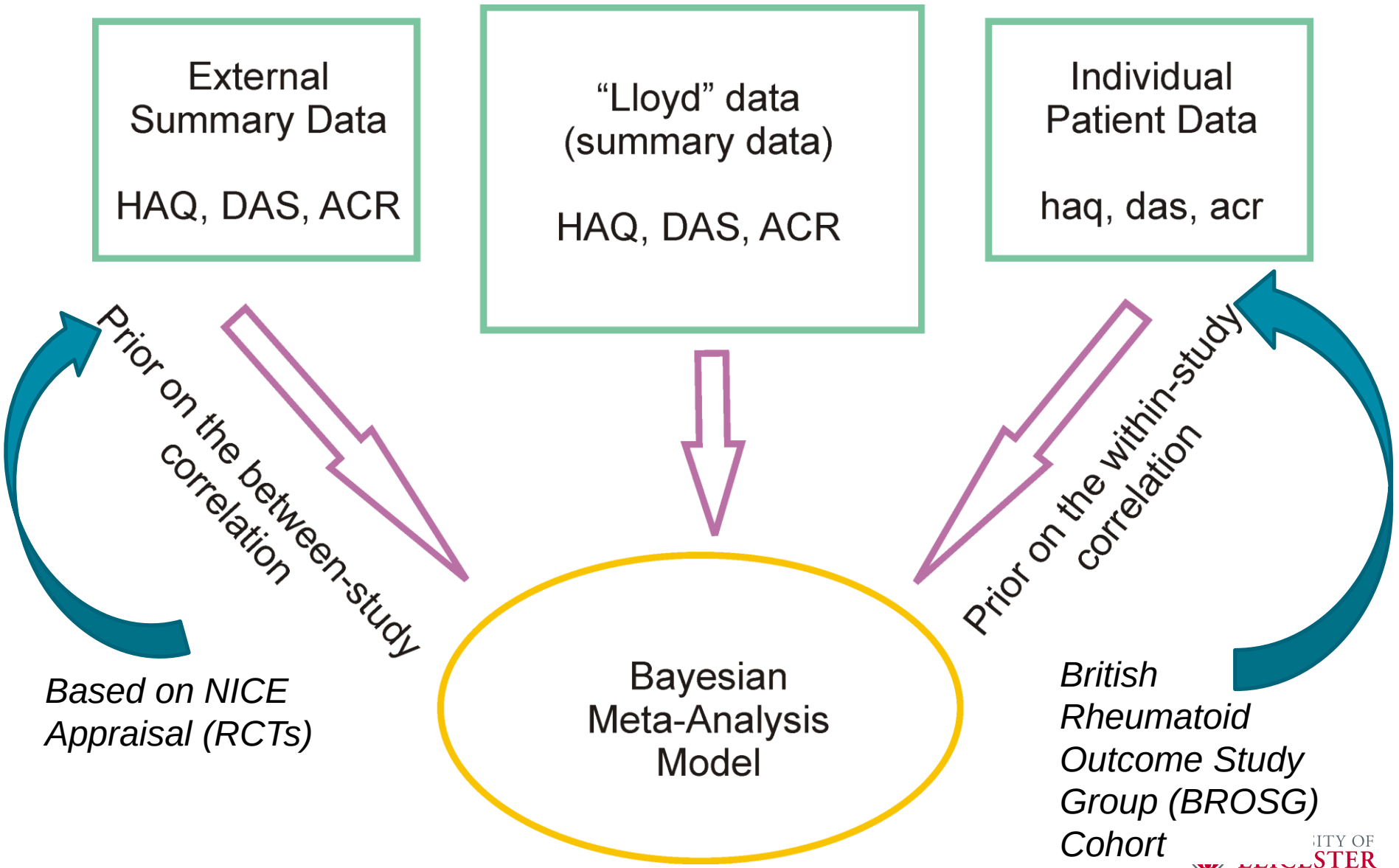
Example: Rheumatoid Arthritis (RA)

- S. Lloyd *et al*. The effectiveness of anti-TNF-alpha therapies when used sequentially in rheumatoid arthritis patients: a systematic review and meta-analysis. *Rheumatology* (2010) 49(12), 2313-2321.
- Meta-analyses of 3 outcomes of rheumatoid arthritis (RA):
  - American College of Rheumatology (**ACR**)
  - Disease Activity Score (**DAS**)
  - Health Assessment Questionnaire (**HAQ**)
- Showed benefit of anti-TNF- inhibitors when used sequentially.
- In economic models evaluating treatments in RA, **EQ-5D** is used and is usually *derived* from HAQ.

Multiple Outcomes: RA, Lloyd *et al*.

Study	HAQ	DAS28	ACR20
Bennet 2005	✓	✓	
Bingham 2009	✓	✓	✓
Bombardieri 2007	✓	✓	✓
Haroui 2004	✓		✓
Hyrich 2008	✓		
Iannone 2009	✓		
Navarro-Sarabia 2009	✓	✓	
Van der Bijl 2008	✓	✓	✓
Buch 2007		✓	✓
Cohen 2005		✓	
Di Poi 2007		✓	
Finckh 2007		✓	
Hjardem 2007		✓	
Laas 2008		✓	
Nikas 2006		✓	✓
Wick 2005		✓	✓
Karlsson 2008			✓
Buch 2005			✓
Van Vollenhoven 2003			✓

Multivariate MA Approach to RA (Bujkiewicz *et al*, 2013)

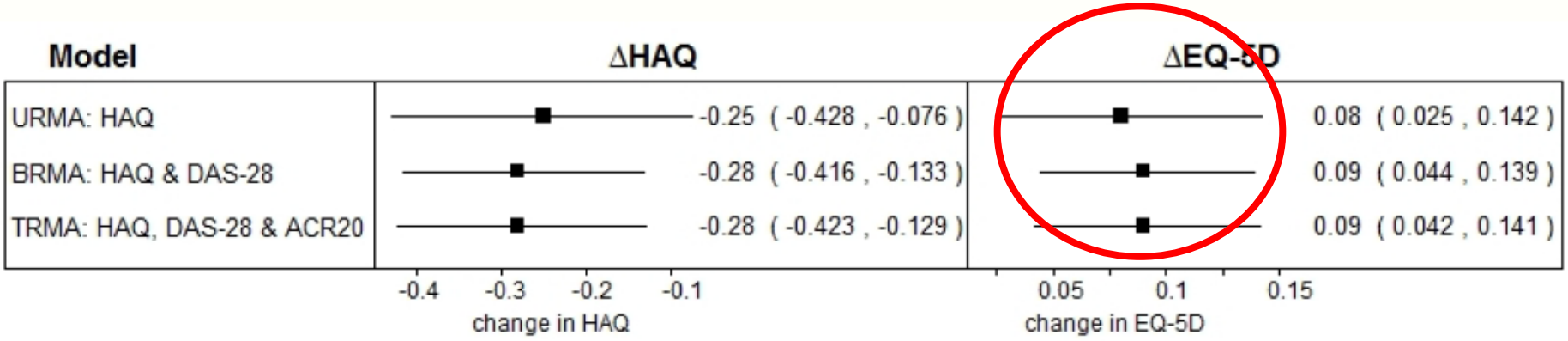


Multivariate Model: Results

	posterior mean (SE) [95% HPDI]				
	URMA: HAQ	URMA: DAS-28	URMA: ACR20	BRMA	TRMA
HAQ	-0.25 (0.09) [-0.43,-0.09]			-0.28 (0.07) [-0.41,-0.14]	-0.28 (0.07) [-0.42,-0.13]
DAS		-1.57 (0.13) [-1.84,-1.31]		-1.51 (0.08) [-1.67,-1.35]	-1.51 (0.09) [-1.70,-1.33]
ACR			0.62 (0.05) [0.53,0.71]		0.61 (0.05) [0.52,0.71]
τ_H	0.21 (0.09) [0.08,0.38]			0.21 (0.07) [0.10,0.35]	0.22 (0.07) [0.10,0.36]
τ_D		0.44 (0.11) [0.25,0.67]		0.44 (0.11) [0.24,0.67]	0.44 (0.11) [0.25,0.66]
τ_A			0.52 (0.19) [0.20,0.90]		0.53 (0.19) [0.22,0.91]
ρ_b^{DH}				0.89 (0.12) [0.65,0.994]	0.84 (0.18) [0.46,0.99]
ρ_b^{AH}					-0.14 (0.31) [-0.64,0.49]

Mapping from HAQ to EQ-5D: Results

Model	Number of cohorts/studies	ΔHAQ	$\Delta DAS-28$	$ACR20$	$\Delta EQ-5D$
URMA	8/8	-0.25 (-0.43, -0.09)	–	–	0.08 (0.025, 0.141)
BRMA	18/16	-0.28 (-0.41, -0.14)	-1.51 (-1.67, -1.35)	–	0.09 (0.041, 0.138)
TRMA	21/19	-0.28 (-0.42, -0.13)	-1.51 (-1.70, -1.33)	61% (52%, 71%)	0.09 (0.042, 0.139)



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Benefits & Limitations

- Benefits:
  - Potential increase in precision/reduction in uncertainty
  - External/RWE is not necessarily used directly
  - Useful when RCTs only report limited HTA-relevant endpoints, e.g. EQ-5D
- Limitations:
  - Relies on external/RWE especially for correlations between outcomes
  - Not always transparent and can increase methodological uncertainty

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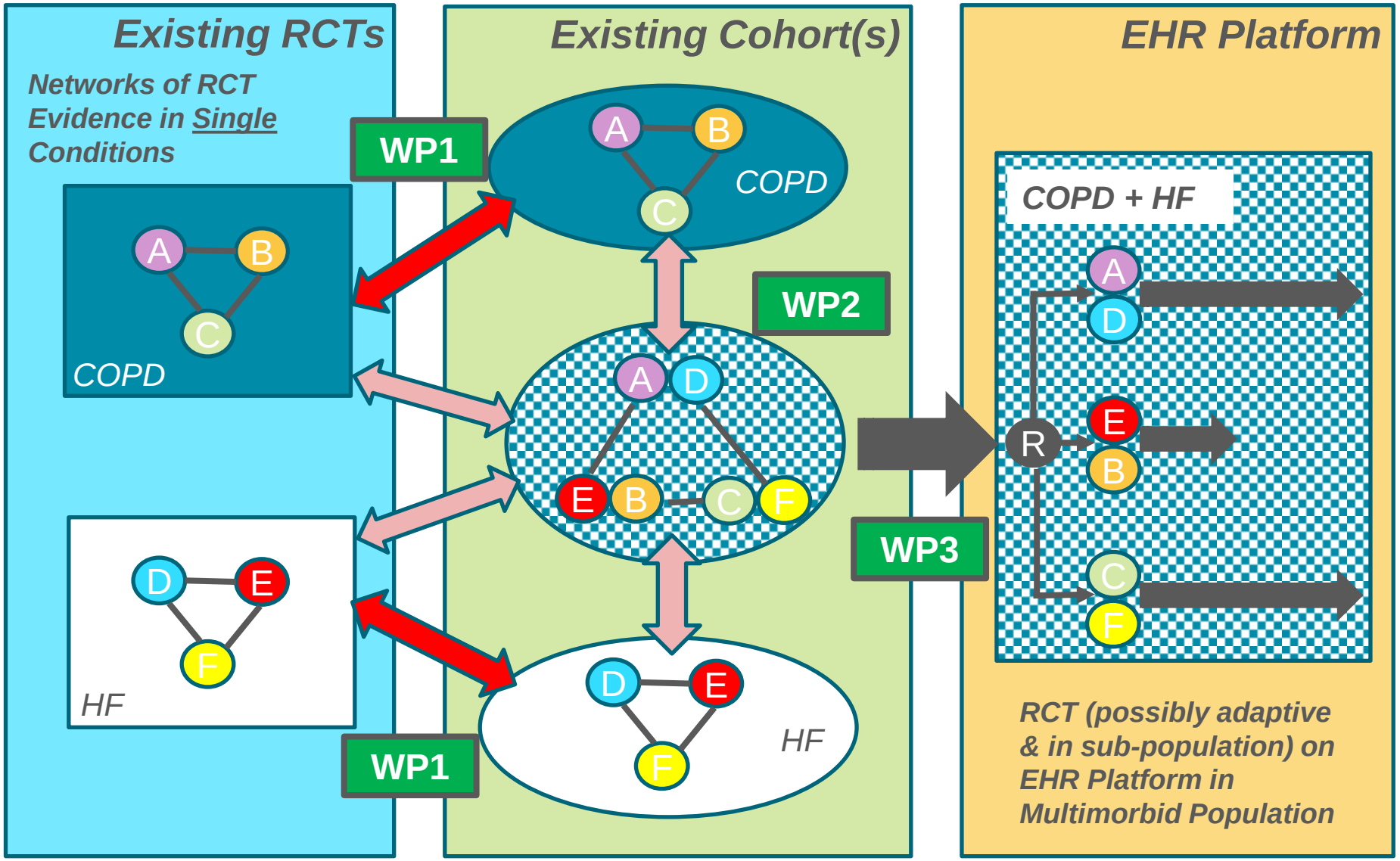
Discussion

- Use of RWE will increase – because of changing nature of RCTs & availability of RWE e.g. (linked) EHRs
- Formal use of RWE presents challenges (rigour) & opportunities (relevance) – other approaches not discussed …
- AI/ML applied to RWE …
  - Confounding and selection effects
  - Understanding of “data generation mechanism”
  - Informative observations e.g. BP in primary care
- Other situations in which ES & RWE can help …
  - Choosing comparator in future RCT
  - Estimating effects in other settings, e.g. 1L/2L
  - Helping design RCTs in other populations e.g. multimorbidity – HDR UK

Developing & Evaluating Methods for Harnessing EHRs to Generalise RCT Findings to Multimorbid Populations & Design of Future RCTs



WP4 – Stakeholders Workshops

HDRUK Health Data Research UK

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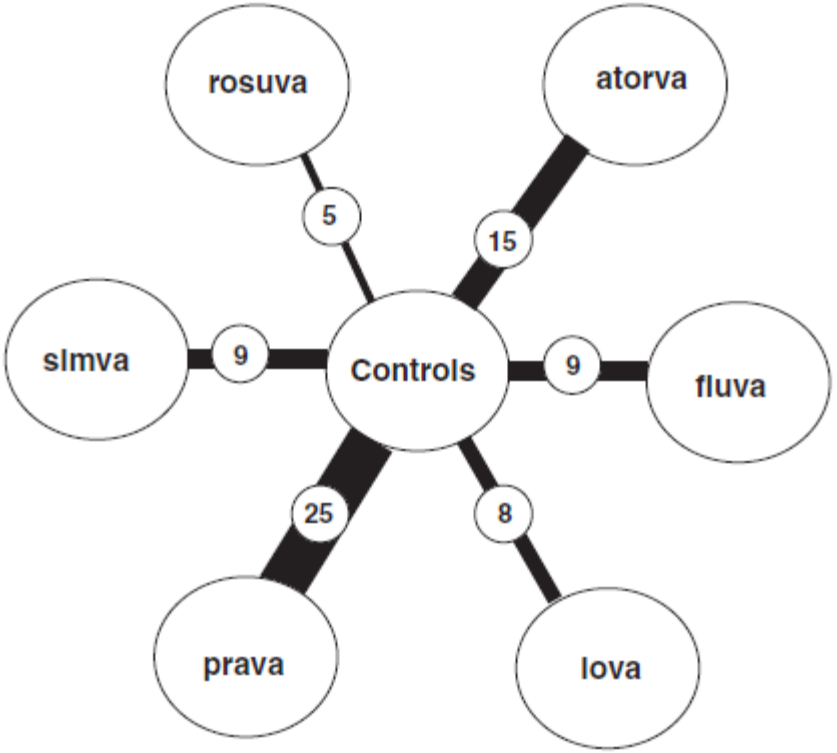
Thank you
&
What Questions do you have?

Backup Slides

Extension to Network Meta-Analysis (NMA)



Mills EJ *et al*, Q J Med 2011; 104:109–124.

Mapping from HAQ to EQ-5D

$$EQ-5D = a + b \times HAQ,$$

where $a \sim N(\mu_a, s_a^2)$ and $b \sim N(\mu_b, s_b^2)$, and $\mu_a = 0.628$, $\mu_b = -0.327$, $s_a = 0.034$, $s_b = 0.021$.

This relationship can be assumed to remain the same at any time point, hence the relationship between the change from baseline of EQ-5D and the change from baseline of HAQ can be modelled as

$$\Delta EQ-5D = b \times \Delta HAQ.$$

Augmenting NMAs with RWE when estimating treatment sequences