Flexible generic framework for evidence synthesis in health technology assessment

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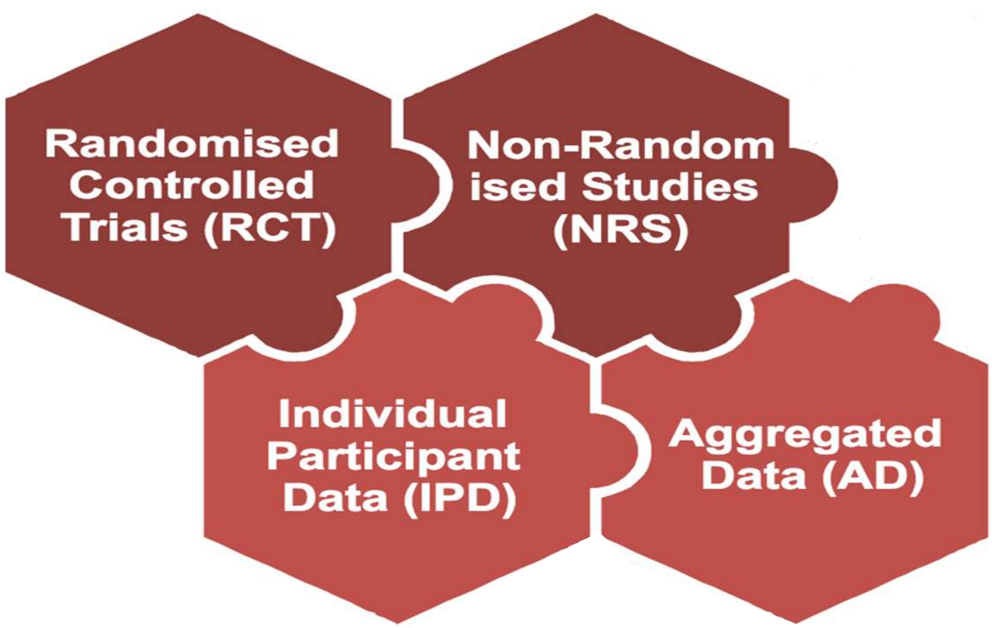
Goal



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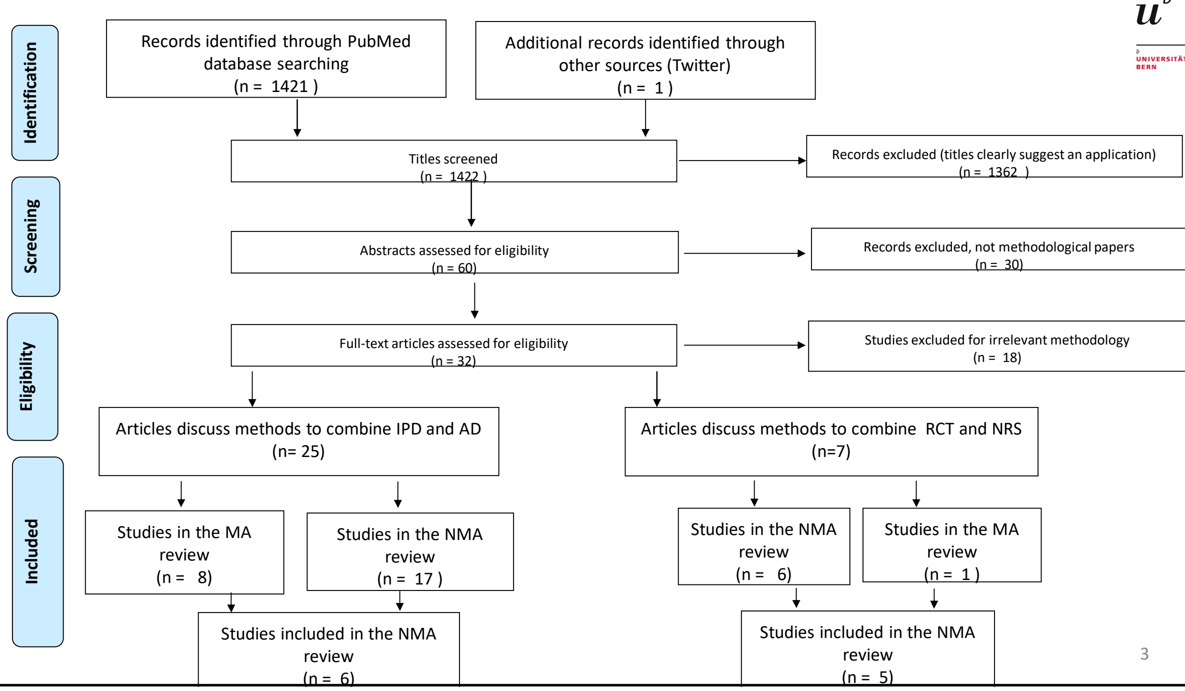
Flowchart of IPD-AD-RCT-NRS NMA



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Models to combine IPD and AD NMR

1. Three-level hierarchical NMR model (3LH-NMR) (Saramago 2012, Leahy 2012, Donegan 2012)
2. Multilevel network meta-regression (ML-NMR) (Leahy 2012, Phillippo 2020)
3. Matching-adjusted indirect comparisons (MAIC) (Signorovitch 2010)
4. Simulated treatment comparisons (STC) (Caro 2010)

Models to combine RCT and NRS NMR

1. Naïve approach
2. Using NRS as an informative prior
3. Design-adjusted model
4. Multilevel hierarchical model

Dias 2010, Schmitz 2013, Cameron 2015 and Efthimiou 2017, Verde 2020

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Models to combine IPD and AD NMR

1. Three-level hierarchical NMR model (3LH-NMR) (Saramago 2012, Leahy 2012, Donegan 2012)
2. Mu… k meta- reg… MR) (Leahy 2012, Phillippo 2020)
3. Matching-adjusted indirect …
4. Simulated treatment comparisons (STC) (Caro 2010)

Problems in R Implementation

- simple indirect comparison
- MAIC perform poorly in simulations

Models to combine RCT and NRS NMR

1. Naïve approach
2. Using NRS as an informative prior
3. Design-adjusted model
4. Mu… odel

Dias 2010, Schmitz 2013, Cameron 2015 and Efthimiou 2017, Verde 2020

several study designs and several studies within each design

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IPD-AD network meta-regression: 3LH-NMR

1. IPD studies

For i individual in j study with k treatment

$$y_{ijk} \sim Bernoulli(p_{ijk})$$
$$\text{logit}(p_{ijk}) =$$
$$u_j + \beta_1 x_{ijk} + \beta_{2,k}^{W}(x_{ijk} - x_{.jk}) + \beta_{2,k}^{B} x_{.jk} + \delta_{jbk}$$

2. AD studies

For j study with k treatment

$$y_{.jk} \sim Binomial(p_{.jk})$$
$$\text{logit}(p_{.jk}) =$$
$$u_j + \beta_{2,k}^{B} x_{.jk} + \delta_{jbk}$$

3. Exchangeable effects:

$\delta_{jbk} \sim N(d_k - d_b, \tau^2)$, $\beta_{2,k}^{B} \sim N(B_k^B - B_b^B, \sigma_B^2)$ and $\beta_{2,k}^{W} \sim N(B_k^W - B_b^W, \sigma_W^2)$

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Generic NMR model

3LH-NMR | Naïve approach

1. IPD studies

For RCT and NRS

$$y_{ijk} \sim Bernoulli(p_{ijk})$$
$$\text{logit}(p_{ijk}) = u_j + \beta_1 x_{ijk} + \beta^W_{2,k}(x_{ijk} - x_{.jk}) + \beta^B_{2,k} x_{.jk} + \delta_{jbk}$$

2. AD studies

For RCT and NRS

$$y_{.jk} \sim Binomial(p_{.jk})$$
$$\text{logit}(p_{.jk}) = u_j + \beta^B_{2,k} x_{.jk} + \delta_{jbk}$$

3. Exchangeable effects:

$\delta_{jbk} \sim N(d_k - d_b, \tau^2)$, $\beta^B_{2,k} \sim N(B^B_k - B^B_b, \sigma^2_B)$ and $\beta^W_{2,k} \sim N(B^W_k - B^W_b, \sigma^2_W)$

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Generic NMR model

3LH-NMR | Naïve approach

1. IPD –NMR

For RCT and NRS

$y_{ijk} \sim Bernoulli(p_{ijk})$

2. AD –NMR

For RCT and NRS

$y_{.jk} \sim Binomial(p_{.jk})$

$\text{logit}(p_{.jk}) =$

This assumes NRS and RCTs of high risk bias contributes the same (according to their precision) with low risk of bias RCTs

We introduce R_j which reflects the risk of bias in study j

$\delta_{jbk} \sim N(d_k - d_b, \tau^2)$, $\beta^B_{2,k} \sim N(B^B_k - B^B_b, \sigma^2_B)$ and $\beta^W_{2,k} \sim N(B^W_k - B^W_b, \sigma^2_W)$

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Generic NMR model

3LH-NMR | Design-adjusted

1. IPD studies

For RCT and NRS

$$y_{ijk} \sim Bernoulli(p_{ijk})$$
$$\text{logit}(p_{ijk}) =$$
$$u_j + \beta_1 x_{ijk} + \beta^W_{2,k}(x_{ijk} - x_{.jk}) + \beta^B_{2,k} x_{.jk} + \delta_{jbk} + \gamma_j R_j$$

2. AD studies

For RCT and NRS

$$y_{.jk} \sim Binomial(p_{.jk})$$
$$\text{logit}(p_{.jk}) =$$
$$u_j + x_{.jk}\beta^B_{2,k} + \delta_{jbk} + \gamma_j R_j$$

3. Exchangeable effects:

$\delta_{jbk} \sim N(d_k - d_b, \tau^2)$ $\beta^B_{2,k} \sim N(B^B_k - B^B_b, \sigma^2_B)$ and $\beta^W_{2,k} \sim N(B^W_k - B^W_b, \sigma^2_W)$,

4. Bias assumptions

$\gamma_j \sim N(g, \sigma^2_g), R_j \sim Bern(\pi_j)$

$$R_j = \begin{cases} \pi_{low} \sim beta(1,20) \\ \pi_{unclear} \sim beta(1,1) \\ \pi_{high} \sim beta(20,1) \end{cases}$$

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Generic NMR model

3LH-NMR | Informative Prior

1. IPD –NMR

For RCT

$$y_{ijk} \sim Bernoulli(p_{ijk})$$
$$\text{logit}(p_{ijk}) =$$
$$u_j + \beta_1 x_{ijk} + \beta^W_{2,k}(x_{ijk} - x_{.jk}) + \beta^B_{2,k} x_{.jk} + \delta_{jbk}$$

2. AD –NMR

For RCT

$$y_{.jk} \sim Binomial(p_{.jk})$$
$$\text{logit}(p_{.jk}) =$$
$$u_j + x_{.jk}\beta^B_{2,k} + \delta_{jbk}$$

3. Exchangeable effects:

$\delta_{jbk} \sim N(d_k - d_b, \tau^2)$ $\beta^B_{2,k} \sim N(B^B_k - B^B_b, \sigma^2_B)$ and $\beta^W_{2,k} \sim N(B^W_k - B^W_b, \sigma^2_W)$

First: NRS model

d^{NRS}_k, V^{NRS} are data

4. Priors

Second: RCT model

$u_j, B^W_k, B^B_k \sim \text{N}(0, 10^4), \tau, \sigma_B, \sigma_W \sim \text{Unif}(0, 10)$, $d_k \sim \text{N}\left(d^{NRS}_k, V^{NRS}\right)$

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Case study

- Relapsing remitting multiple sclerosis (RRMS)
- Binary outcome: relapse in 2 years (0/1)
- Covariate = age (reference to the mean age 37 yrs) – between and within–study interaction are the same

Study	Type of data	Design/RoB	Probability of risk	Treatment compared	Sample size
DEFINE	IPD	RCT/high risk	Beta(3,1)	Dimethyl fumarate Placebo	1234
CONFIRM	IPD	RCT/high risk	Beta(3,1)	Dimethyl fumarate Glatiramer acetate Placebo	1417
AFFIRM	IPD	RCT/low risk	Beta(1,20)	Natalizumab Placebo	939
Bornstein	AD	RCT/high risk	Beta(3,1)	Glatiramer acetate Placebo	50
Johnson	AD	RCT/unclear risk	Beta(1,1)	Glatiramer acetate Placebo	251
Swiss cohort	IPD	NRS/high risk	Beta(30,1)	All	290

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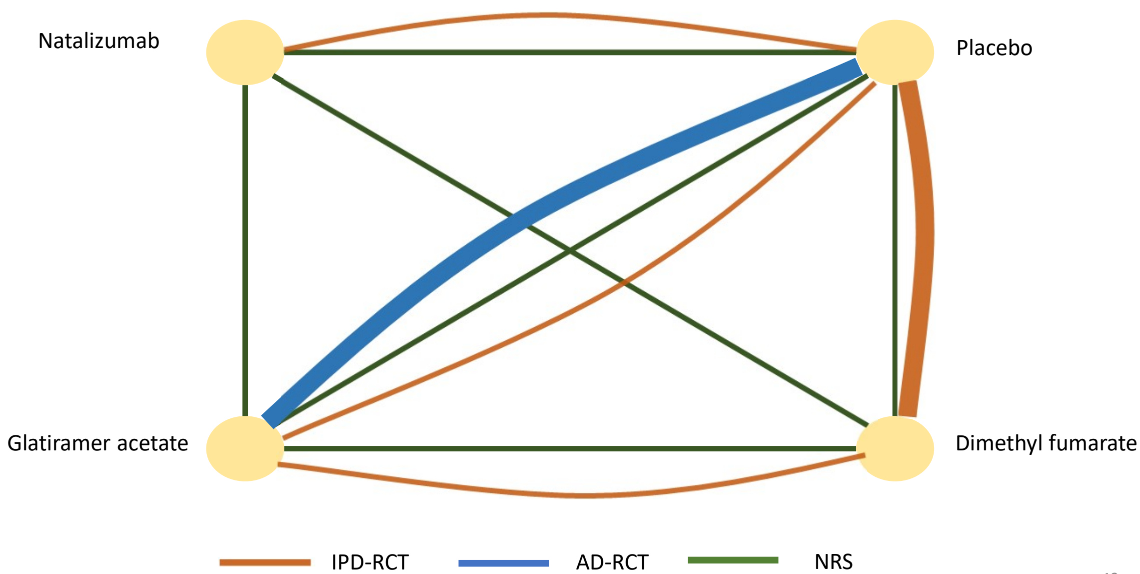
Network diagram



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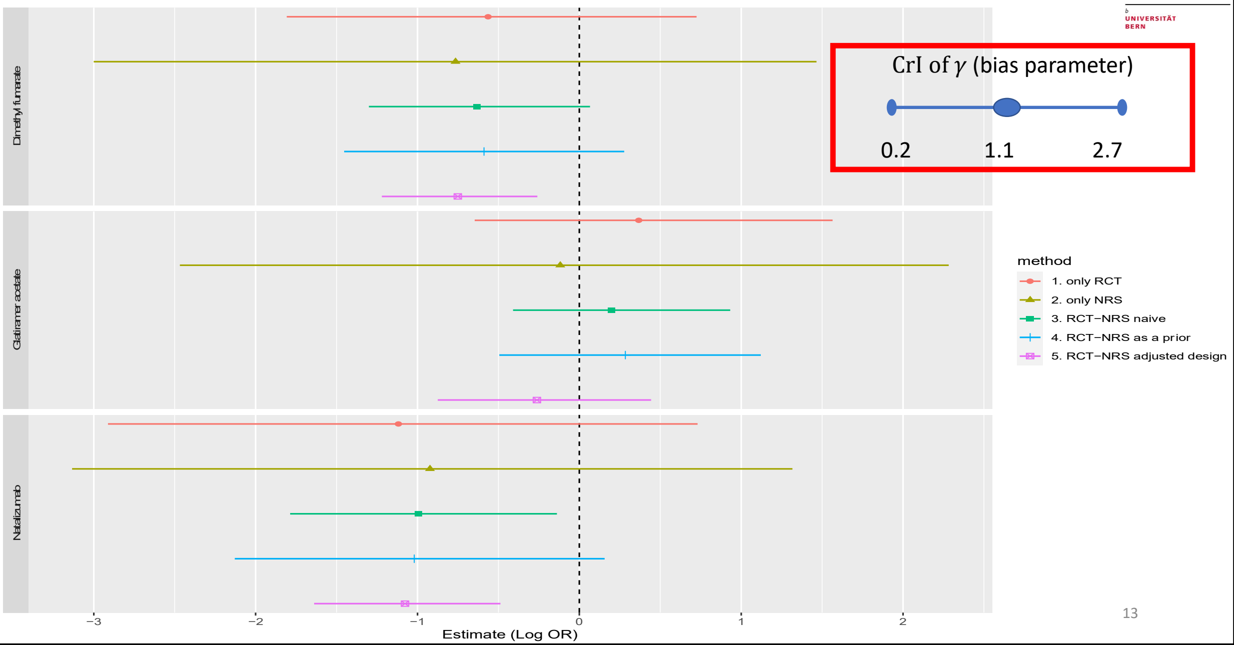
Results (response active vs placebo for 37 yrs)



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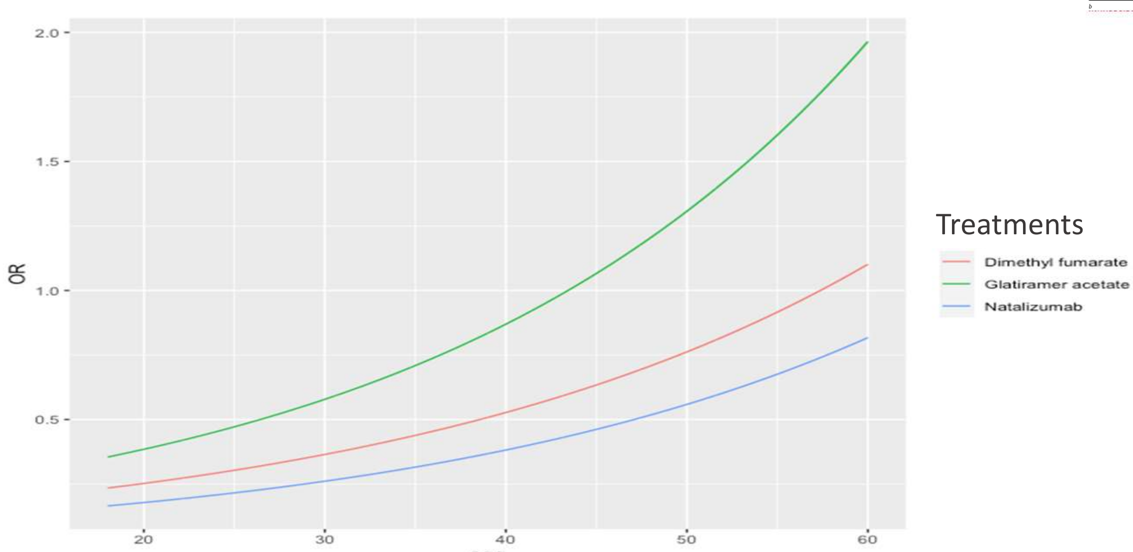
Results (OR vs age in design-adjusted model)



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Summary

- Introduce 3 generic framework approaches
- Adding the observational evidence increase the precision
- We have to acknowledge the differences between RCT and NRS

Further development

- Extend ML-NMR with design-adjustment
- Include single-arm trials
- Implement the model in larger network
- Sensitivity analysis especially for bias parameters

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