A COMPARATIVE REVIEW OF BAYESIAN NETWORK META-ANALYSIS: A USAGE CASE STUDY

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Note: some stat terminologies - may skip given the timing

Lilly

About my summer

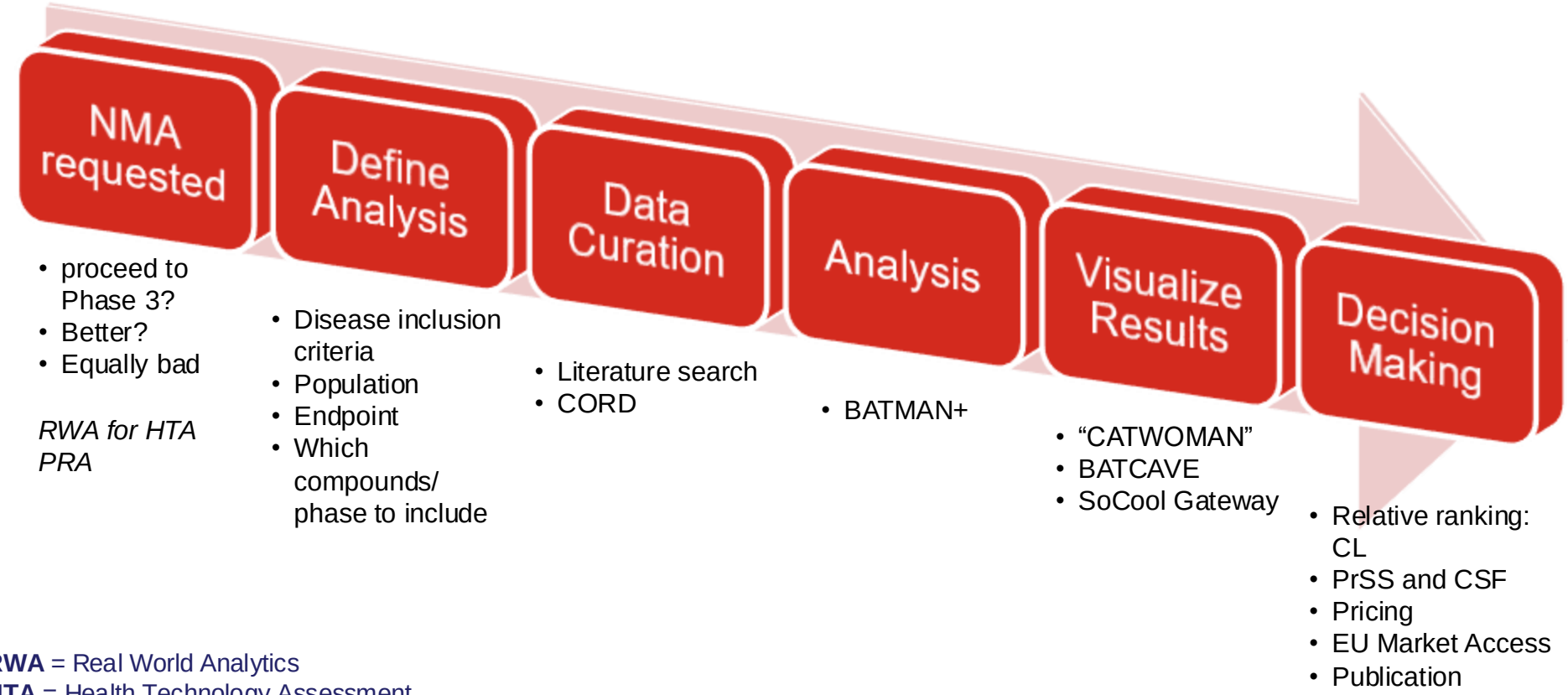
- UNC biostats → Innovation Computational Statistics
- BATMAN+ (BAyesian Tool for the Meta-Analysis of Networks), Lilly's in-house evidence-synthesis tool
- Comparative review for BNMA (Bayesian Network Meta-Analysis) automated packages, which is just one of the functions BATMAN+ can perform

Something else BATMAN+ can do:

- Indirect Comparisons Meta Analysis (ICMA)
- Matching adjusted Indirect Comparisons (MAIC)
- Model-Based Network Meta Analysis (MBNMA): longitudinal dosage/ time
- Multi-level Network Meta Analysis (MultiNMA) for a mixture of patient-level (IPD) and aggregated (AgD) data
- Contrast-based, Arm-based NMA

etc…

Lilly NMA Start to Finish



RWA = Real World Analytics
HTA = Health Technology Assessment
PRA = Pricing, Reimbursement, and Market Access
CORD = Clinical Outcomes Research Database
BATCAVE = Bayesian interActive compeTitive landsCApe Visual Exploration
CL = Competitive Landscape
PrSS = Probability of success
CSF = critical success factor. Lilly jargon. A quantitative goal for a trial

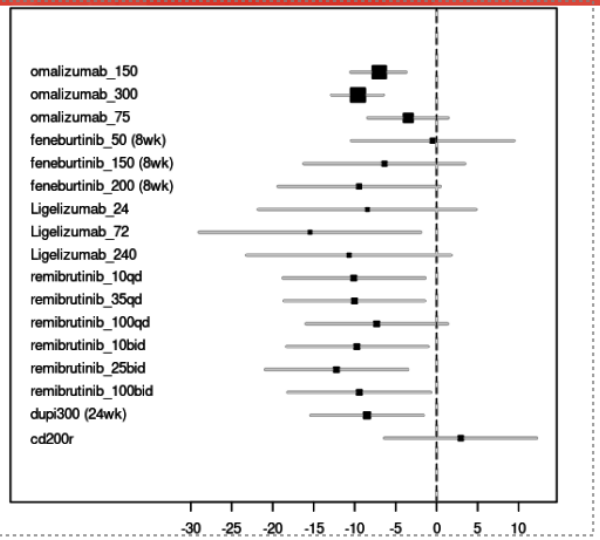
Example: Taltz asset planning

Quantitative Assessment of Current Competitive Landscape

Includes the 3 Xoliar registration studies and 3 regional phase 3s.

Ligelizumab phase2b data, phase 3 data has not been disclosed. We know if beat placebo but failed against oma.

Dupi data is from cupid A and they only reported 24 weeks.



CFB UAS7 at week 12 (relative to placebo)

- Endpoint: CFB UAS7
- Number of studies: 10
- Time point: 12 weeks (unless noted)
- Patient Population: Antihistamine refractory
- Study Selection: only randomized studies
- No Discounting is applied

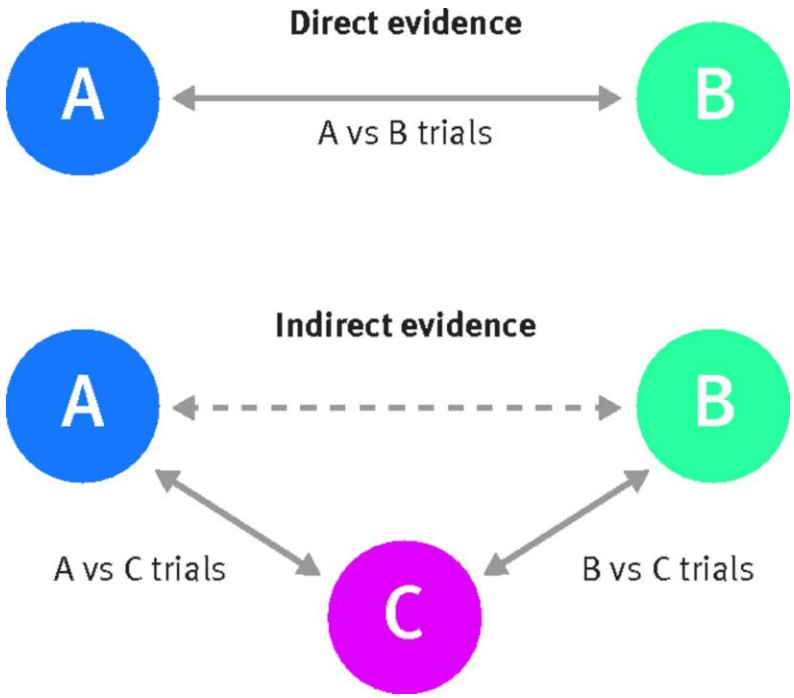
- Cutoff Date for trial inclusion May 2022
- Date model was fit: 2022/11/16
- Version controlled location of results:
- Validation Details: Peer Review

Conclusions/Insights/Takeaways:

- This is not the population we are studying.
- Few treatments are showing a much stronger effect than the only approved compound: Xoliar (omalizumab)

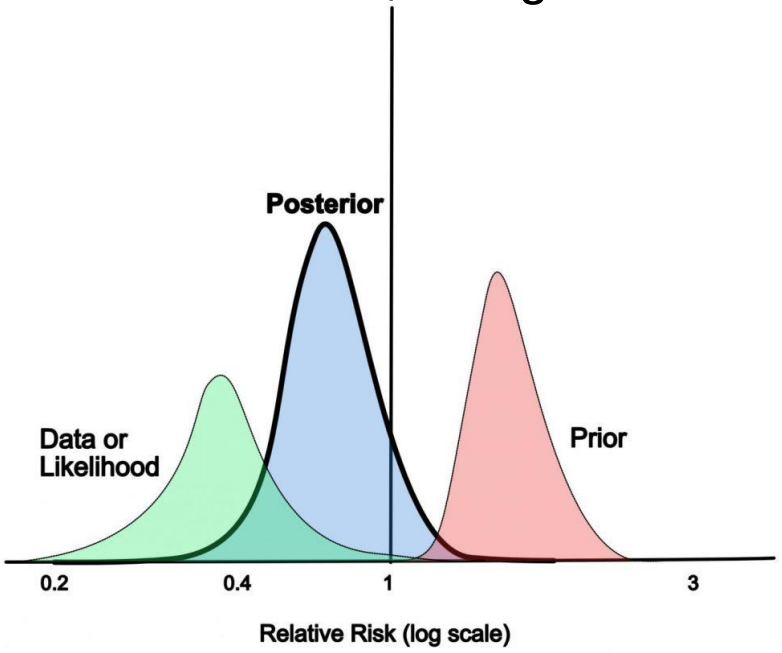
Network Meta Analysis

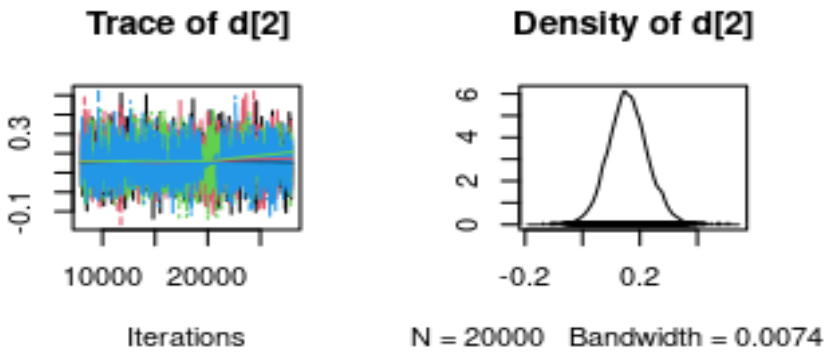
- statistical method to draw conclusions about multiple-treatment comparisons
- Simultaneously synthesize both direct and indirect evidence
- Produces estimates of relative effects between any 2 treatments in network
- Yields more precise estimates than pairwise meta-analysis (MA)

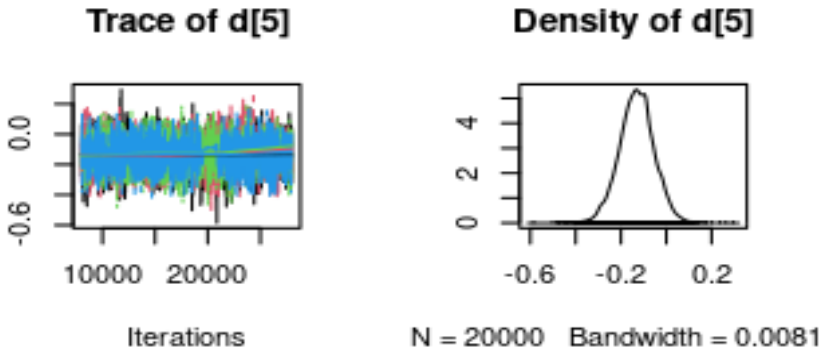


Bayesian Network Meta Analysis

- more prevalent and flexible method over Frequentist's approach
- Markov Chain Monte Carlo (MCMC)
- Check convergence and get estimates from posterior dist.
- A bit more time, though!







Random VS Fixed effect Model

- **Random** (often): true effect size is random across studies. Thus account for in-between trial variation (heterogeneity assumption).
- **Fixed**: true effect size is a fixed constant. Good for small network.

- Assume a network with N studies (indexed as i) containing k treatments
- Binomial Bayesian hierarchical model:

$r_{ik} \sim Bin(n_{ik}, p_{ik}), i = 1, \ldots, N$ (Likelihood)

$logit(p_{ik}) = \mu_i + \delta_{ibk} * I(k \neq b)$ (Link function)

$\delta_{ibk} \sim N(d_{bk}, \tau_{bk}^2)$ *(*Random effects*)*

$\mu_i, d_{bk}, \tau_{bk} \sim$ priors. (Prior distributions)

Necessity of fitting baseline model

- Everyone compares to placebo/standard care
- This introduces biased estimates
- Need to adjust for baseline risk to predict accurately

R packages for NMA on CRAN

- General NMA: ‘NMA’ and ‘meta’

- *Niche:*
- ‘nmaINLA’ uses **INLA methodology** instead of traditional MCMC.
- ‘rankinma’ **various ranking plots** for NMA.
- ‘rnmamod’ can address (aggregate) **missing** participant outcome data.
- ‘multinma’ takes IPD/AgD level data, or a **mixture of both**. This package was used in BATMAN pacman analysis.
- ‘metapack’ allows easy access to **regression-modeling of the variances** (of the treatment effects) and response covariance matrices.

NMA = network meta analysis
INLA = integrated nested Laplace approximation
IPD = individual patient data
AgD = aggregated data (just the summary of IPD)

My selection

5 candidates

- **multinma**, 2020 - used in BATMAN+ for ABNMA (arm-based)
- **pcnetmeta**, 2014 - arm based NMA. used in BATMAN+ for MultiNMA (“pacman”)
- **bnma**, 2020
- **gemtc**, 2012
- **BUGSnet**, 2019

BNMA

- Feed data
- network plot to validate feasibility
- model specification
- MCMC
- Assess convergence and model fit

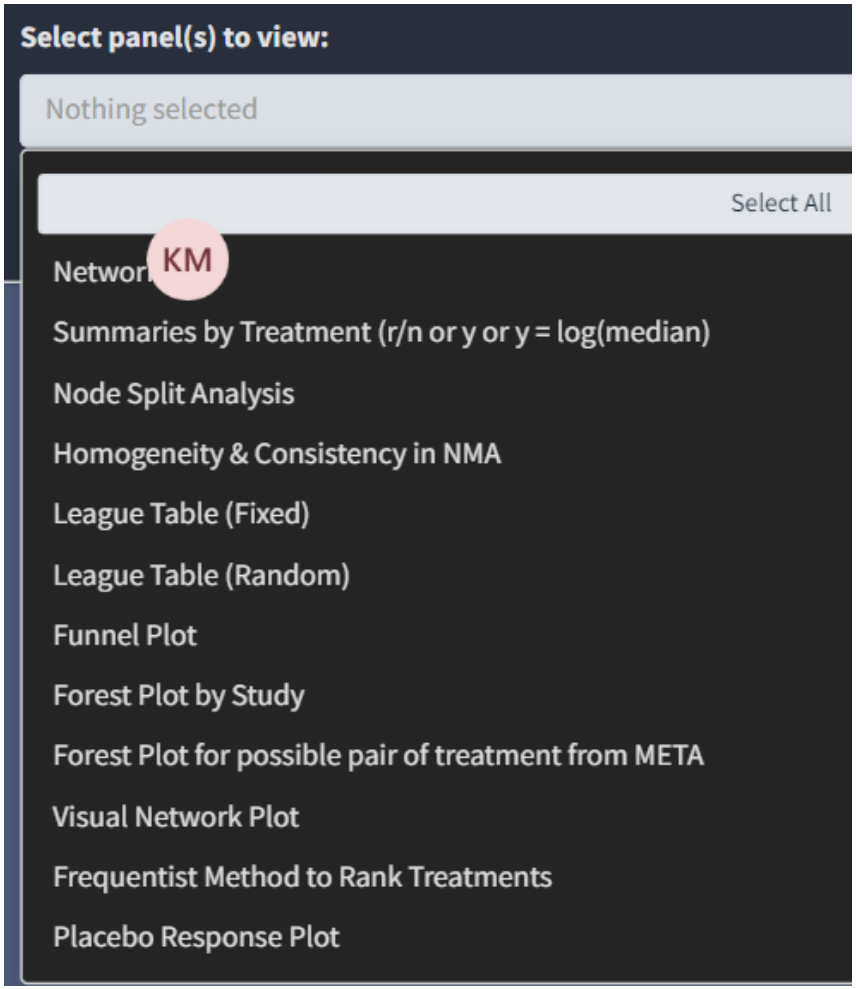
Compare and Contrast

Review- Data input, framework, feasibility

Tasks	Features	BATMAN	multinma	pcnetmeta	bnma	gemtc	BUGSnet
Forms of input data	Arm-level						
	Contrast-level				Y		
Class of outcome	Binomial						
	Multinomial	Y	Y	N	Y	N	N
	Count	Y	N	N	N	Y	Y
	Continuous	Y	Y	N	Y	Y	Y
	Time-to-event	Y	Y	N	N	N	Y
	Survival	Y	Y	Y	N	Y	Y
Link function	Identity (normal)	Y	Y	N	N	Y	Y
	Cloglog (poisson)	Y	Y	N	N	N	Y
	Logit (binomial/ multinomial)				Y		
	Probit (binomial/ multinomial)	Y	Y	Y	N	N	N
	Reciprocal	N	**Y**	N	N	N	N
	Log	Y	Y	N	N	Y	Y
Descriptive measures	Number of studies	Y	Y	N	N	Y	Y
	Sample size	Y	Y	N	N	Y	Y
	Multi-arm studies	N	N	N	N	Y	Y
	Covariate	N	N	N	N	N	**Y**
	treatments	Y	N	N	N	Y	Y
Feasibility panels	Network plot	Y	Y	N	Y	Y	Y

Review- About feasibility

- Mostly adopted from R package *netmeta*, a frequentist NMA approach package
- League table showing all pairwise comparisons
- Funnel plot to see prediction precision
- NMA assumptions tested by p-value
- Can add more from **BUGSnet**



Review- Model Specification

Tasks	Features	BATMAN	multinma	pcnetmeta	bnma	gemtc	BUGSnet
Model	Fixed Model			Y			
	Random Model						
	Baseline Risk	Y	Y	N	Y	N	N
Covariates	Meta-regression	Y	Y	N	Y	Y	Y

In **bnma**, you can assume different relationships between treatments and baseline risk (e.g., common, independent, or exchangeable).

Review- MCMC and convergence

Tasks	Features	BATMAN	multinma	pcnetmeta	bnma	gemtc	BUGSnet
Baseline and relative effect parameters prior	Normal distribution with heuristic initial values	Y	-	Y	Y	-	Y
	Restricted to change variance only	-	Y	-	-	Y	-
Heterogeneity prior	Uniform	Y	N	Y	Y	Y	Y
	Inverse Gamma	Y	N	Y	Y	Y	Y
	Half normal	Y	Y	N	Y	N	N
	Log normal	Y	N	N	N	Y	N
	Wishart	N	N	**Y**	**Y**	N	N
	Beta	N	N	N	N	N	**Y**
	Normal	N	**Y**	N	N	N	N
	Cauchy	N	**Y**	N	N	N	N
	Student t	N	**Y**	N	N	N	N
Assess convergence	trace plot	Y	N	N	Y	Y	Y
	Gelman-Rubin	Y	N	N	Y	Y	Y
	Automatic?	N	N	N	**Y**	N	N

Review- Assumptions and output

Tasks	Features	BATMAN	multinma	pcnetmeta	bnma	gemtc	BUGSnet
Assumptions-homogeneity	Q-statistic	Y	N	N	N	N	Y
	Global I^2	N	N	N	N	Y	Y
Assumptions-consistency	Residual deviance	Y	Y	N	Y	N	N
	Inconsistency model	Y	Y	N	Y	N	Y
	Unrelated Mean Effect model	Y	Y	N	Y	Y	Y
	Unrelated Study Effect model	N	N	N	N	Y	N
	Node split model	deprecated	Y	N	Y	Y	N
Effect size measures	RR	Y	N	Y	Y	Y	Y
	OR			Y			
	RD	Y	N	Y	Y	N	Y
	HR	Y	Y	N	N	N	Y
	MD	Y	N	N	N	Y	Y
	AR	Y	Y	Y	N	N	N
	NNT	Y	N	N	Y	N	N
	ER	Y	N	Y	Y	N	N
abs. stand. diff	ASD	Y	N	N	N	N	N
Ranking	Probabilities	Y	Y	Y (1st only)	Y	Y	Y
	Rankograms	Y	Y	N	Y	Y	Y
	SUCRA	Y	Y	N	Y	N	Y
Others	Himalayan	Y	N	N	N	N	N
	Ridge	Y	N	N	N	N	N
	Forest			Y			

From the review

- We can add:
- heterogeneity prior, link function
- auto convergence check
- more feasibility panels

- They don’t have:
- more output than us
- more relative effect parameters
- Built-in, automated TFL pipeline

Usage-based Case Study: single endpoint, univariate outcome

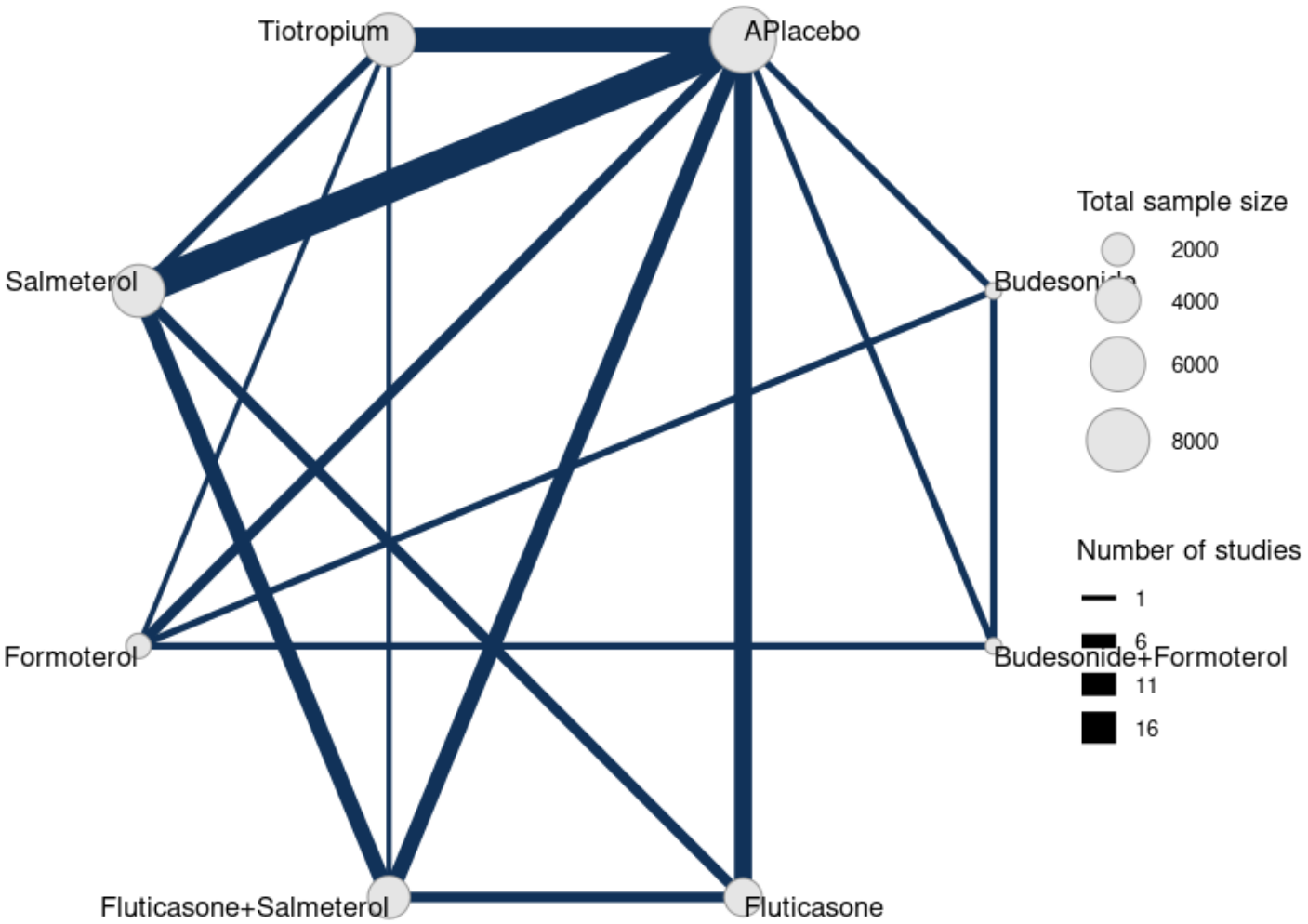
Baker 2009 Dataset

Randomized controlled trials on pharmacologic treatments for chronic obstructive pulmonary disease (COPD).
Binary outcome- occurrence means "*one or more episodes of COPD exacerbation*"

- 39 studies
  - 29 2-arm
  - 10 multi-arm
  - 28235 patients

- 8 arms
- Fluticasone (Fe)
- Budesonide (Be)
- Salmeterol (Sl)
- Formoterol (Fl)
- Tiotropium (Tm)
- Fluticasone + Salmeterol (Fe+Sl)
- Budesonide + Formoterol (Be+Fl)
- Placebo (PCB)

Network Plot by multinma



Forest

Model and MCMC setup

Random effect model

- without adjustment on baseline risk
- no inclusion of covariate
- Link function: binomial logit

Priors

- treatment effect ~ N (0, 100^2)
- in-between trial variation (heterogeneity parameter):
  - Either ~Unif (0,10) (BATMAN, bnma, pcnetmeta, gemtc, BUGSnet)
  - half Normal with a scale factor of 5 (multinma)

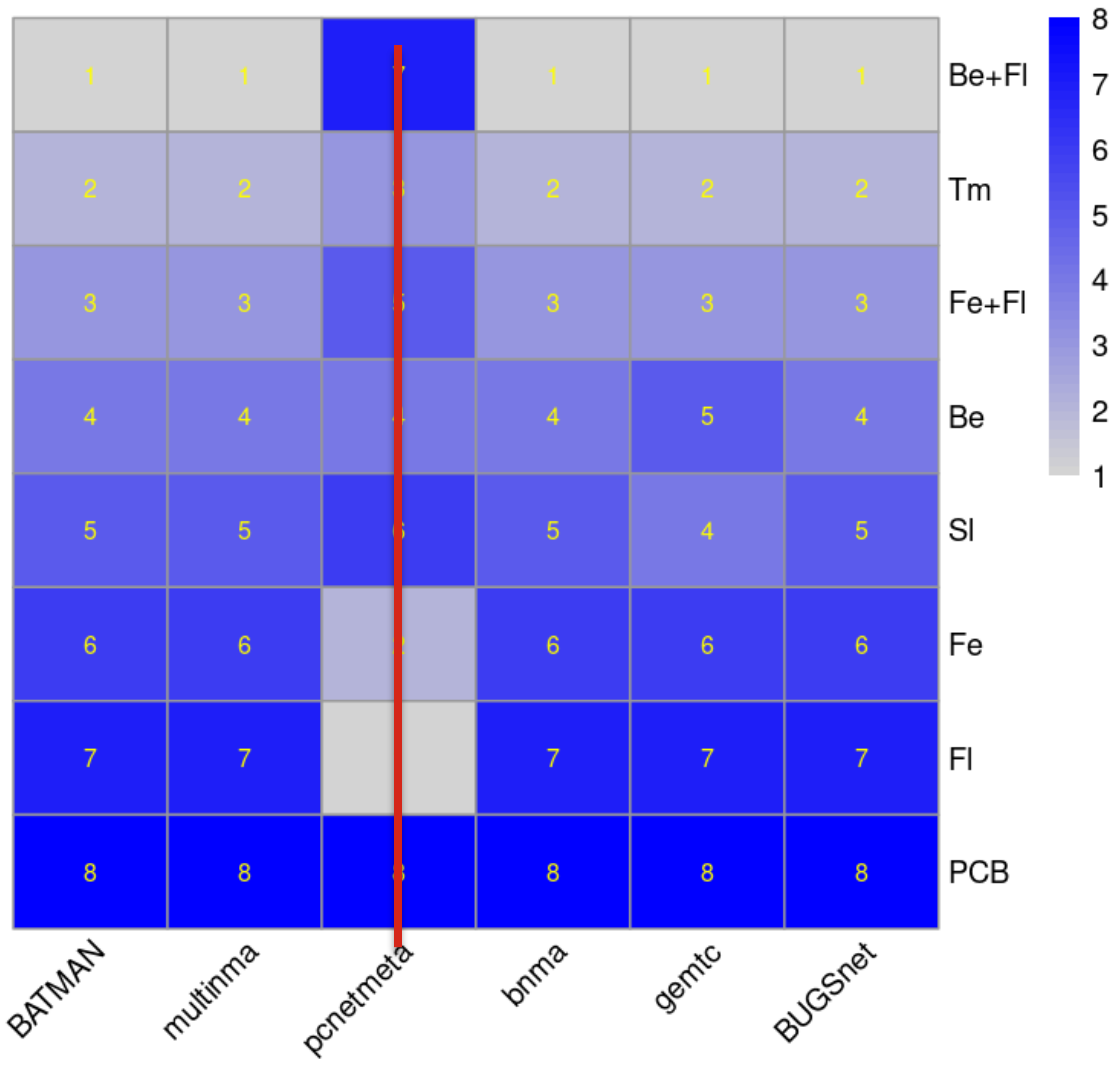
- MCMC:
- 8,000 burn in + 20,000 iterations= 28,000 samples
- 4 chains

Odds Ratio relative to placebo was measured

Smaller OR = greater efficacy since direction is negative

However, package **pcnetmeta** yields unconverged sequences – largely due to computational burden from MVN matrix invert calculation

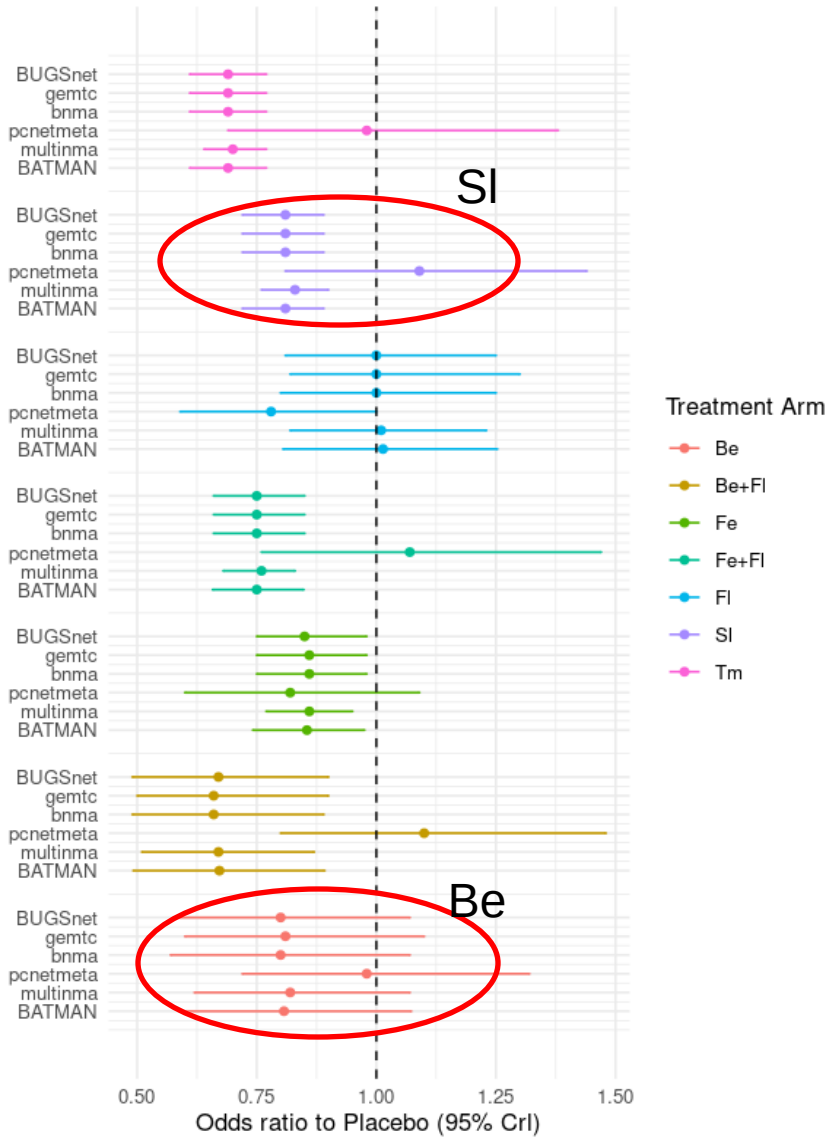
Treatment ranking

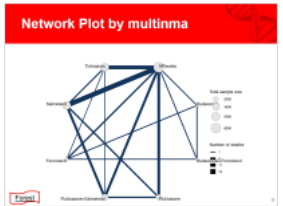


Treatment ranking

Package	Ranking (1st to 8th, best to worst)							
BATMAN	Be+Fl	Tm	Fe+Fl	Be	Sl	Fe	Fl	PCB
multinma	Be+Fl	Tm	Fe+Fl	Be	Sl	Fe	Fl	PCB
~~**pcnetmeta**~~	~~Fl*~~	~~Fe*~~	~~Tm*~~	~~Be*~~	~~Fe+Fl*~~	~~Sl*~~	~~Be+Fl*~~	~~PCB~~
bnma	Be+Fl	Tm	Fe+Fl	Be*	Sl	Fe	Fl	PCB
gemtc	Be+Fl	Tm	Fe+Fl	Sl	Be	Fe	Fl	PCB
BUGSnet	Be+Fl	Tm	Fe+Fl	Be	Sl	Fe	Fl	PCB

Forest Plot (by treatment)





Speed

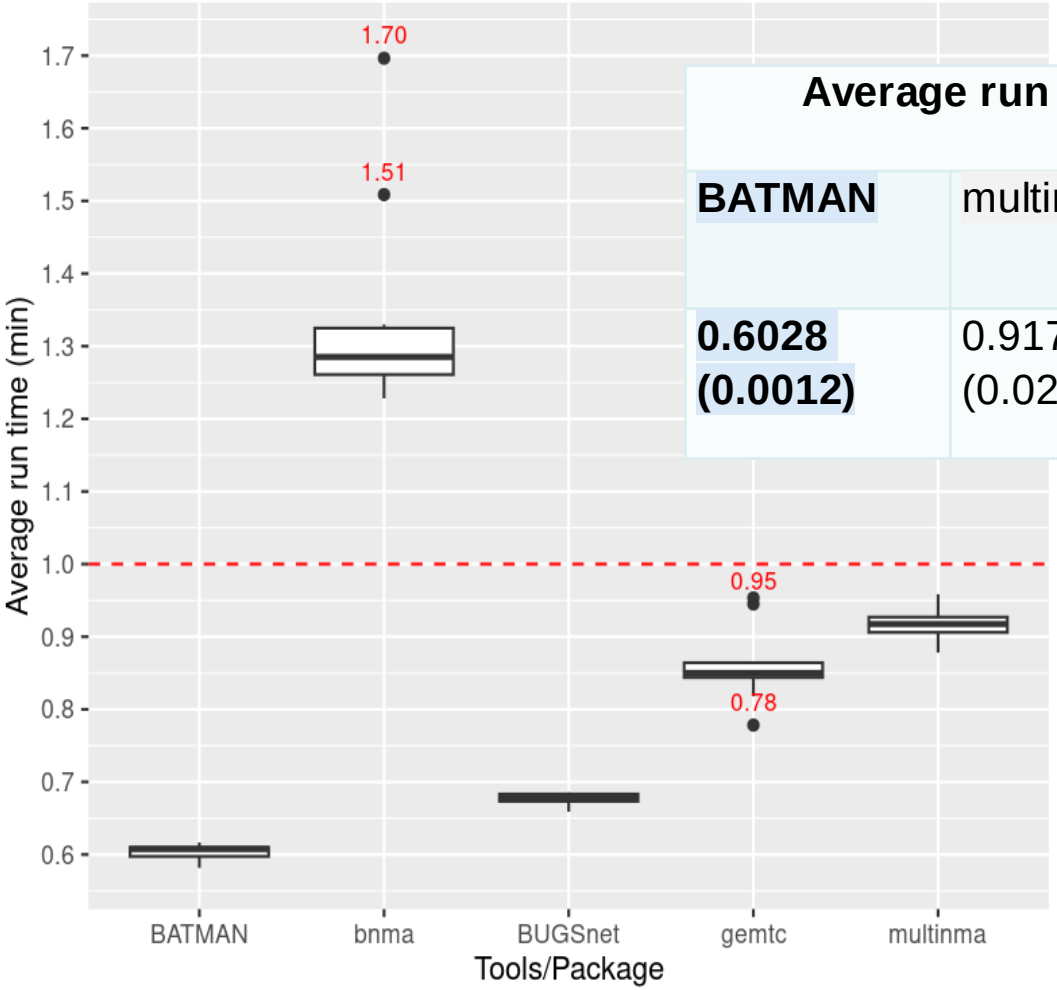
```
time <- c()
for (i in 1:10){
start_time = sys.time()
[MCMC sampling code]
end_time = sys.time()
time[i]<- end_time – start_time
}
```

Average run time in minutes (standard deviation)
[*pcnetmeta* excluded]

BATMAN	multinma	bnma	gemtc	BUGSnet
0.6028 (0.0012)	0.9172 (0.021)	1.3413 (0.148)	0.861 (0.053)	0.6767 (0.008)

Speed

Average computation time for 28,000 samples



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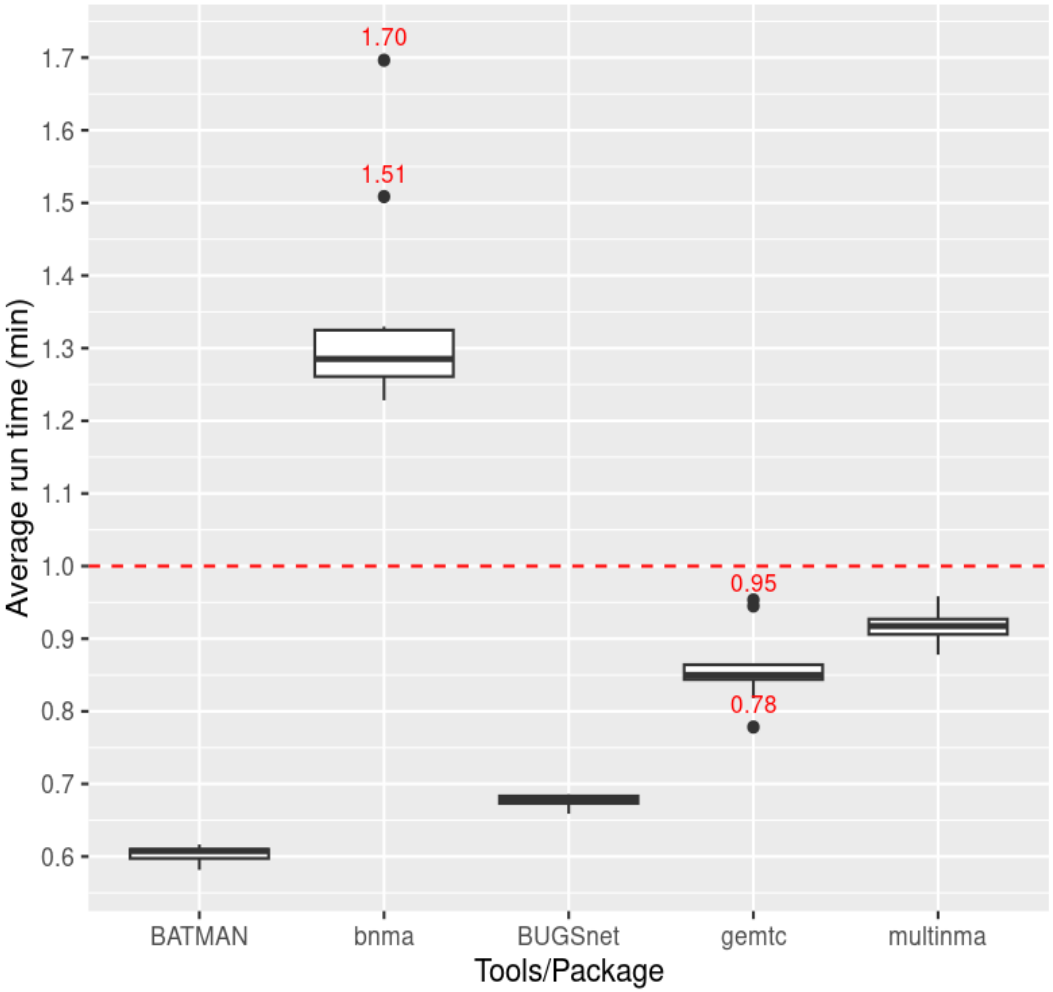
Limitation…

Average computation time for 28,000 samples



1. Number of studies
2. Modeling differences: For BATMAN, the computational time is measured by the relative effect model from the independent modeling that gets tested. This means that packages with less computational time demonstrate much superiority compared to BATMAN, as preprocessing steps are accounted for in the total run time.
3. Variability from the high-performance computing environment: cluster core availability, network load, and other concurrent processes.

Summary & Pros

- Validate efficiency and accuracy for BATMAN

Features	Advantages
High-level	automated TFL system
	customized output (batch forest plots)
	efficiency: parameter file for future use
	cross model comparison reports
Data input	comprehensive class of outcome
	binomial to nominal conversion
	individual patient data (IPD) & aggregated (AgD) friendly
	flexible data manipulation
	simultaneous/ independent modelling option
	auto check validity on different models
Sensitivity	exclusion of studies
	exclusion of outlier

Comparators

	multinma	pcnetmeta	bnma	gemtc	BUGSnet
publish yr (update yr)	2020 (2024)	2014 (2022)	2020 (2024)	2012 (2023)	2019 (2021)
highlight	- flexible model specification	- tidy output - one step to fit	- convergence check - reasonable and dispersed initial values if unspecified - comprehensive output - exhaustive inconsistency modelling	comprehensive output	- comprehensive output for feasibility - easy network setup - concise coding statements
limitation	limited flexibility in MCMC setup	- limited graphical output - B/W TFL	- cannot fit covariate	not flexible data read in	current version does not support categorical covariates with > 3 levels

Future Direction

Features	What to do next?
Feasibility	add study information on network plot (now showing study count only) (*gemtc*)
	more feasibility panels (*BUGSnet*)
Model Specification	add Wishart distribution option for heterogeneity priors
Model Output	summarize SUCRA plots in one panel
	set output file format filters (.png, .txt, .pdf) to custom results
	create standard Tables, Figures, and Listings based on templates for Health Technology Assessments (HTA) submissions
Diagnostics	automated validation for convergence (*bnma*)
	provided reasons of failed run
	quantified inconsistency heatmap (*netmeta*, Figure 6)

Limitation

- Other types of responses unchecked
- Fitted a simple model
- Painful speed for IPD and survival data
- Result consistency with respect to different priors/ initial values

Acknowledgements

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Internship stats committee: Fangyu Wang, Emily Gebhardt, Xiangdong Liu, Bala Dhungana

Fellows: Jane Ma, Holly Cui, Joshua Korley

etc …

Reference

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13. Immunology_CLA_Activities.pptx

14. Data_curation_through_NMA.pptx

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Collaborator: Xiaofei Wang, Michael Sonksen

CONTENTS

Paper: *24intern_BNMA_paper.docx*
R code: *24intern_BNMA_code (S.1).zip*
Inquiries: kma1@unc.edu

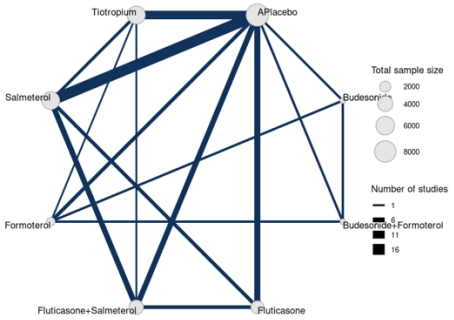
Thanks for having me this summer

Lilly

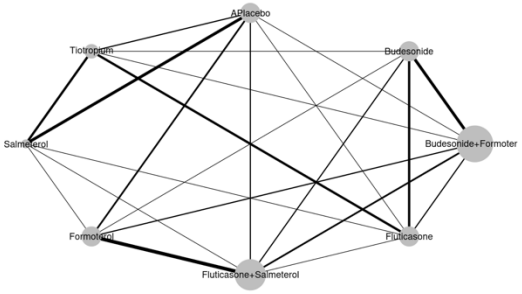
EXTRA SLIDES

Network Plot

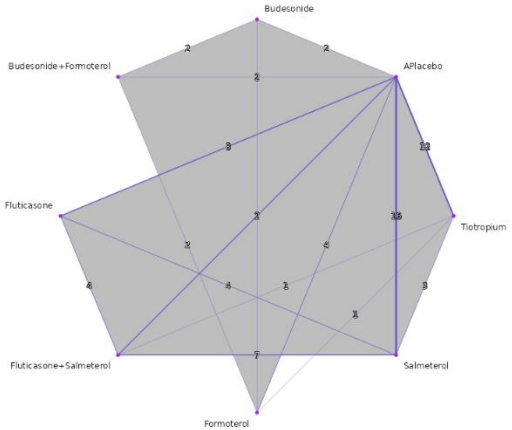
multinma



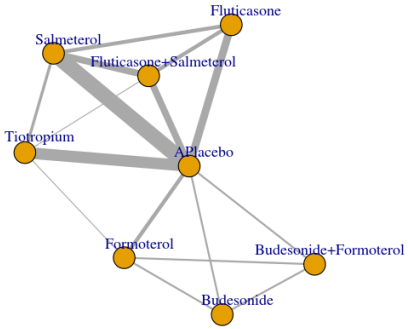
pcnetmeta



BATMAN



gemtc, bnma



BUGSnet