Living network meta-analysis

Living Evidence Network "state of the science" webinar

21 Mar 2019

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Trusted evidence.
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LIVING NETWORK META-ANALYSIS

the next step in evidence synthesis

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Webinar on living network meta-analyses
21 March 2019

Acknowledgements: Georgia Salanti, Dimitris Mavridis, Philippe Ravaud, Perrine Crequit, Andrea Cipriani

Outline

- Introduction to network meta-analysis (NMA)
- Example of a living NMA (LNMA)
- Challenges in the process of LNMAs
- Future work on LNMAs

Introduction to network meta-analysis

Why we need network meta-analysis?

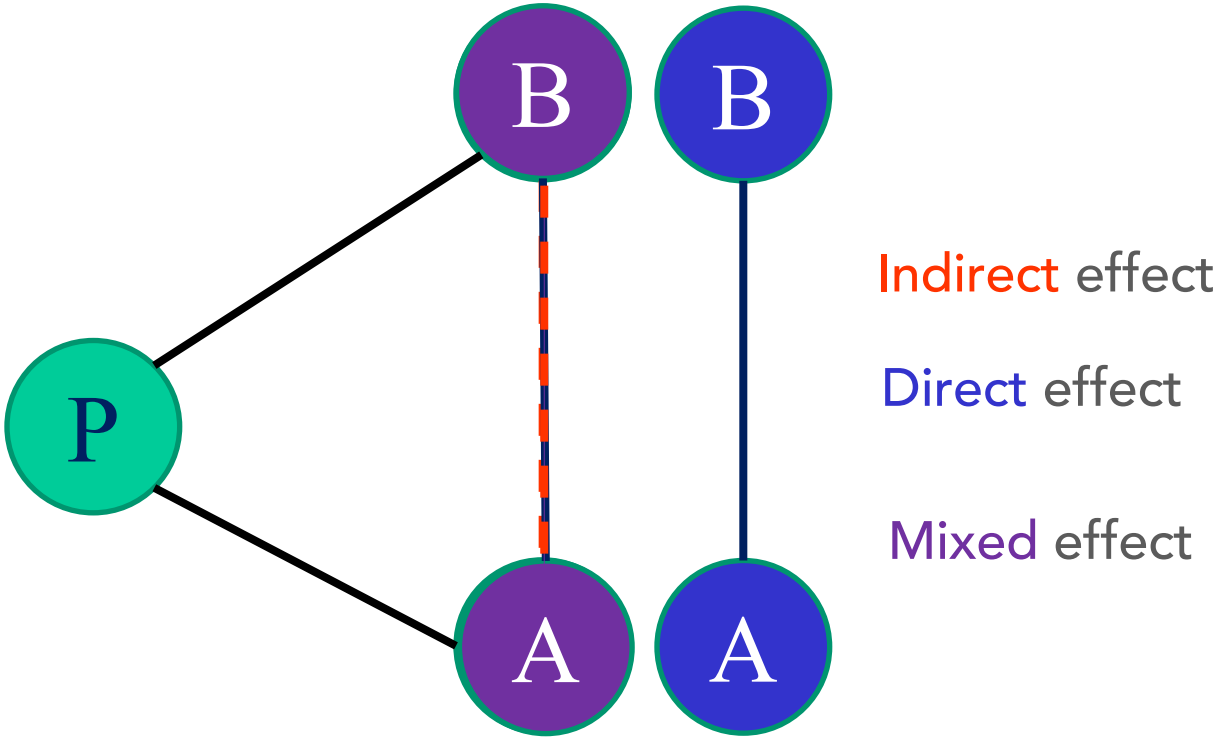
"Although Mirtazapine is likely to have a faster onset of action than Sertraline and Paroxetine no significant differences were observed..."

"...meta-analysis highlighted a trend in favour of Sertraline over other Fluoxetine"

"...statistically significant differences in terms of efficacy .... between Fluoxetine and Venlafaxine, but the clinical meaning of these differences is uncertain..."

"Venlafaxine tends to have a favorable trend in response rates compared with duloxetine"

Indirect and mixed comparisons



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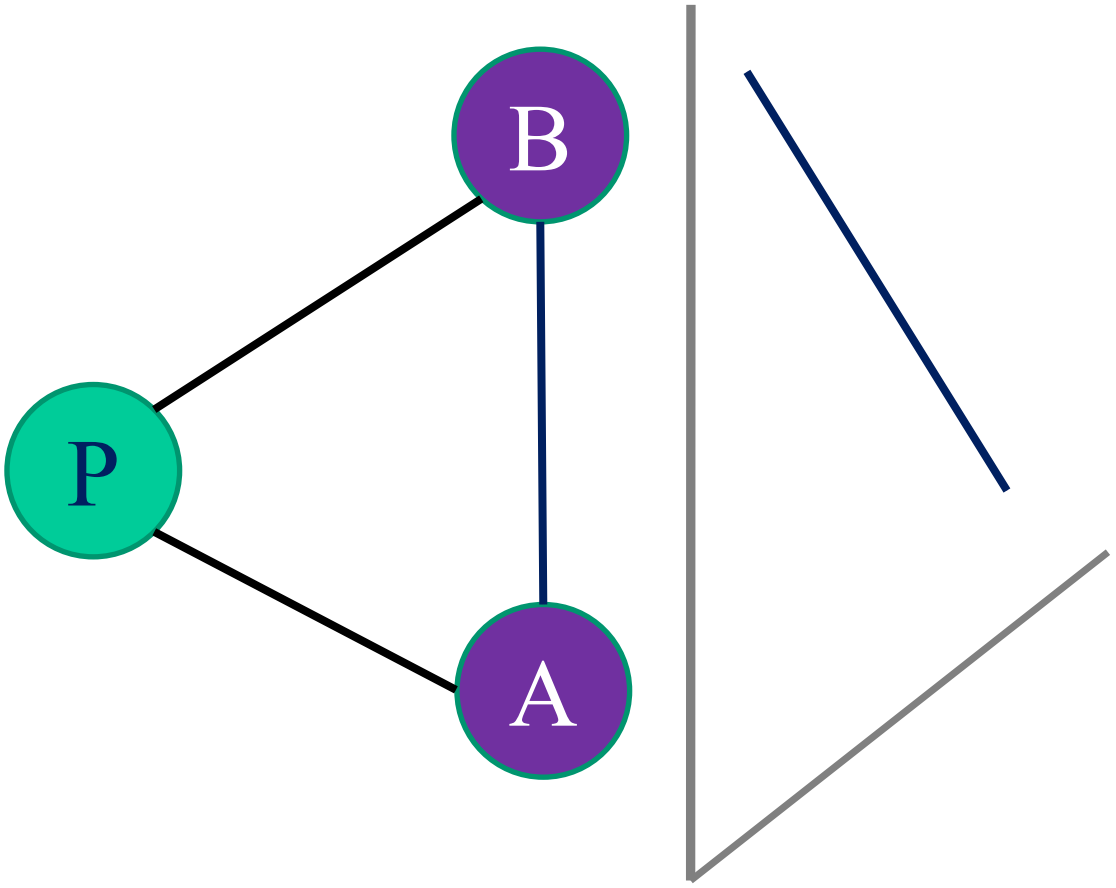
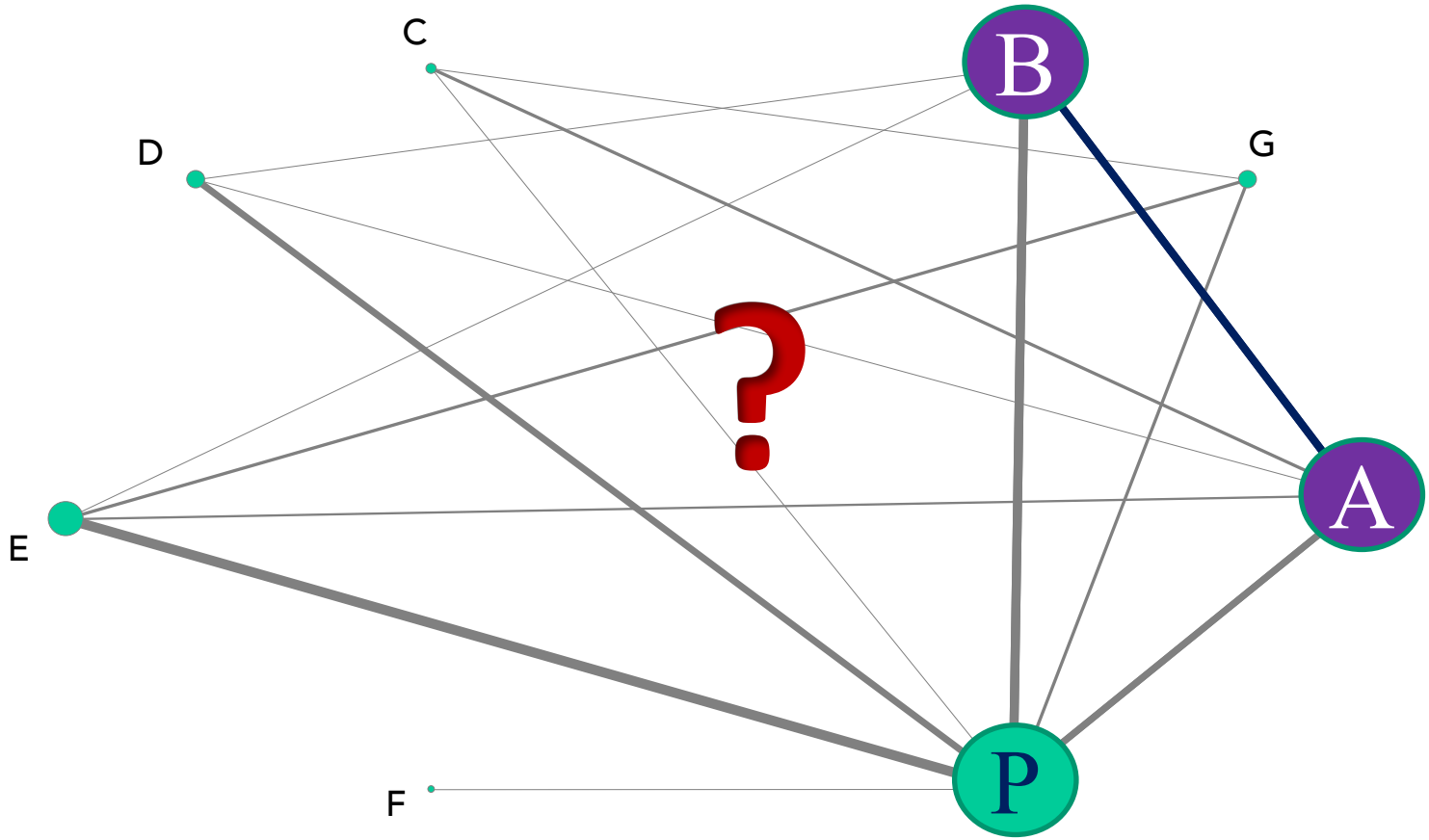


Full network of interventions

which are the most appropriate treatments to recommend,
for which population and under which setting?



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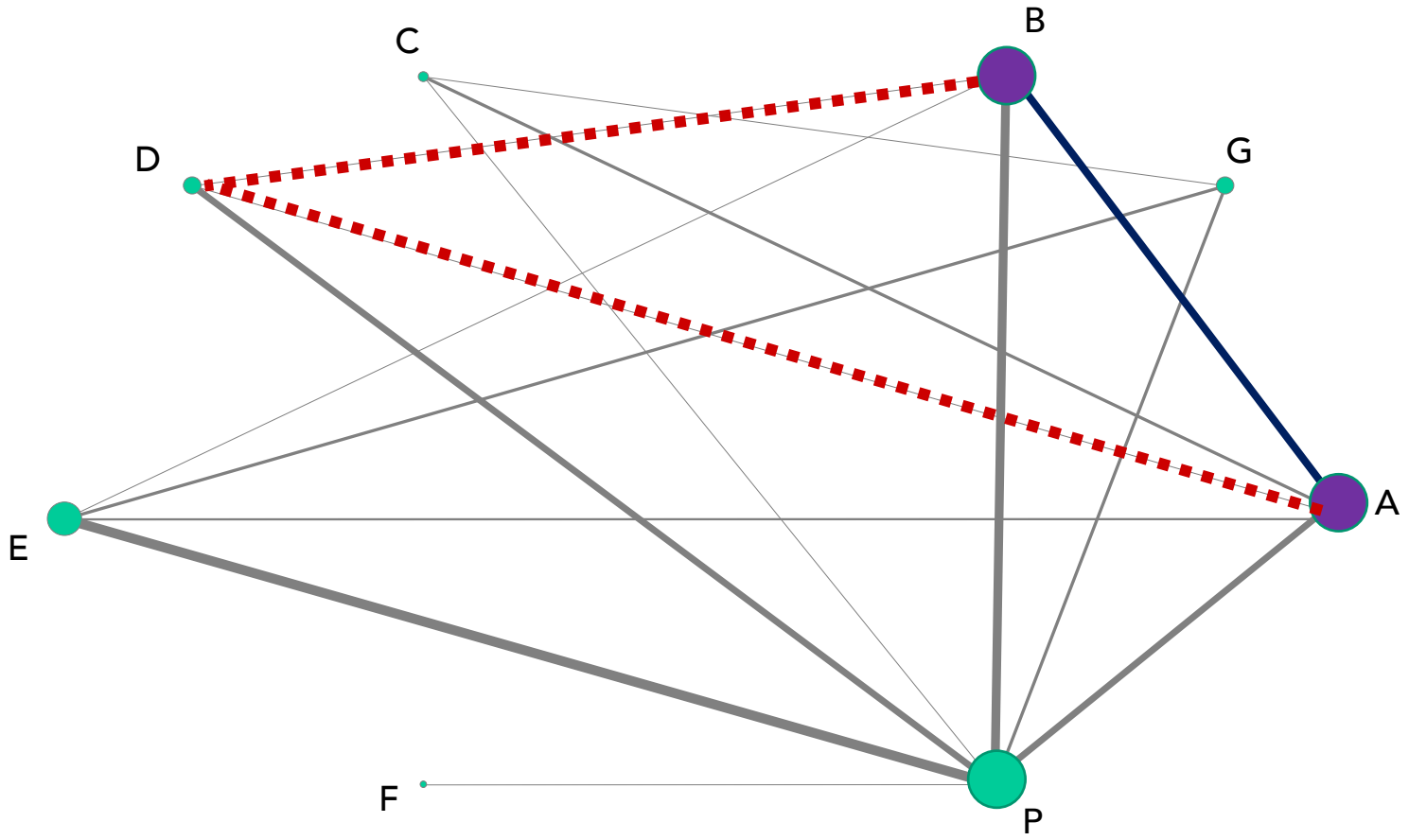

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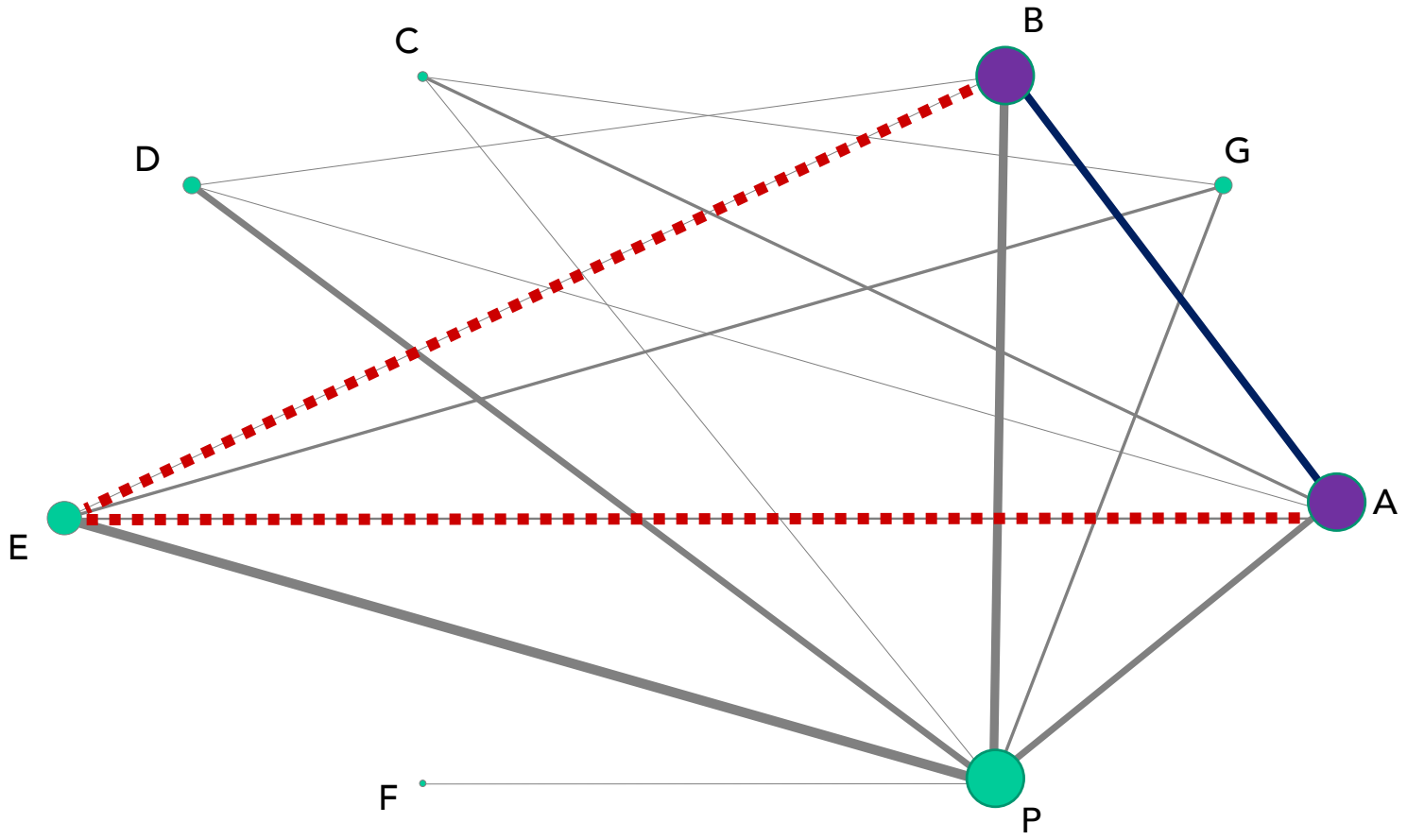

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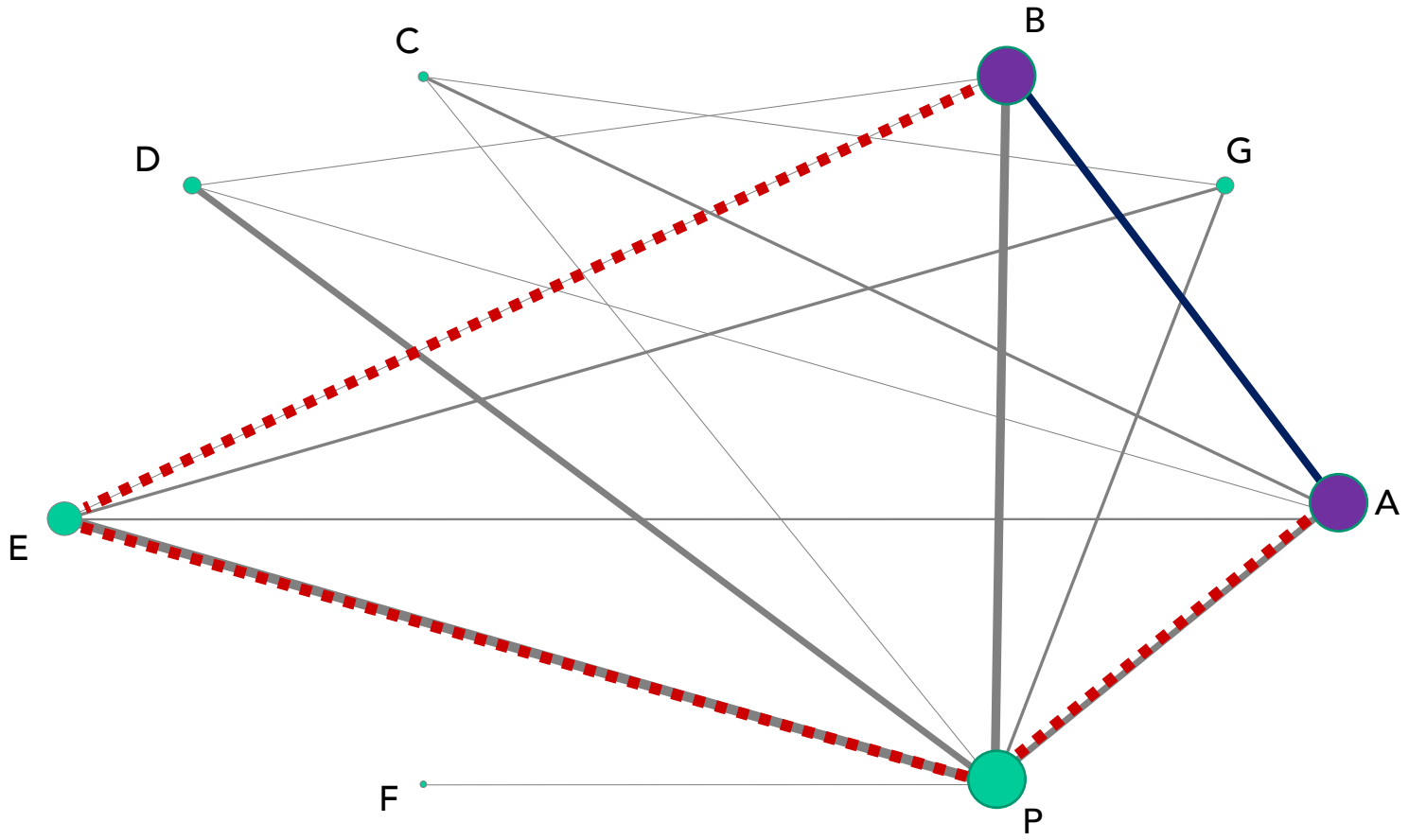

Full network of interventions

which are the most appropriate treatments to recommend,
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Agom	0·72 (0·55 to 0·92)	0·80 (0·54 to 1·15)	0·89 (0·66 to 1·19)	0·57 (0·42 to 0·77)	0·62 (0·47 to 0·82)	0·97 (0·74 to 1·27)	0·85 (0·68 to 1·05)	0·69 (0·51 to 0·97)	0·79 (0·58 to 1·09)	0·81 (0·61 to 1·05)	0·70 (0·44 to 1·14)	0·81 (0·65 to 1·00)	0·53 (0·36 to 0·80)	0·86 (0·66 to 1·13)	0·69 (0·48 to 0·98)	0·74 (0·58 to 0·92)	1·24 (0·71 to 2·19)
0·96 (0·76 to 1·24)	**Amit**	1·10 (0·78 to 1·58)	1·23 (0·94 to 1·64)	0·79 (0·60 to 1·05)	0·87 (0·66 to 1·15)	1·35 (1·05 to 1·74)	1·18 (0·99 to 1·42)	0·97 (0·74 to 1·24)	1·10 (0·84 to 1·45)	1·12 (0·89 to 1·42)	0·98 (0·62 to 1·55)	1·12 (0·95 to 1·34)	0·74 (0·51 to 1·10)	1·20 (0·97 to 1·47)	0·96 (0·70 to 1·31)	1·02 (0·83 to 1·26)	1·72 (1·00 to 3·05)
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1·13 (0·88 to 1·47)	1·18 (0·93 to 1·49)	1·30 (0·88 to 1·93)	**Cita**	0·64 (0·47 to 0·87)	0·70 (0·51 to 0·95)	1·09 (0·85 to 1·42)	0·96 (0·76 to 1·21)	0·78 (0·57 to 1·06)	0·89 (0·64 to 1·23)	0·91 (0·68 to 1·21)	0·79 (0·49 to 1·32)	0·91 (0·71 to 1·17)	0·60 (0·41 to 0·87)	0·97 (0·74 to 1·25)	0·77 (0·53 to 1·13)	0·83 (0·64 to 1·07)	1·40 (0·78 to 2·48)
1·20 (0·91 to 1·59)	1·24 (0·98 to 1·58)	1·37 (0·93 to 2·04)	1·06 (0·82 to 1·38)	**Clom**	1·10 (0·80 to 1·51)	1·71 (1·27 to 2·29)	1·49 (1·16 to 1·90)	1·22 (0·88 to 1·67)	1·40 (1·00 to 1·92)	1·41 (1·05 to 1·91)	1·24 (0·76 to 2·00)	1·42 (1·12 to 1·79)	0·94 (0·62 to 1·41)	1·51 (1·15 to 1·96)	1·21 (0·83 to 1·73)	1·29 (0·99 to 1·67)	2·20 (1·22 to 3·90)
1·06 (0·82 to 1·37)	1·10 (0·84 to 1·42)	1·21 (0·81 to 1·81)	0·93 (0·71 to 1·22)	0·88 (0·66 to 1·18)	**Dulo**	1·56 (1·19 to 2·01)	1·37 (1·06 to 1·73)	1·12 (0·80 to 1·53)	1·28 (0·91 to 1·75)	1·30 (0·96 to 1·72)	1·13 (0·69 to 1·83)	1·30 (1·02 to 1·63)	0·86 (0·57 to 1·29)	1·38 (1·04 to 1·80)	1·10 (0·76 to 1·59)	1·18 (0·92 to 1·49)	1·99 (1·13 to 3·52)
0·90 (0·71 to 1·14)	0·93 (0·74 to 1·17)	1·03 (0·70 to 1·51)	0·79 (0·65 to 0·97)	0·75 (0·58 to 0·97)	0·85 (0·67 to 1·08)	**Esci**	0·87 (0·70 to 1·09)	0·71 (0·53 to 0·96)	0·81 (0·60 to 1·11)	0·83 (0·63 to 1·08)	0·72 (0·45 to 1·18)	0·83 (0·67 to 1·03)	0·55 (0·37 to 0·81)	0·88 (0·69 to 1·12)	0·70 (0·49 to 1·00)	0·75 (0·60 to 0·94)	1·27 (0·73 to 2·25)
1·20 (0·99 to 1·48)	1·25 (1·06 to 1·48)	1·38 (0·97 to 1·97)	1·06 (0·87 to 1·29)	1·00 (0·81 to 1·24)	1·14 (0·91 to 1·44)	1·34 (1·12 to 1·61)	**Fluo**	0·82 (0·64 to 1·04)	0·94 (0·72 to 1·20)	0·95 (0·77 to 1·16)	0·83 (0·54 to 1·30)	0·95 (0·83 to 1·09)	0·63 (0·44 to 0·90)	1·01 (0·84 to 1·21)	0·81 (0·60 to 1·09)	0·87 (0·74 to 1·01)	1·46 (0·85 to 2·53)
1·20 (0·91 to 1·61)	1·25 (0·99 to 1·59)	1·38 (0·93 to 2·07)	1·06 (0·82 to 1·39)	1·00 (0·76 to 1·32)	1·14 (0·85 to 1·54)	1·34 (1·03 to 1·75)	1·00 (0·80 to 1·25)	**Fluv**	1·14 (0·84 to 1·56)	1·16 (0·89 to 1·52)	1·01 (0·62 to 1·71)	1·16 (0·90 to 1·49)	0·77 (0·51 to 1·17)	1·23 (0·94 to 1·63)	0·99 (0·69 to 1·42)	1·06 (0·80 to 1·38)	1·78 (1·00 to 3·24)
1·07 (0·80 to 1·44)	1·11 (0·86 to 1·43)	1·23 (0·81 to 1·85)	0·94 (0·71 to 1·26)	0·89 (0·67 to 1·19)	1·01 (0·74 to 1·38)	1·19 (0·90 to 1·58)	0·89 (0·70 to 1·13)	0·89 (0·67 to 1·17)	**Miln**	1·02 (0·75 to 1·37)	0·88 (0·54 to 1·44)	1·02 (0·80 to 1·31)	0·67 (0·45 to 1·03)	1·08 (0·82 to 1·44)	0·86 (0·60 to 1·25)	0·93 (0·71 to 1·22)	1·56 (0·89 to 2·84)
0·93 (0·72 to 1·21)	0·97 (0·77 to 1·21)	1·07 (0·73 to 1·57)	0·82 (0·65 to 1·05)	0·78 (0·60 to 1·01)	0·88 (0·67 to 1·16)	1·04 (0·82 to 1·32)	0·78 (0·64 to 0·94)	0·78 (0·60 to 0·99)	0·87 (0·66 to 1·15)	**Mirt**	0·87 (0·55 to 1·41)	1·00 (0·82 to 1·23)	0·66 (0·45 to 0·99)	1·06 (0·84 to 1·35)	0·85 (0·62 to 1·18)	0·91 (0·73 to 1·13)	1·53 (0·89 to 2·72)
1·15 (0·76 to 1·76)	1·19 (0·80 to 1·78)	1·32 (0·80 to 2·20)	1·01 (0·67 to 1·54)	0·96 (0·63 to 1·45)	1·09 (0·71 to 1·68)	1·28 (0·86 to 1·94)	0·96 (0·66 to 1·40)	0·95 (0·63 to 1·46)	1·07 (0·70 to 1·67)	1·23 (0·82 to 1·86)	**Nefa**	1·15 (0·74 to 1·78)	0·75 (0·43 to 1·32)	1·23 (0·77 to 1·90)	0·98 (0·57 to 1·64)	1·04 (0·66 to 1·65)	1·76 (0·90 to 3·56)
1·01 (0·82 to 1·24)	1·05 (0·89 to 1·23)	1·16 (0·81 to 1·64)	0·89 (0·72 to 1·09)	0·84 (0·68 to 1·03)	0·96 (0·76 to 1·19)	1·12 (0·93 to 1·35)	0·84 (0·73 to 0·95)	0·84 (0·67 to 1·04)	0·94 (0·75 to 1·18)	1·08 (0·89 to 1·30)	0·88 (0·60 to 1·27)	**Paro**	0·66 (0·46 to 0·94)	1·06 (0·88 to 1·28)	0·85 (0·63 to 1·15)	0·91 (0·77 to 1·07)	1·53 (0·90 to 2·66)
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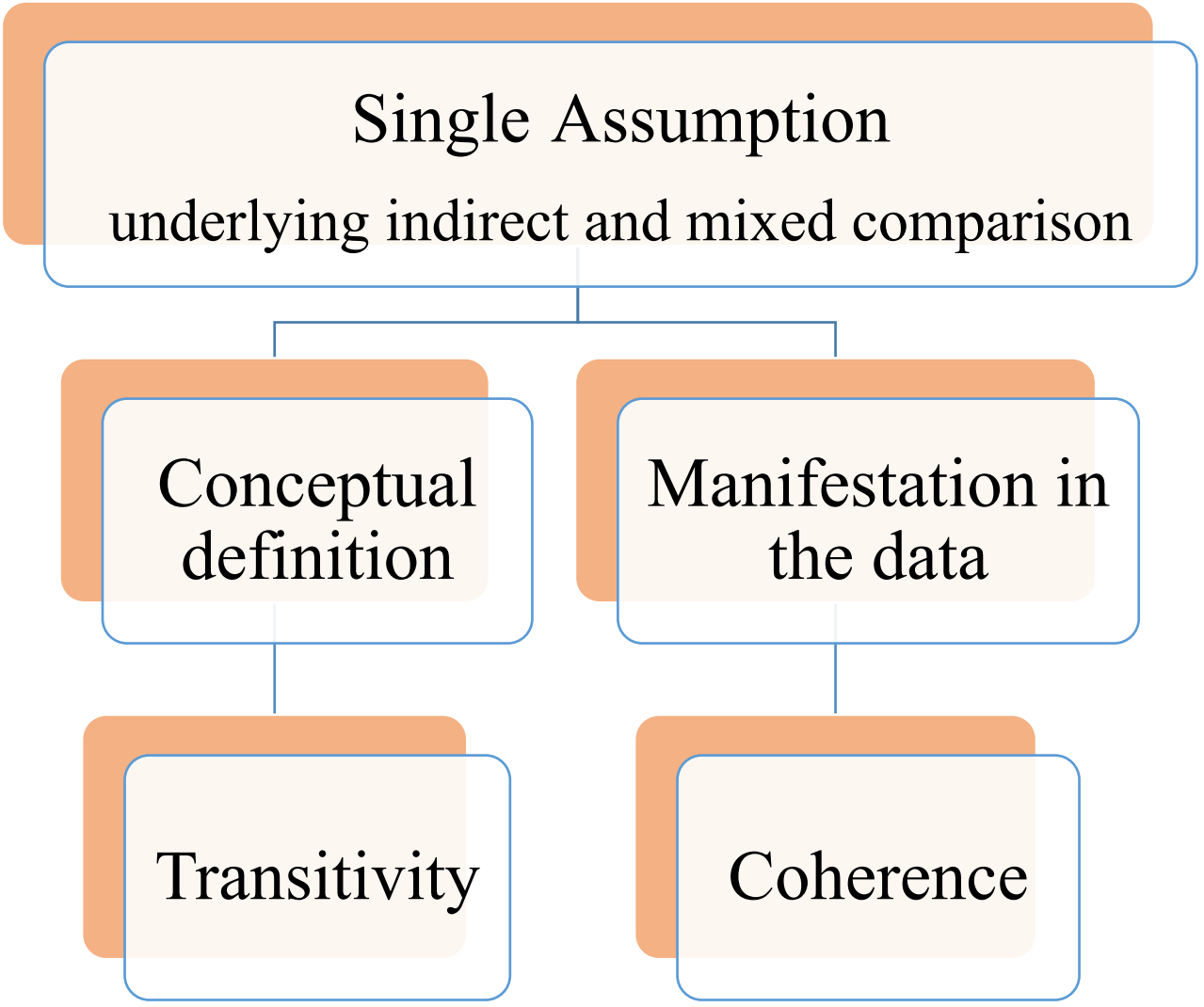
0·73 (0·42 to 1·26)	0·76 (0·44 to 1·29)	0·83 (0·45 to 1·54)	0·64 (0·37 to 1·11)	0·61 (0·35 to 1·05)	0·69 (0·40 to 1·20)	0·81 (0·47 to 1·39)	0·60 (0·36 to 1·02)	0·60 (0·34 to 1·05)	0·68 (0·39 to 1·20)	0·78 (0·45 to 1·34)	0·63 (0·33 to 1·19)	0·72 (0·43 to 1·22)	0·51 (0·28 to 0·92)	0·68 (0·39 to 1·16)	0·54 (0·30 to 0·95)	0·72 (0·43 to 1·19)	**Vort**

Assumptions underlying network meta-analysis



Assumptions underlying network meta-analysis

In the outset	When you find the studies	When you extract the outcomes
The treatments we compare are *in principle* jointly randomizable	The groups of studies that compare them do not differ with respect to the distribution of effect modifiers	Direct and indirect treatment effects are in statistical agreement
They have the same indication, I can imagine a mega-trial with all treatments being compared etc	**You can test this assumption if you have enough studies per comparison**	**Various statistical tests**

Example of a living network meta-analysis

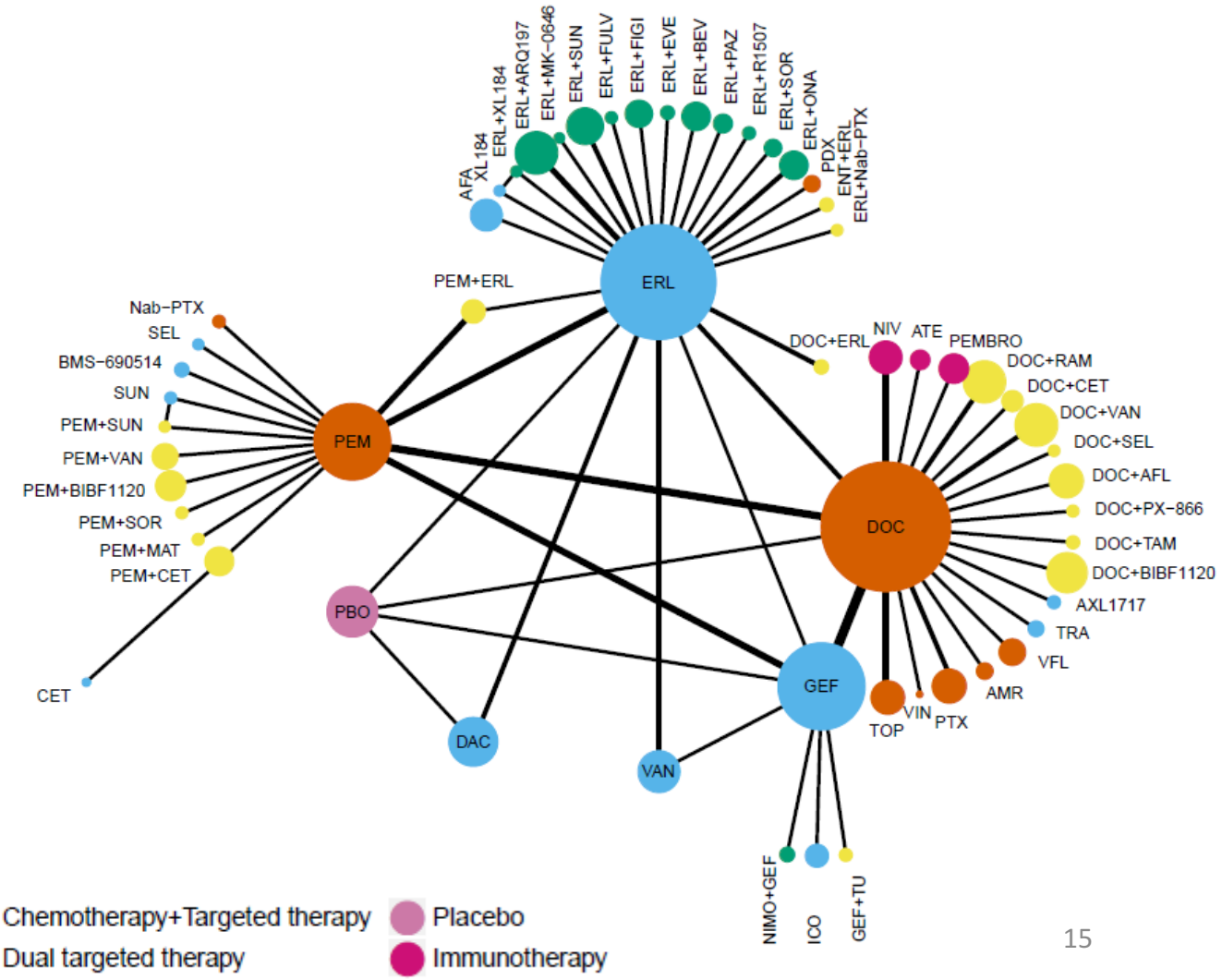
2nd line treatments of advanced non-small cell lung cancer

Treatments (n=58)

Trials (n =92)

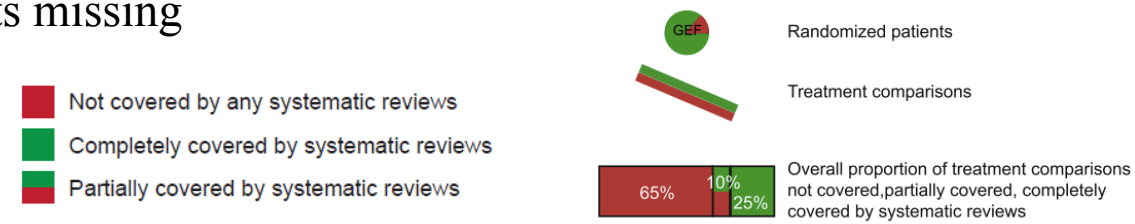
Patients (n=32 434)

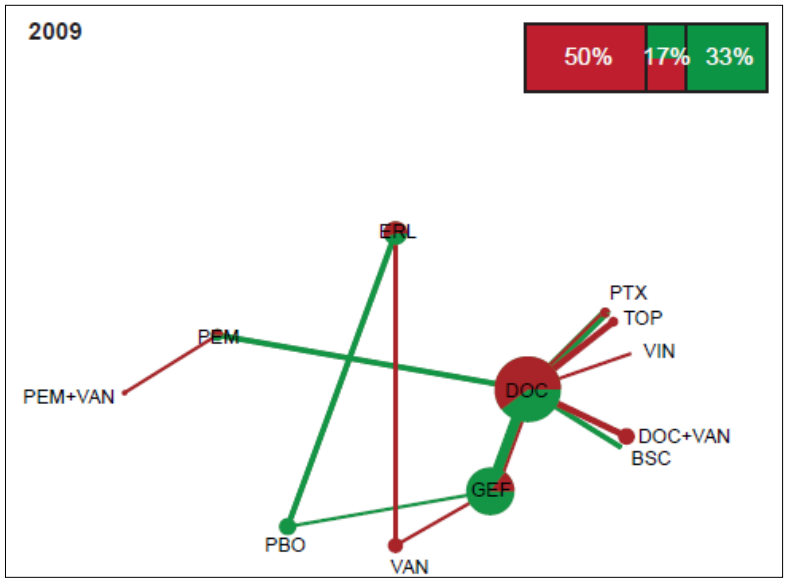
29 Systematic reviews

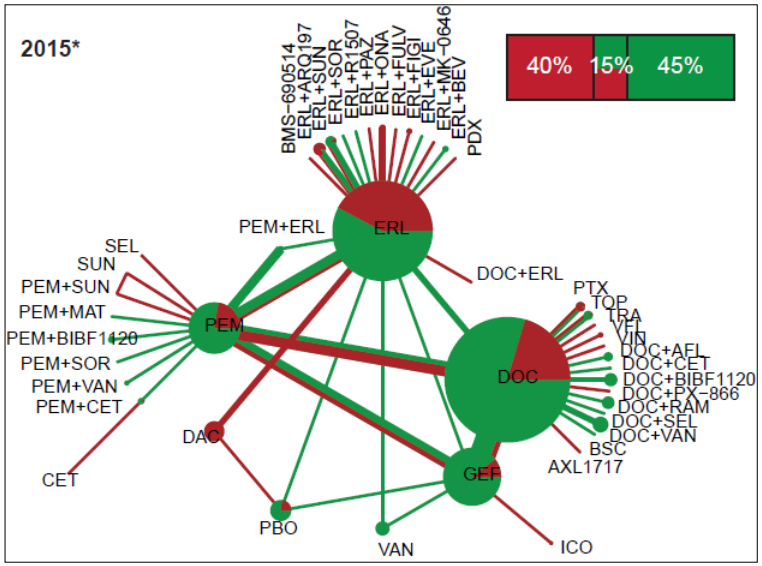


2nd line treatments of advanced non-small cell lung cancer

- Each year, between 2009 and 2015, the evidence covered by all existing systematic reviews was consistently incomplete
  - 40% to 66% of treatments missing
  - 45% to 70% of trials missing.
  - 30% to 58% of patients missing

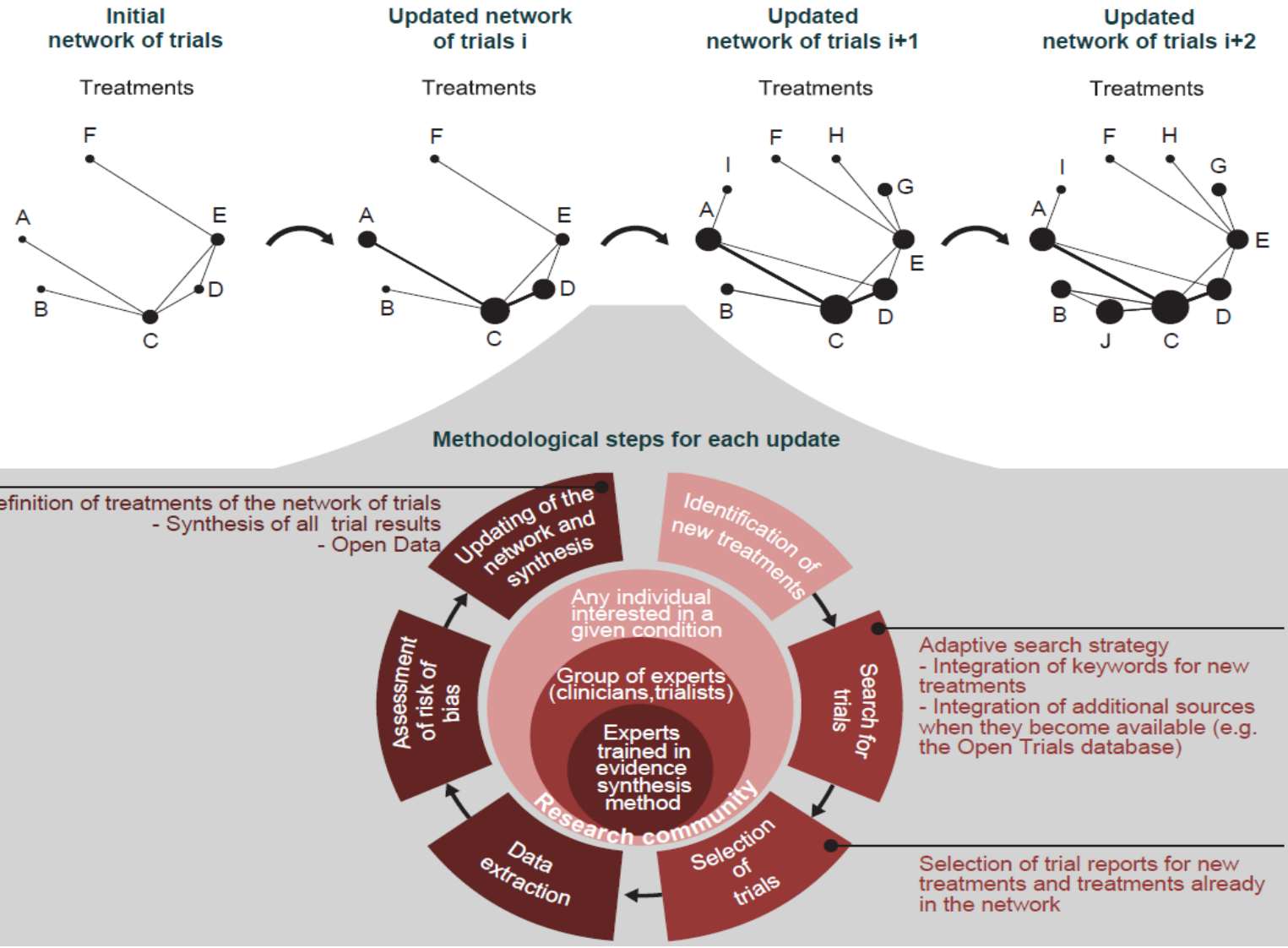




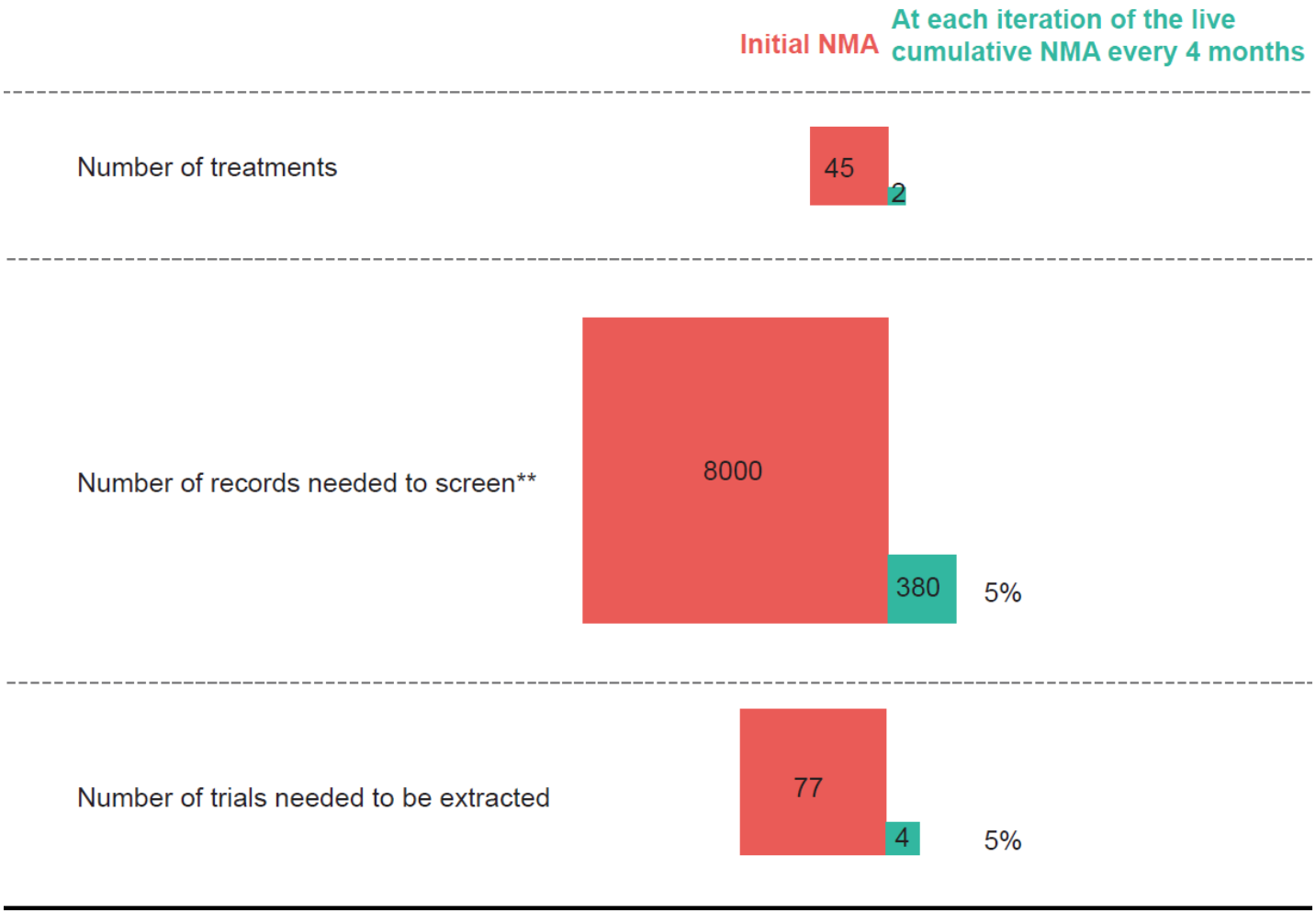


Challenges in the process of living network meta-analyses

The concept of living network meta-analysis



Work-load for the NSCLC example

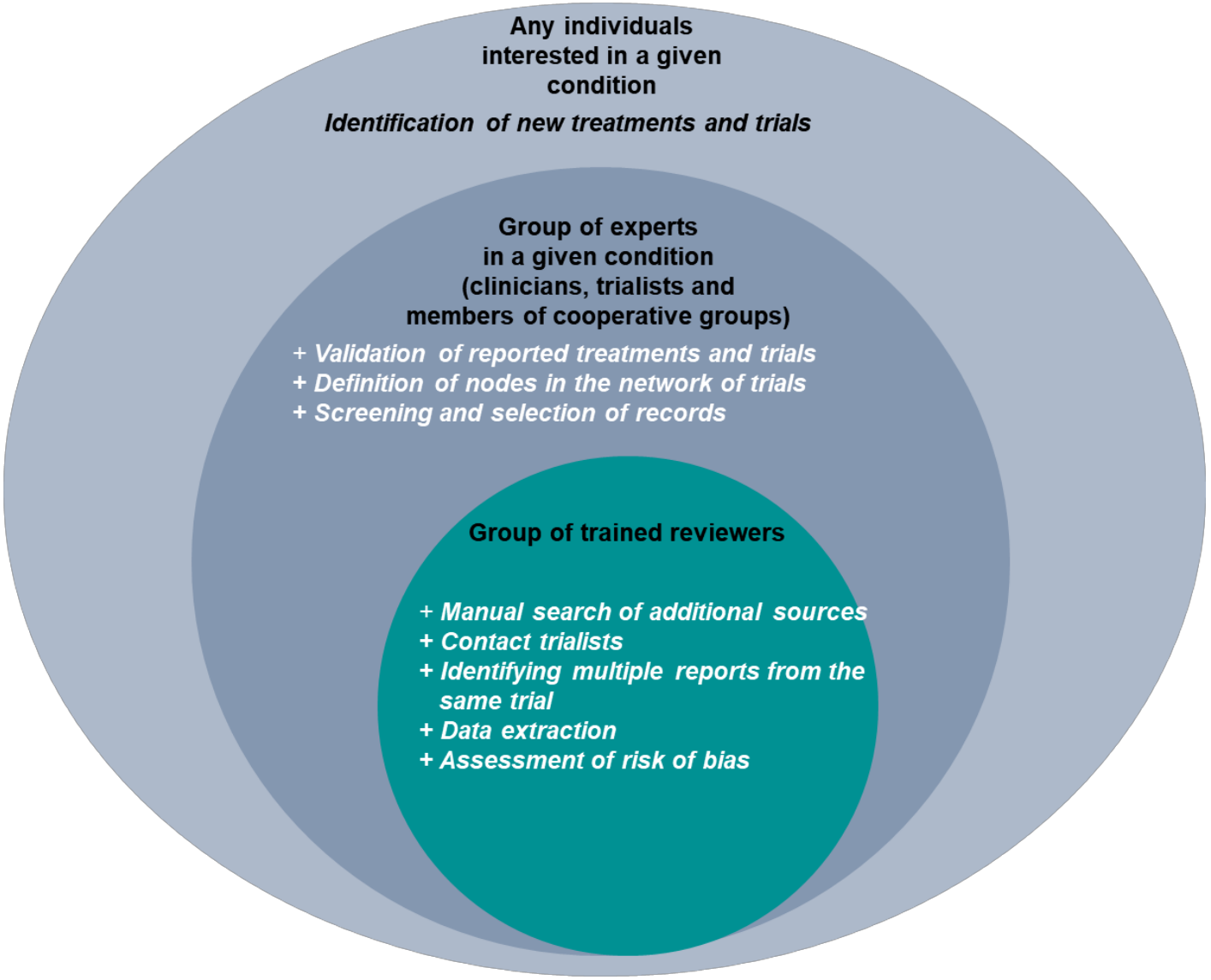


→ Investing a massive amount of resources to produce a NMA and not maintaining it afterwards does not make sense

Issues with updating network meta-analyses

- The initial research question might become outdated over time
- Adding new treatments might threaten the validity of the NMA assumptions
  - treatments evaluated only in one trial and connected weakly to the network often introduce heterogeneity and incoherence
- How to exploit any type of information within the NMA framework
- How useful are in the network old treatments evaluated in possibly low-quality studies?

Building a research community

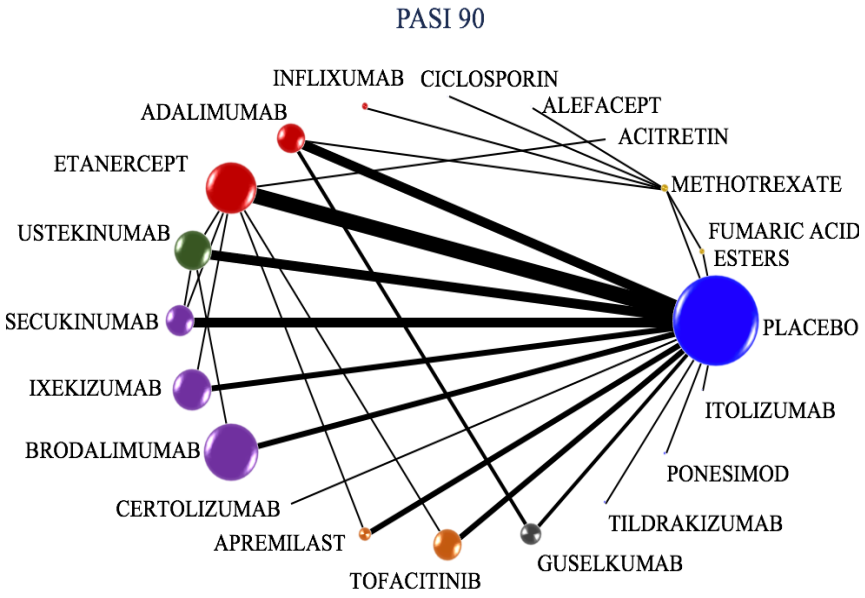


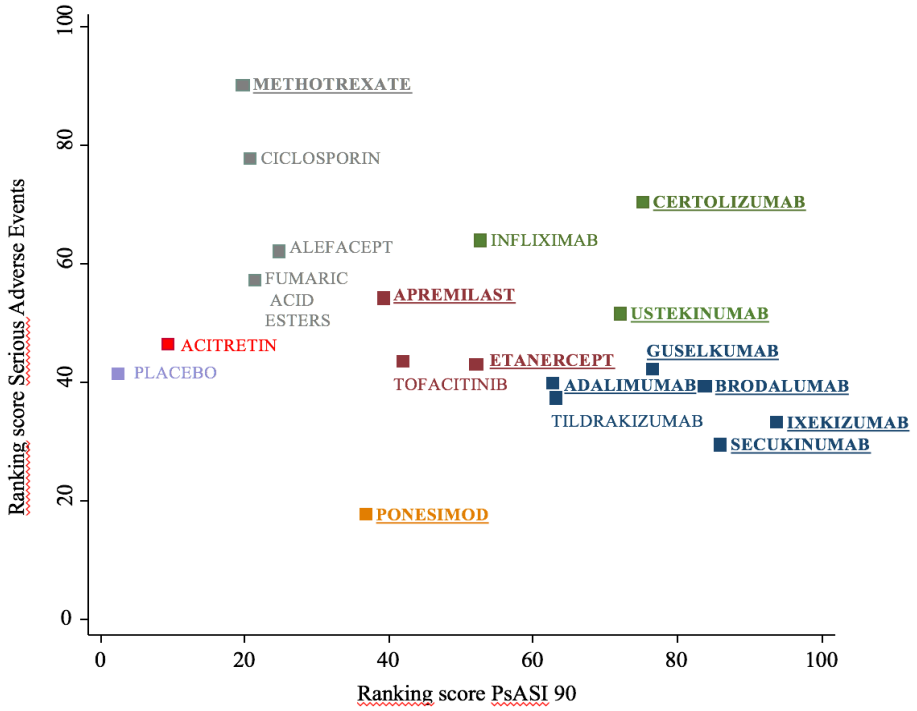
Building a research community

- Developing **a living community for one condition**
- A community including systematic reviewers but also clinicians, patients, trialists, methodologists, statisticians and guidelines experts
- Leveraging this community to improve beyond evidence synthesis the whole production of evidence

Future work on LNMAs

Treatments for chronic plaque psoriasis





Methodological work

- Development of formal statistical and non-statistical criteria upon the inclusion and exclusion of treatments at each iteration
  - trade-off between increasing the amount of data and threating the assumptions of the analysis
- Development of methods allowing to share information across networks and to incorporate information from external evidence
  - networks with sparse data often fail to provide useful and meaningful results
- How new evidence can affect the results
  - can results change?

http://livenetworkmetaanalysis.com

Live cumulative network meta-analysis

Home What? Why? How? When? Contribute About

We need a comprehensive, up-to-date synthesis of evidence for all treatments available for a given disease

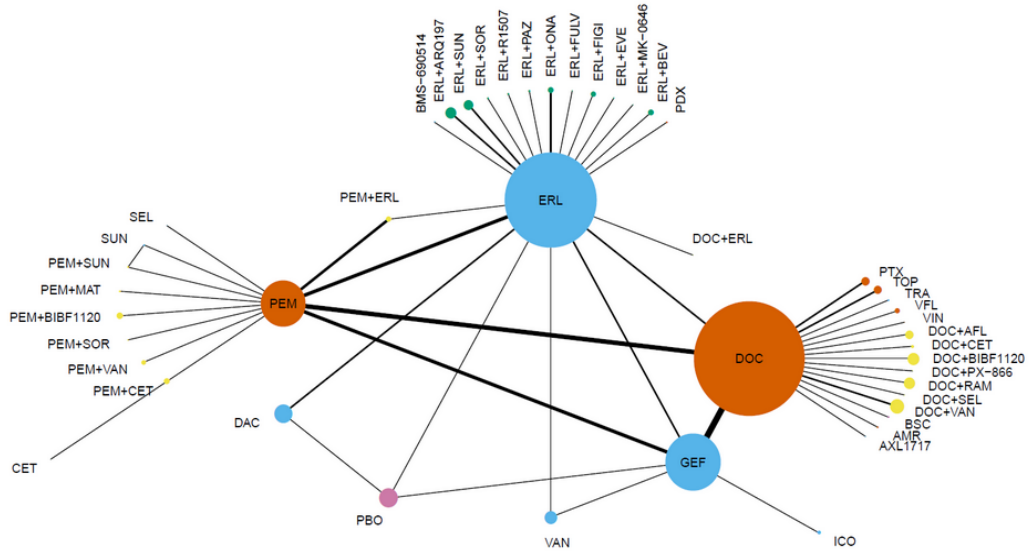
For many conditions, multiple competing treatments are available, many of which have been assessed in randomized trials. Clinicians and patients who are making medical decisions need to know which treatments work best among all treatments available for the condition of interest. They increasingly use meta-analyses that synthesize the results of randomized trials to inform the relative efficacy and safety of the different treatments.

But conventional meta-analyses do not provide an exhaustive up-to-date synthesis of all available treatments, and thus prevent from answering easily to the real questions of interest.

We propose to switch:

- from a series of conventional meta-analyses focusing on specific treatments (many treatments being not considered), performed at a given time and frequently out-of-date
- to a single systematic review and evidence synthesis (with meta-analyses and network meta-analyses) covering all treatments and systematically updated when new trial results become available

We call this approach "live cumulative network meta-analysis".



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Planning for a Living Network
Meta-Analysis of Treatments for Rheumatoid Arthritis

Dr. Glen Hazlewood & Dr Samuel Whittle
March 2019

Rationale

- RA is common, and causes pain, disability and reduced quality of life
- Disease-modifying drugs (DMARDs) are effective in reducing symptoms and signs of RA and improve long-term outcomes
- In recent years, novel DMARDs (bDMARDs & tsDMARDs) have joined older drugs (csDMARDs) as potential therapies for individuals with RA
- There are now multiple therapeutic options, with varying effects on important outcomes, and different adverse effect profiles
- New drugs continue to emerge

Rationale

- The array of treatment options makes NMA an attractive option
- A living approach to evidence synthesis is important in RA:
    - High burden of disease
    - Rapidly-evolving evidence base
    - Up-to-date synthesis of all available therapies is important for shared decision-making in this chronic disease
- Opportunity to develop living treatment guidelines

Existing NMA

Cochrane Library

Cochrane Database of Systematic Reviews

Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis: A network meta-analysis (Review)

Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe DJA, Bombardier C

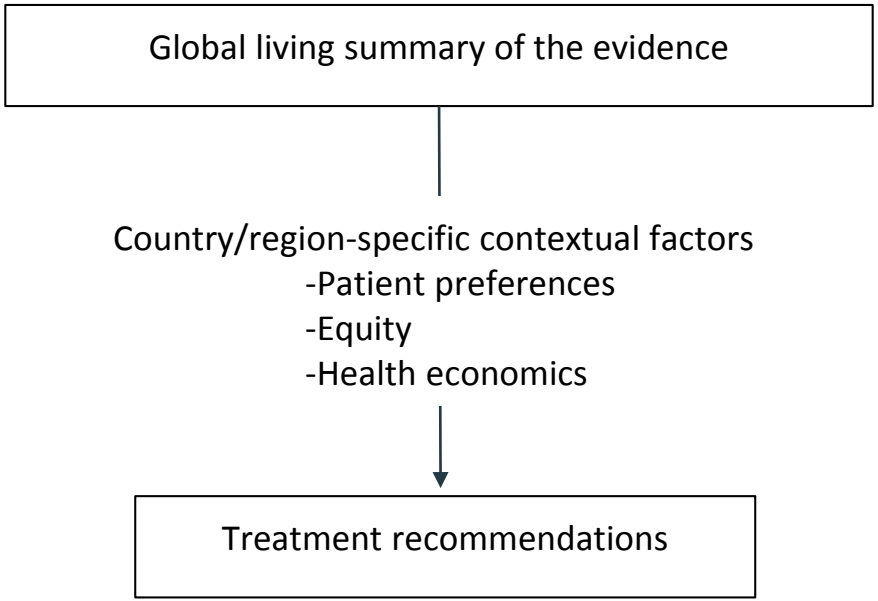
Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe DJA, Bombardier C.
Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis: A network meta-analysis.
Cochrane Database of Systematic Reviews 2016, Issue 8. Art. No.: CD010227.
DOI: 10.1002/14651858.CD010227.pub2.

www.cochranelibrary.com

Living Guidelines Project in Rheumatoid Arthritis

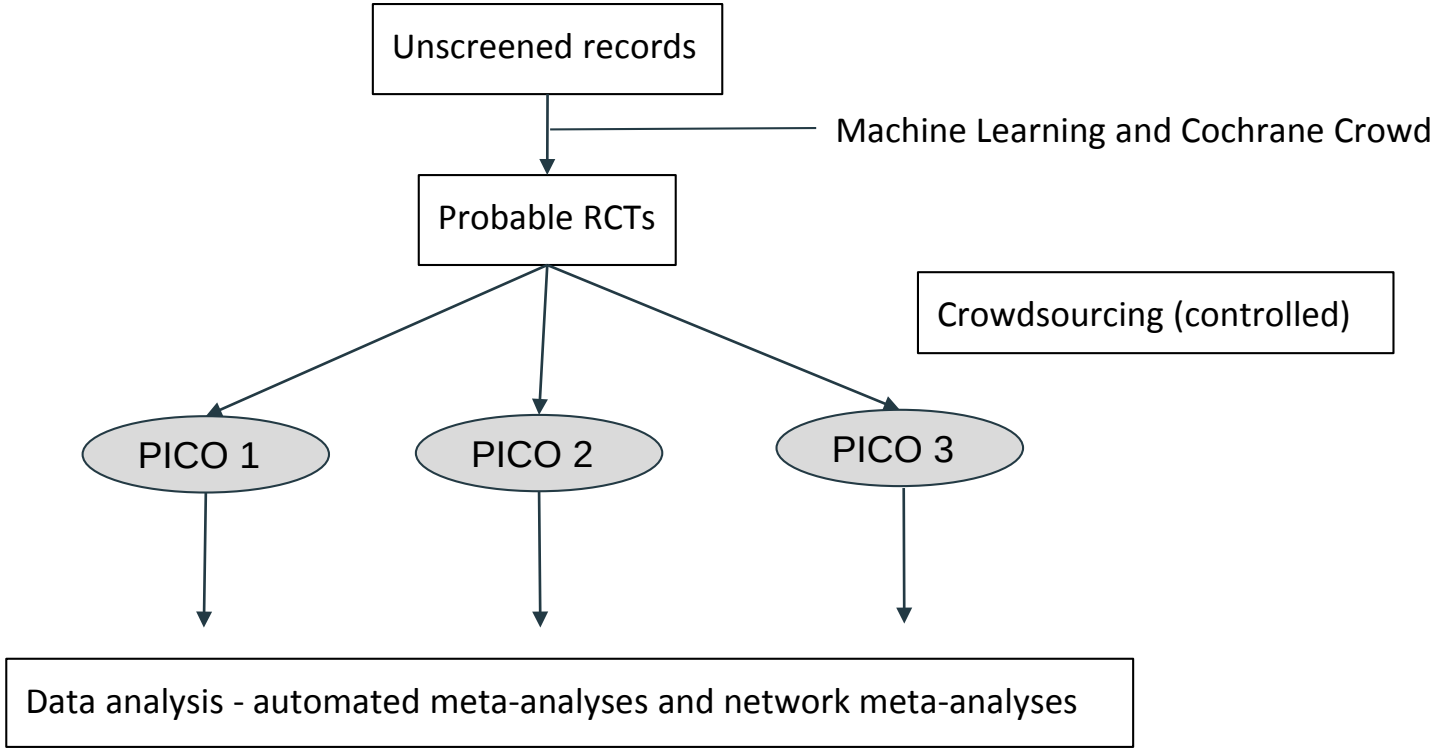
- Collaborative approach to ongoing evidence reviews: CRA, Cochrane, Australia & NZ (ANZMUSC), ACR
- Each group makes their own recommendations
- Opportunity to add other collaborators as project evolves

Globalizing the evidence, localizing the decision



Planned methods

- RCTs, adults with RA, any DMARD, outcomes under discussion
- **PICO sorting –** 3 groups (MTX-naive, MTX-IR, bDMARD-IR)
- Covidence for PICO annotation, data extraction, RoB assessment
- Data synthesis: Random-effect Bayesian network meta-analysis
- Node-splitting analysis for consistency; meta-regression for heterogeneity


Unscreened records
Machine Learning and Cochrane Crowd
Probable RCTs
Crowdsourcing (controlled)
PICO 1
PICO 2
PICO 3
Data analysis - automated meta-analyses and network meta-analyses

Question 1: It is an RCT?

↓

Question 2: Is the population adults with rheumatoid arthritis?

↓

Question 3: Is the intervention a DMARD? - - - → RCTs of non-DMARDs (future classification)

↓

Question 4: Are corticosteroids/glucocorticoids being used as part of the intervention?

↓

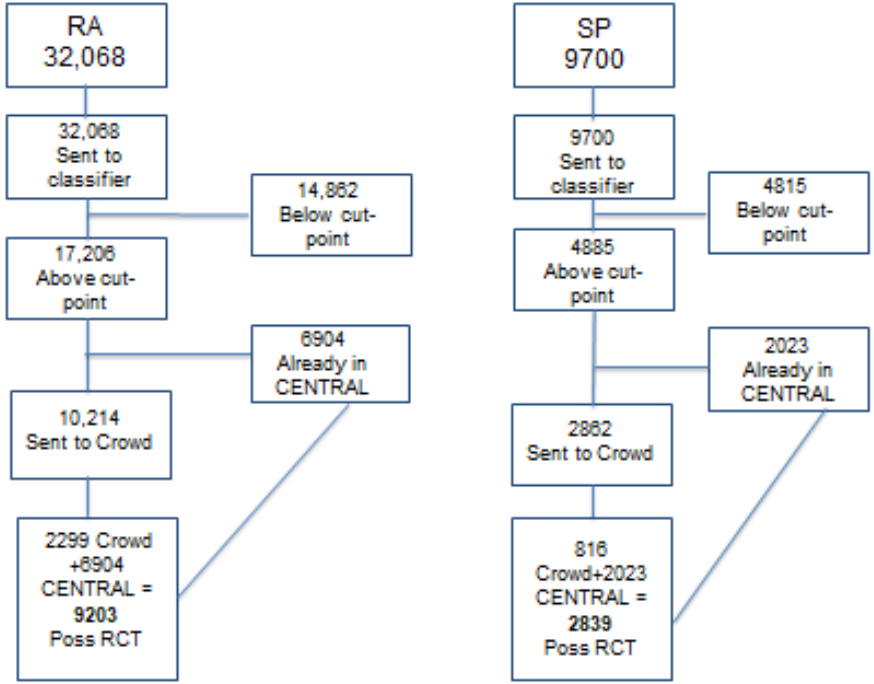
Question 5: Is reduction of treatment the randomized intervention?

↓

Question 6: What type of population is included?
1) DMARD naïve/minimally exposed;
2) DMARD inadequate response;
3) Biologics inadequate response;
4) Mixed populations;
5) Unclear from abstract

PICO sorting

PICO Annotation



Initial Search Results

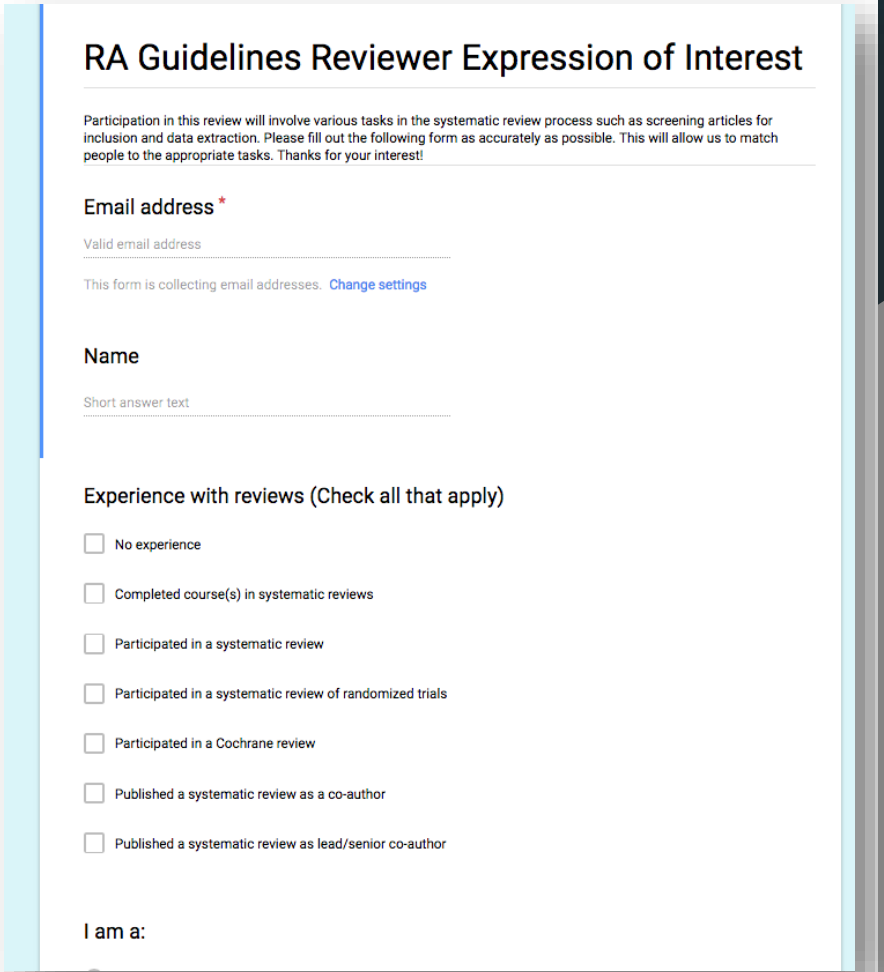
Covidence Data Extraction Forms

Characteristic	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	Arm 7	Arm 8	Arm 9	Arm 10	Overall
Age	50.9	52.5	48.9								50.9
Female	0.78	0.84	0.76								0.79
Disease duration, years (mean/median)	7.9	5.8	6.9								6.9
Proportion RF	0.88	0.88	0.89								0.88
Proportion prior MTX											
Proportion prior DMARD including MTX											
Number of prior DMARDs including MTX											
Proportion prior TNF											
Proportion prior non-TNF biologic											
Proportion taking MTX during study											
Dose MTX target											
Dose MTX min											
Dose MTX max											
Mean MTX dose											

Training

- Canadian and Australian early career rheumatologists and trainees
- Initial e-mail expression of interest

- Incentives:
  - Learning
  - Listed as collaborator/author
  - Individual thank-you letter of contribution?



RA Guidelines Reviewer Expression of Interest

Participation in this review will involve various tasks in the systematic review process such as screening articles for inclusion and data extraction. Please fill out the following form as accurately as possible. This will allow us to match people to the appropriate tasks. Thanks for your interest!

Email address *

Valid email address

This form is collecting email addresses. Change settings

Name

Short answer text

Experience with reviews (Check all that apply)

- [ ] No experience
- [ ] Completed course(s) in systematic reviews
- [ ] Participated in a systematic review
- [ ] Participated in a systematic review of randomized trials
- [ ] Participated in a Cochrane review
- [ ] Published a systematic review as a co-author
- [ ] Published a systematic review as lead/senior co-author

I am a:

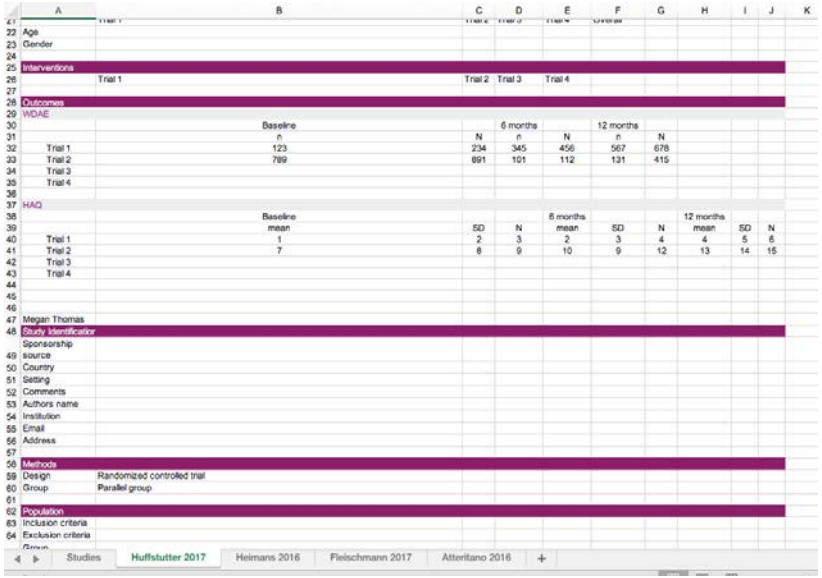
Cochrane classmate

Classmate enables you to use the Cochrane Crowd tasks as learning activities

Automating the analyses

- Planned project for PhD student (Kamso Mujaab)
- Goal: Take the data in covidence and automate the NMA analyses in R, including:
  - Main results
  - All data necessary to inform the quality of evidence ratings (GRADE), including inconsistency testing
  - Formatting into a summary of findings table

Auto-generation of SoF tables

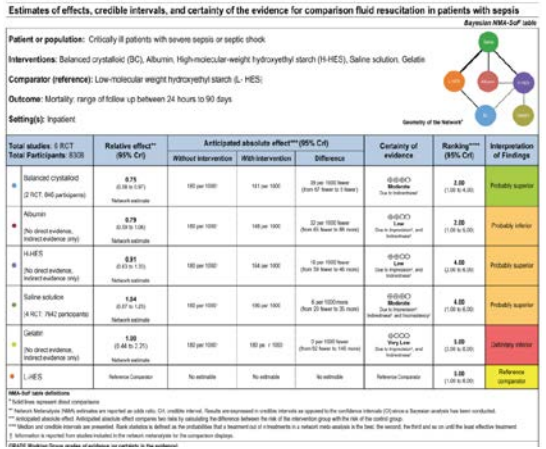


	A	B	C	D	E	F	G	H	I	J	K
22	Age										
23	Gender										
24											
25	Interventions										
26		Trial 1	Trial 2	Trial 3	Trial 4						
27											
28	Outcomes										
29	WDAE										
30		Baseline			6 months		12 months				
31		n	N		n	N	n	N			
32	Trial 1	123	234		345	456	567	678			
33	Trial 2	789	891		101	112	131	415			
34	Trial 3										
35	Trial 4										
36											
37	HAQ										
38		Baseline			6 months		12 months				
39		mean	SD	N	mean	SD	N	mean	SD	N	
40	Trial 1	1	2	3	2	3	4	4	5	6	
41	Trial 2	7	8	9	10	9	12	13	14	15	
42	Trial 3										
43	Trial 4										
44											
45											
46											
47	Megan Thomas										
48	Study Identification										
49	Sponsorship source										
50	Country										
51	Setting										
52	Comments										
53	Authors name										
54	Institution										
55	Email										
56	Address										
57											
58	Methods										
59	Design	Randomized controlled trial									
60	Group	Parallel group									
61											
62	Population										
63	Inclusion criteria										
64	Exclusion criteria										

Studies | Huffstutter 2017 | Heimans 2016 | Fleischmann 2017 | Atteritano 2016 | +

Extracted data

NMA-SoF table example 1



Estimates of effects, credible intervals, and certainty of the evidence for comparison fluid resuscitation in patients with sepsis

Bayesian NMA-SoF table

Patient or population: Critically ill patients with severe sepsis or septic shock

Interventions: Balanced crystalloid (BC), Albumin, High-molecular-weight hydroxyethyl starch (H-HES), Saline solution, Gelatin

Comparator (reference): Low-molecular weight hydroxyethyl starch (L- HES)

Outcome: Mortality: range of follow up between 24 hours to 90 days

Setting(s): Inpatient

Geometry of the Network*

Total studies: 6 RCT Total Participants: 8308	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI)			Certainty of evidence	Ranking**** (95% CrI)	Interpretation of Findings
		Without intervention	With intervention	Difference			
Balanced crystalloid (2 RCT, 846 participants)	0.75 (0.58 to 0.97) Network estimate	180 per 1000	161 per 1000	39 per 1000 fewer (from 67 fewer to 5 fewer)	⊕⊕⊕○ Moderate Due to indirectness†	2.00 (1.00 to 4.00)	Probably superior
Albumin (No direct evidence, indirect evidence only)	0.79 (0.59 to 1.06) Network estimate	180 per 1000	148 per 1000	32 per 1000 fewer (from 65 fewer to 86 more)	⊕⊕○○ Low Due to imprecision†, and indirectness†	2.00 (1.00 to 5.00)	Probably inferior
H-HES (No direct evidence, indirect evidence only)	0.91 (0.63 to 1.33) Network estimate	180 per 1000	154 per 1000	16 per 1000 fewer (from 59 fewer to 46 more)	⊕⊕○○ Low Due to imprecision†, and indirectness†	4.00 (2.00 to 6.00)	Probably superior
Saline solution (4 RCT, 7942 participants)	1.04 (0.87 to 1.25) Network estimate	180 per 1000	186 per 1000	8 per 1000 more (from 23 fewer to 45 more)	⊕⊕⊕○ Moderate Due to imprecision† Indirectness† and Inconsistency‡	4.00 (1.00 to 6.00)	Probably superior
Gelatin (No direct evidence, indirect evidence only)	1.00 (0.48 to 2.21) Network estimate	180 per 1000	180 per 1000	0 per 1000 fewer (from 92 fewer to 145 more)	⊕○○○ Very Low Due to imprecision†, and Indirectness†	3.00 (1.00 to 6.00)	Definitely inferior
L-HES	Reference Comparator	No estimable	No estimable	No estimable	Reference Comparator	3.00 (1.00 to 6.00)	Reference comparator

NMA-SoF table definitions

* Solid lines represent direct comparisons

** Network Metanalysis: NMA estimates are reported as odds ratio, CrI, credible interval. Results are expressed in credible intervals as opposed to the confidence intervals (CI) since a Bayesian analysis has been conducted.

*** Anticipated absolute effect: Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

**** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of n treatments is a network meta-analysis is the best, the second, the third and so on until the least effective treatment

† Information is reported from studies included in the network metanalysis for the comparison displays.

GRADE Working Group grades of evidence on certainty in the estimate

GRADE Summary of findings table

Auto-generation of analyses necessary to inform GRADE quality appraisal

- Rating the quality of evidence requires human judgements, but these can be facilitated by automated data summaries for the relevant GRADE domains, and even algorithms to provide 'expected' judgements based on set criteria

Appendix D – GRADE Quality Appraisal

Table D1. Treatment effects for direct, indirect and network meta-analysis evidence and GRADE quality appraisal

		DIRECT EVIDENCE								INDIRECT EVIDENCE			NETWORK META-ANALYSIS	
Intervention	Comparator	Number of trials for direct comparison	Treatment effect (95 % CrI)	Quality of Evidence						Treatment effect (95 % CrI)	P (indirect -direct)	Quality of evidence	Treatment effect (95 % CrI)	Quality of evidence
				Risk of bias	Inconsistency	Indirectness	Imprecision	Publicati on bias	OVERALL					
MTX-naïve: ACR50 response			OR							OR			OR	
MTX+ABAT (IV)	MTX	1	1.83 (1.29 to 2.61)						High	NE			1.84 (1.01 to 3.42)	High
MTX+ABAT (sc)	MTX	1	1.94 (1.15 to 3.29)						High	NE			1.98 (0.94 to 3.97)	High
MTX+ADA	MTX	4	2.11 (1.76 to 2.51)						High	NE			2.10 (1.52 to 2.87)	High
IM/sc MTX+ADA	MTX	0	NA							2.22 (0.80 to 6.06)		Moderate (imprecision)	2.22 (0.80 to 6.06)	Moderate (imprecision)
MTX+CTZ	MTX	1	1.49 (1.10 to 2.04)	Single study with high amount of incomplete outcome data (C-EARLY)					Moderate (study limitations)	NE			1.49 (0.83 to 2.68)	Moderate (study limitations)
MTX+ETN	MTX	2	2.76 (1.74 to 4.40)						High	3.87 (0.62 to 27.37)	0.72	Low (extreme imprecision)	3.00 (2.02 to 4.59)	High

Challenges & Consideratons

- How do we create methods for surveillance for new drugs (eg experimental or novel therapies with names that do not appear in our original search strategy)?
- How do we handle the situation in which a new trial might mean that a trial that was previously excluded due to lack of an indirect evidence link, is now eligible due to a common comparator? Is this a matter of classifying exclusions in a particular way so that they can be easily searched again when the network changes, or some other way?
- What is the best method for balancing machine and human tasks once we enter living mode: ie can we use the data from our Crowd tasks to train machine automation tools for ongoing tasks in the future? How would this look in practice?
- What is the best method for screening new citations when in living mode: manual vs automation (if plans to use trained Crowd, how to ensure durability of participation and acquired skills)? Are there certain tasks that are likely to be better suited to humans vs machines?

Challenges & Consideratons

- How to ensure that we maintain a durable workforce with sufficient expertise to continue the review in living mode, assuming that it may remain in this mode for years?
- What areas specific to LNMAs are amenable to automation?
- Need for *a priori* decisions on when to incorporate new evidence, when to re-publish (eg if change in major outcome or a threshold for new interventions), search frequency & when to take out of living mode; also, the frequency of updating of the review scope and methods (eg search terms, eligibility criteria)
- Where to host our data to 'future proof' the current work and prevent the need for duplication of work in the future (eg is Covidence the best data repository?); including clear rules for 'ownership' of the data and access as the work evolves

The team

- Cochrane: Jordi Pardo, Peter Tugwell
- Australia/NZ (ANZMUSC): Rachelle Buchbinder, Samuel Whittle
- ACR: Liana Fraenkel, Amy Turner, Elie Akl
- Canada:
    - Pauline Hull, Megan Thomas, Kamso Mujaab
    - RA guideline panel: Michel Zummer, Sharon LeClercq, Carter Thorne, Cheryl Barnabe, Claire Bombardier, Peter Tugwell, Nick Bansback, Janet Pope, Claire Barber, Regina Taylor-Gjevre, Mark Tatangelo, Jordi Pardo, Orit Schieir, Pooneh Akhavan, Nancy Santesso, Laurie Proulx, Shahin Jamal, Dianne Mosher, John Thomson, Caylib Durand, Maysoon Eldoma, Paul Haraoui, Anne Dooley, Majed Khrashi, Vivian Bykerk, Dawn Richards

Cochrane

This webinar was presented on behalf of the

Living Evidence Network

To join the Living Evidence Network

email: lsr@cochrane.org

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