



Living network meta-analysis

Living Evidence Network “state of the science” webinar

21 Mar 2019

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Trusted evidence.
Informed decisions.
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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

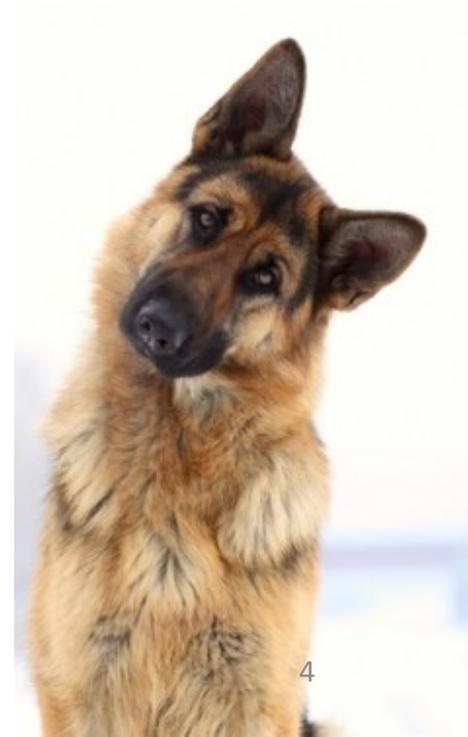
Why we need network meta-analysis?

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

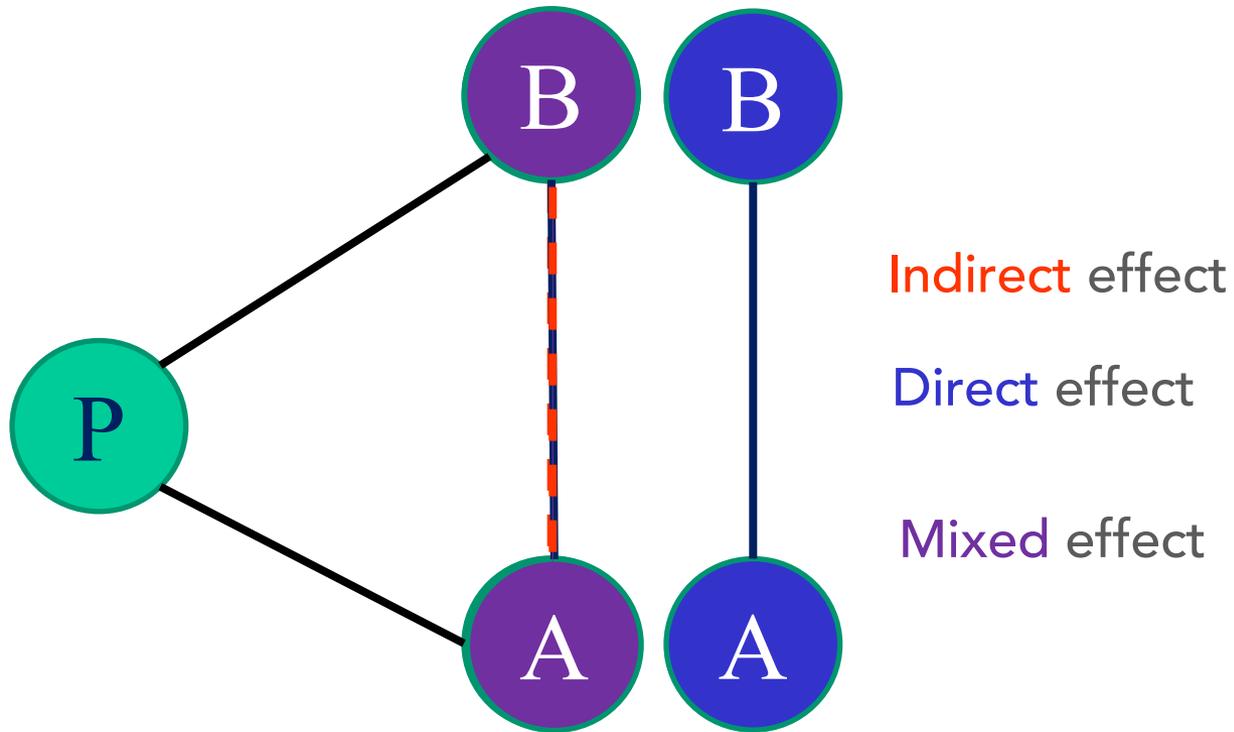
"...meta-analysis highlighted a trend in favour of Sertraline over other Fluoxetine"

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

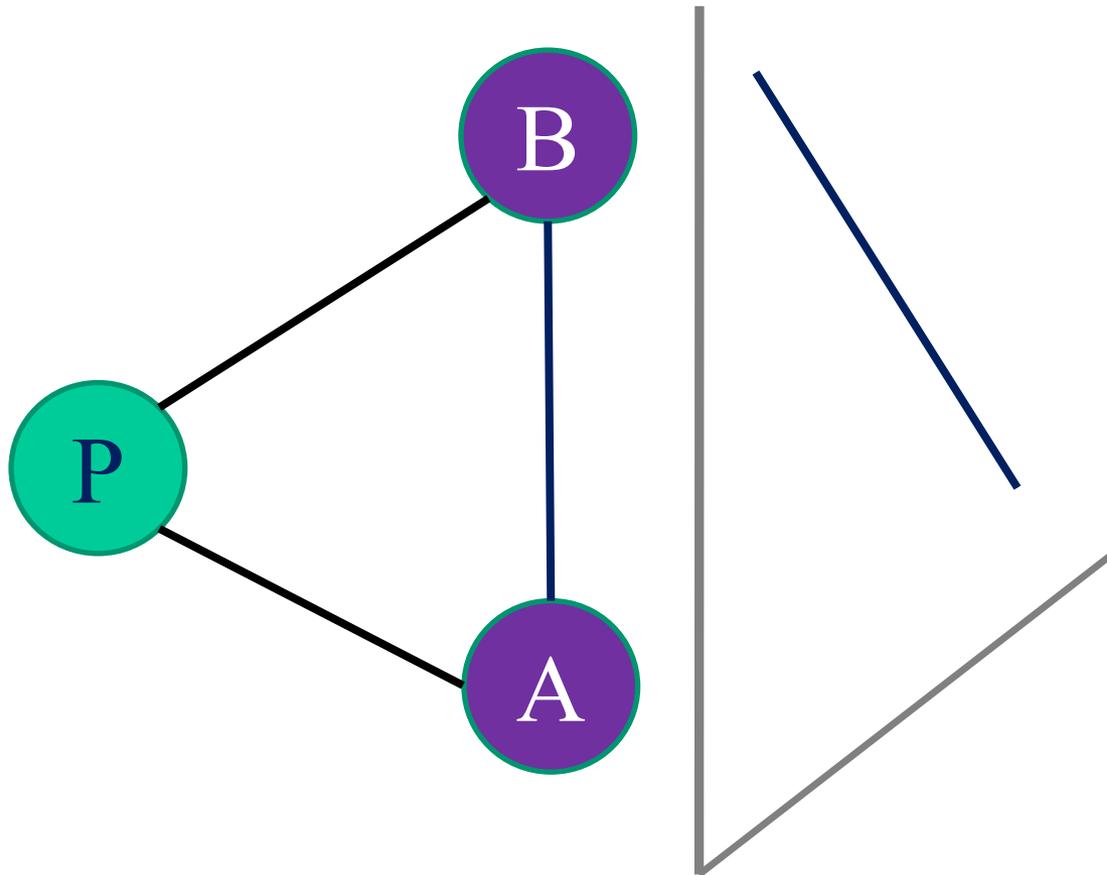
"Venlafaxine tends to have a favorable trend in response rates compared with duloxetine"



Indirect and mixed comparisons

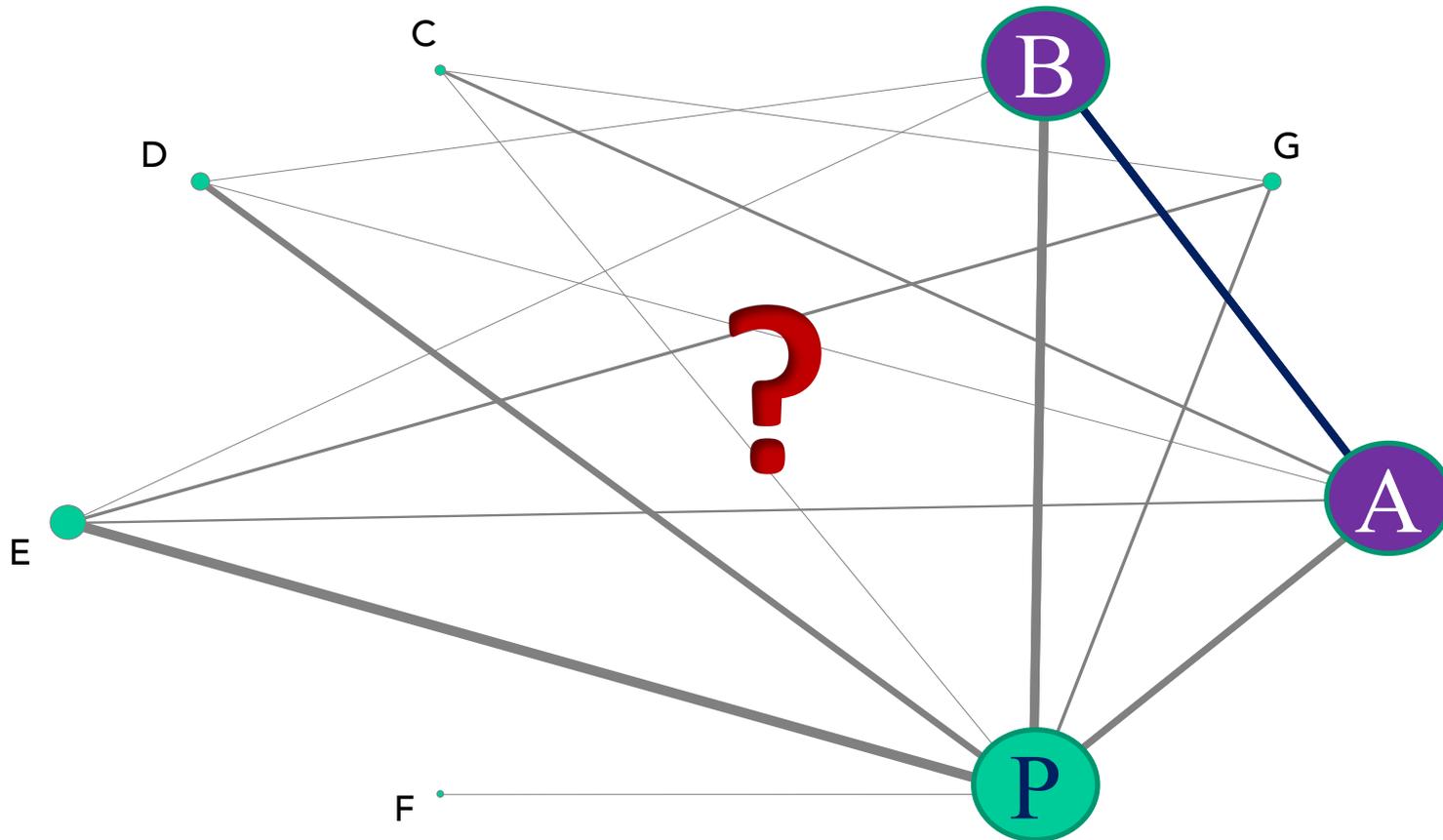


Indirect and mixed comparisons



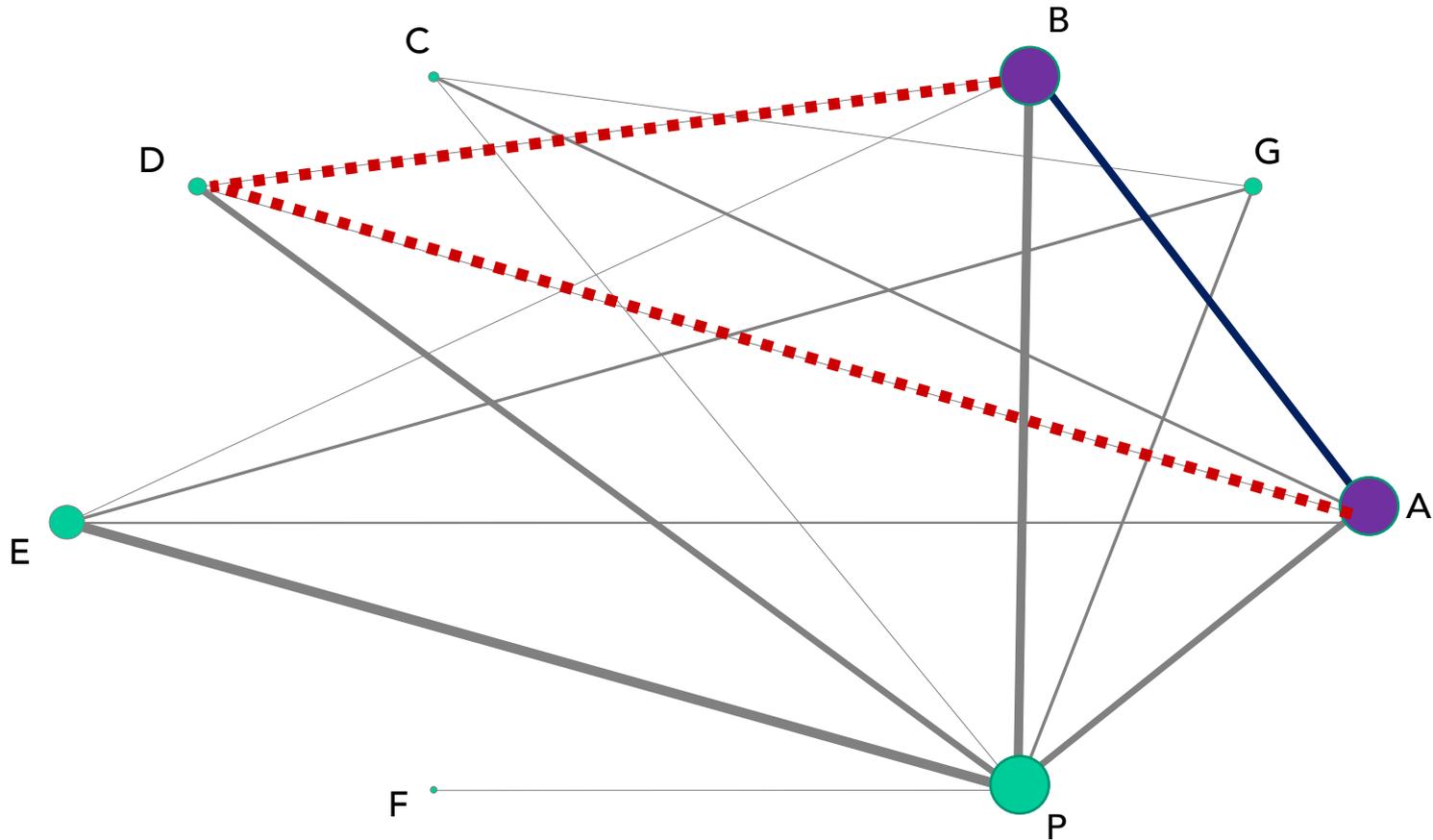
Full network of interventions

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



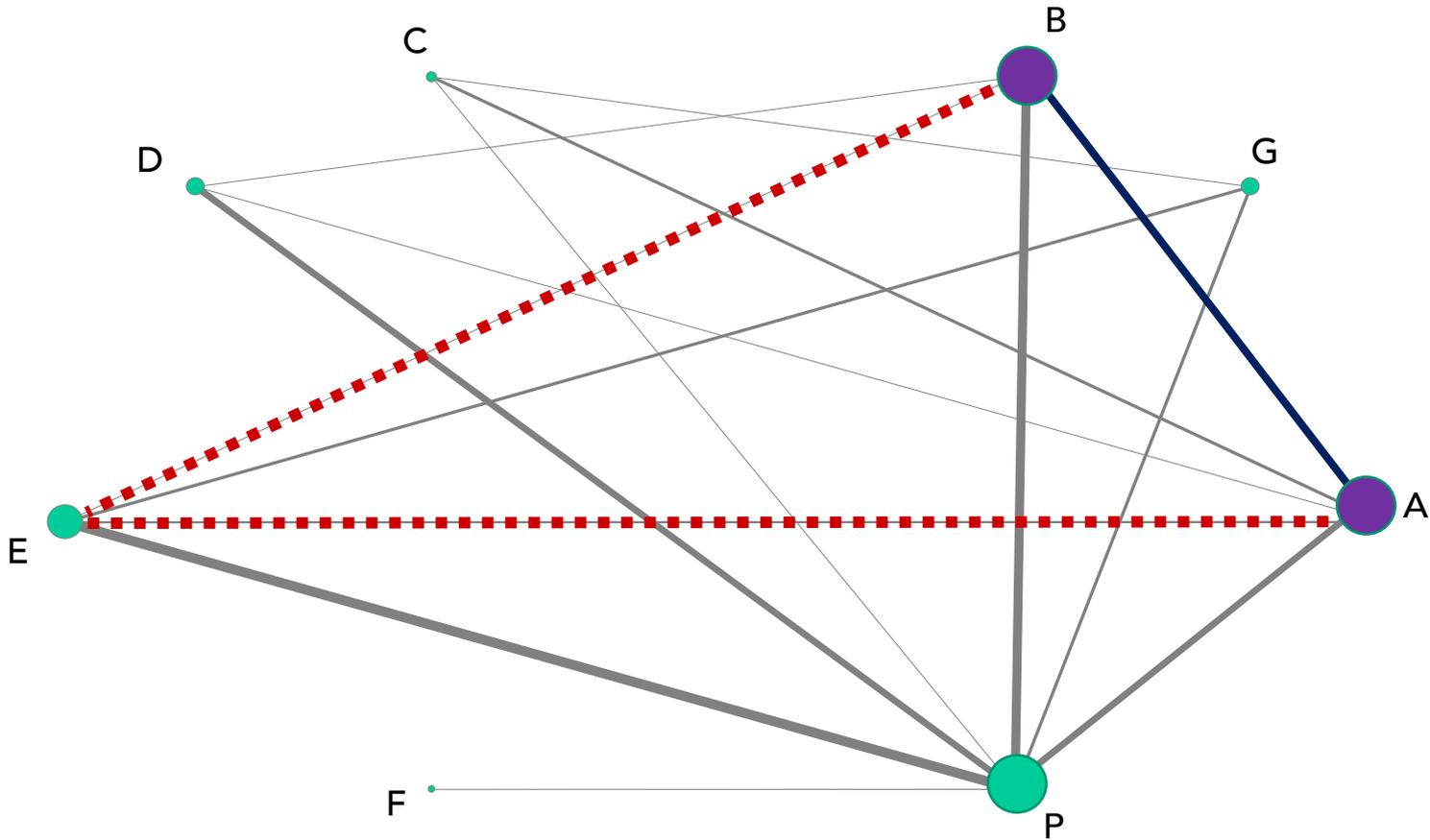
Full network of interventions

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Full network of interventions

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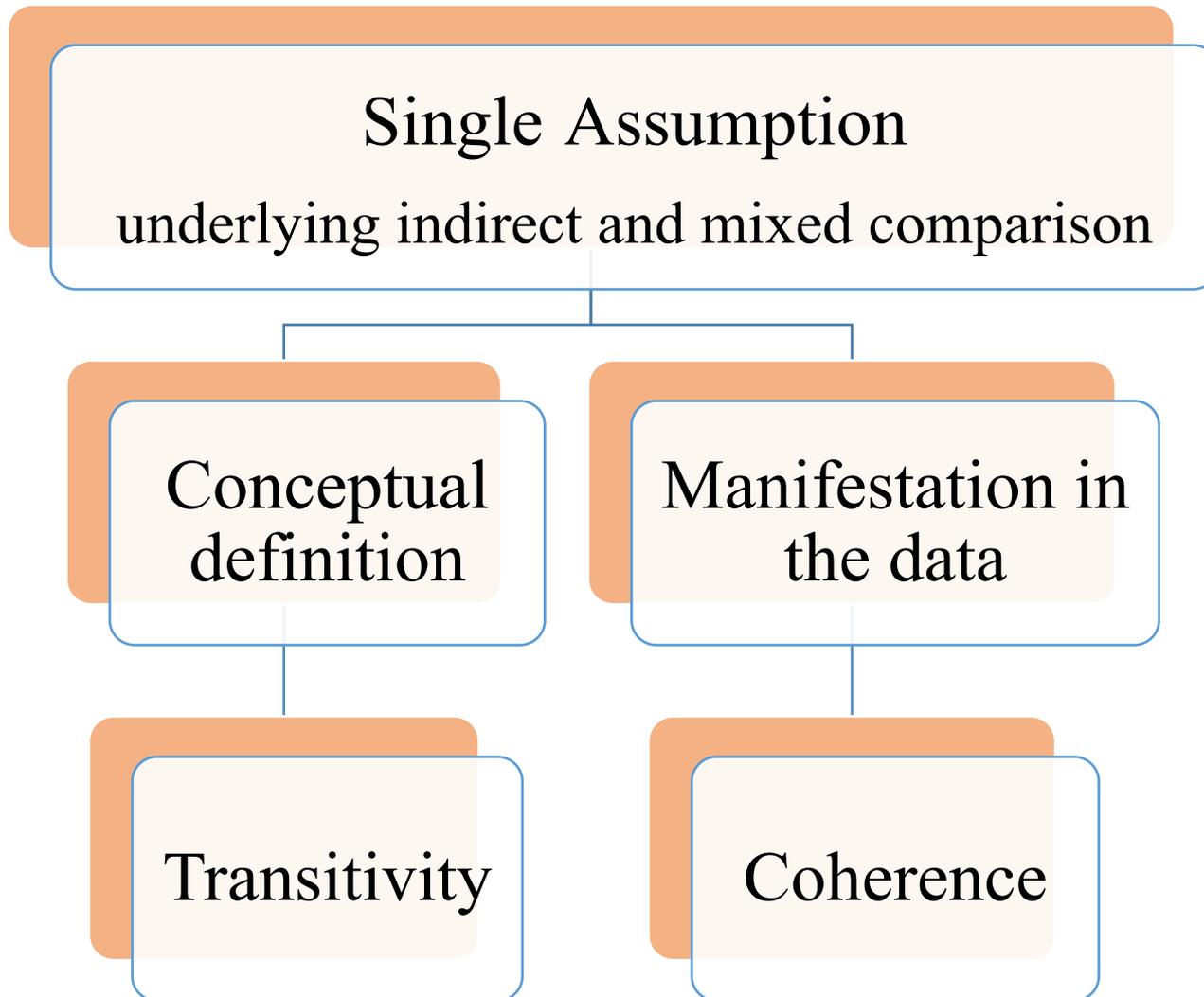


Full network of interventions

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

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)
0-87 (0-59 to 1-30)	0-91 (0-62 to 1-31)	Bupr	1-11 (0-76 to 1-67)	0-71 (0-49 to 1-07)	0-78 (0-53 to 1-18)	1-23 (0-84 to 1-80)	1-07 (0-76 to 1-50)	0-87 (0-59 to 1-30)	1-00 (0-66 to 1-49)	1-01 (0-70 to 1-47)	0-89 (0-51 to 1-54)	1-02 (0-73 to 1-43)	0-67 (0-42 to 1-08)	1-08 (0-75 to 1-56)	0-87 (0-57 to 1-30)	0-92 (0-66 to 1-30)	1-55 (0-85 to 2-94)
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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)
1-44 (1-02 to 2-04)	1-50 (1-07 to 2-07)	1-65 (1-05 to 2-60)	1-27 (0-92 to 1-75)	1-20 (0-84 to 1-70)	1-36 (0-95 to 1-95)	1-60 (1-14 to 2-23)	1-20 (0-88 to 1-62)	1-20 (0-83 to 1-71)	1-35 (0-92 to 1-95)	1-54 (1-09 to 2-17)	1-25 (0-77 to 2-01)	1-43 (1-05 to 1-94)	Rebo	1-61 (1-09 to 2-34)	1-29 (0-81 to 2-01)	1-38 (0-94 to 1-99)	2-32 (1-24 to 4-41)
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1-01 (0-82 to 1-26)	1-05 (0-87 to 1-27)	1-16 (0-82 to 1-65)	0-90 (0-72 to 1-10)	0-85 (0-67 to 1-06)	0-96 (0-77 to 1-21)	1-13 (0-93 to 1-37)	0-84 (0-73 to 0-97)	0-84 (0-66 to 1-07)	0-95 (0-73 to 1-23)	1-09 (0-89 to 1-33)	0-88 (0-59 to 1-30)	1-01 (0-86 to 1-17)	0-70 (0-51 to 0-97)	0-94 (0-78 to 1-13)	0-75 (0-57 to 0-98)	Venl	1-69 (1-01 to 2-86)
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Assumptions underlying network meta-analysis



Assumptions underlying network meta-analysis

In the outset

The treatments we compare are *in principle* **jointly randomizable**

They have the same indication, I can imagine a mega-trial with all treatments being compared etc

When you find the studies

The groups of studies that compare them **do not differ with respect to the distribution of effect modifiers**

You can test this assumption if you have enough studies per comparison

When you extract the outcomes

Direct and indirect treatment effects **are in statistical agreement**

Various statistical tests

Example of a living network meta-analysis

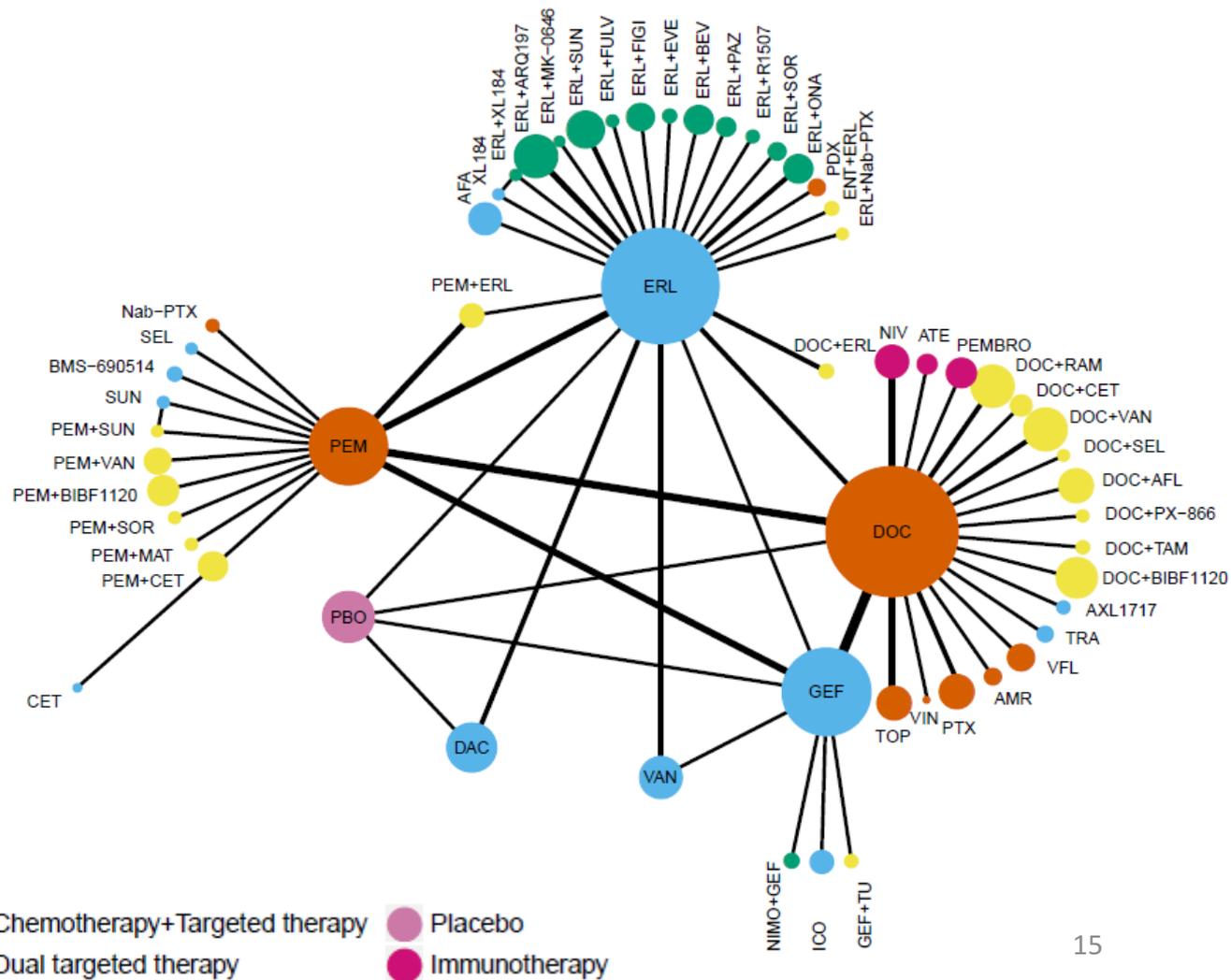
2nd line treatments of advanced non-small cell lung cancer

Treatments (n=58)

Trials (n =92)

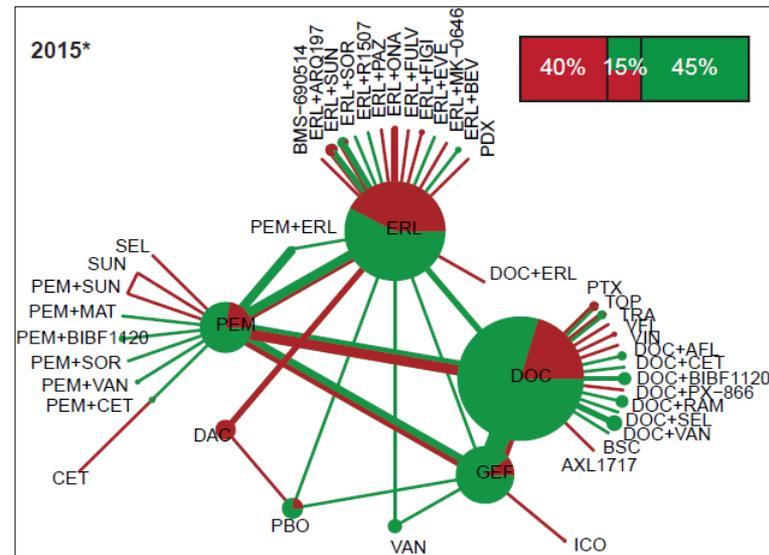
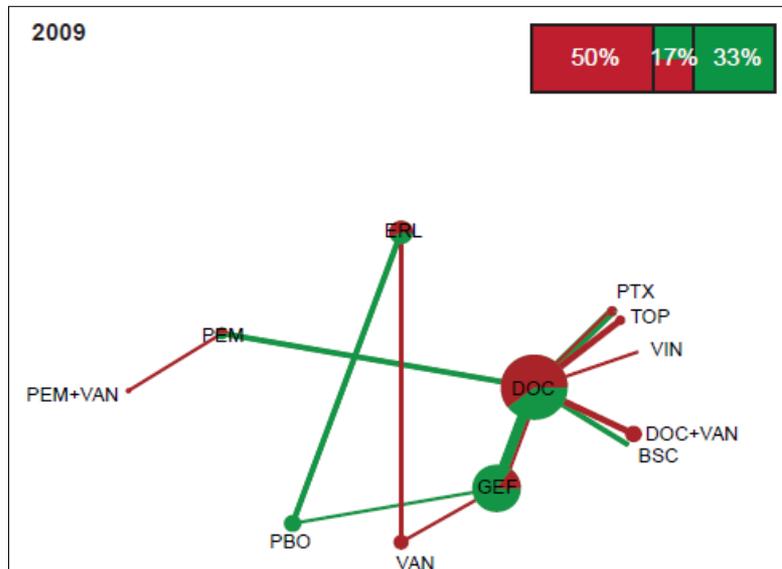
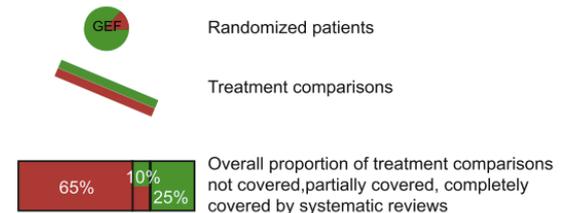
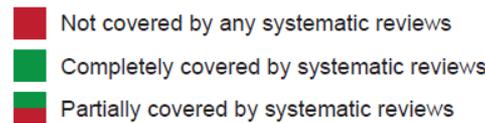
Patients (n=32 434)

29 Systematic reviews



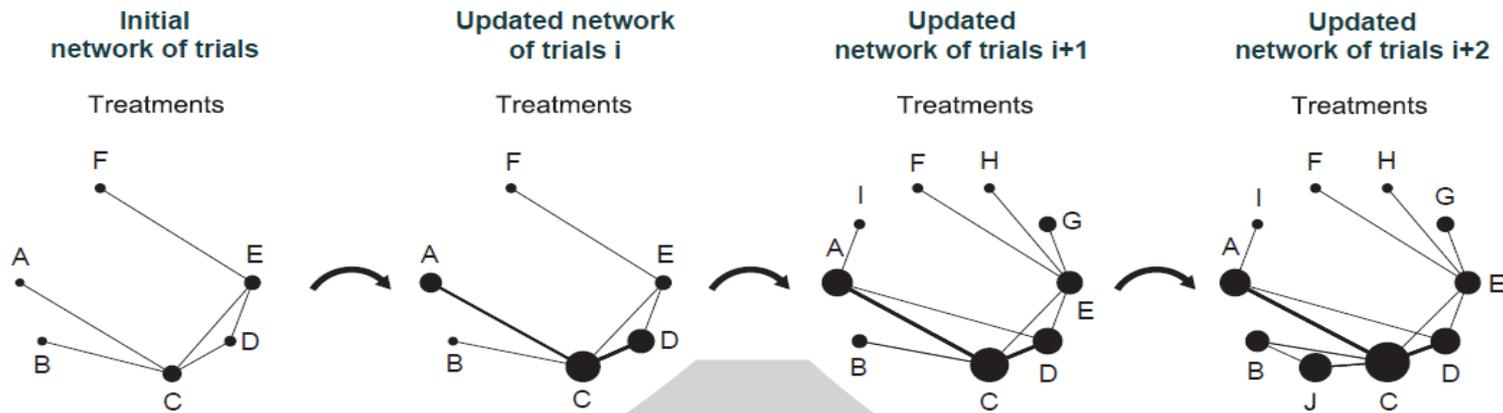
2nd line treatments of advanced non-small cell lung cancer

- 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



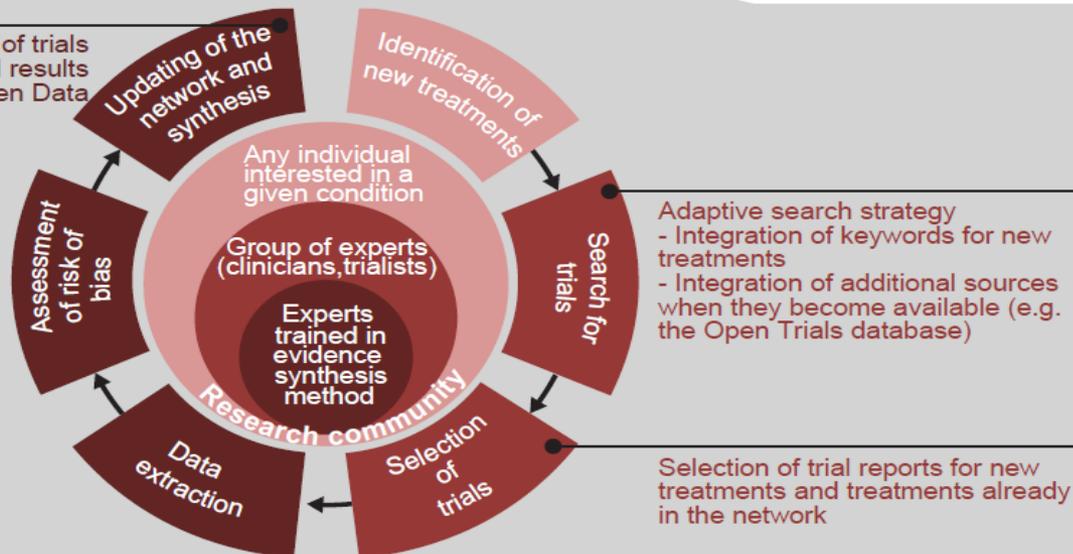
Challenges in the process of living network meta-analyses

The concept of living network meta-analysis

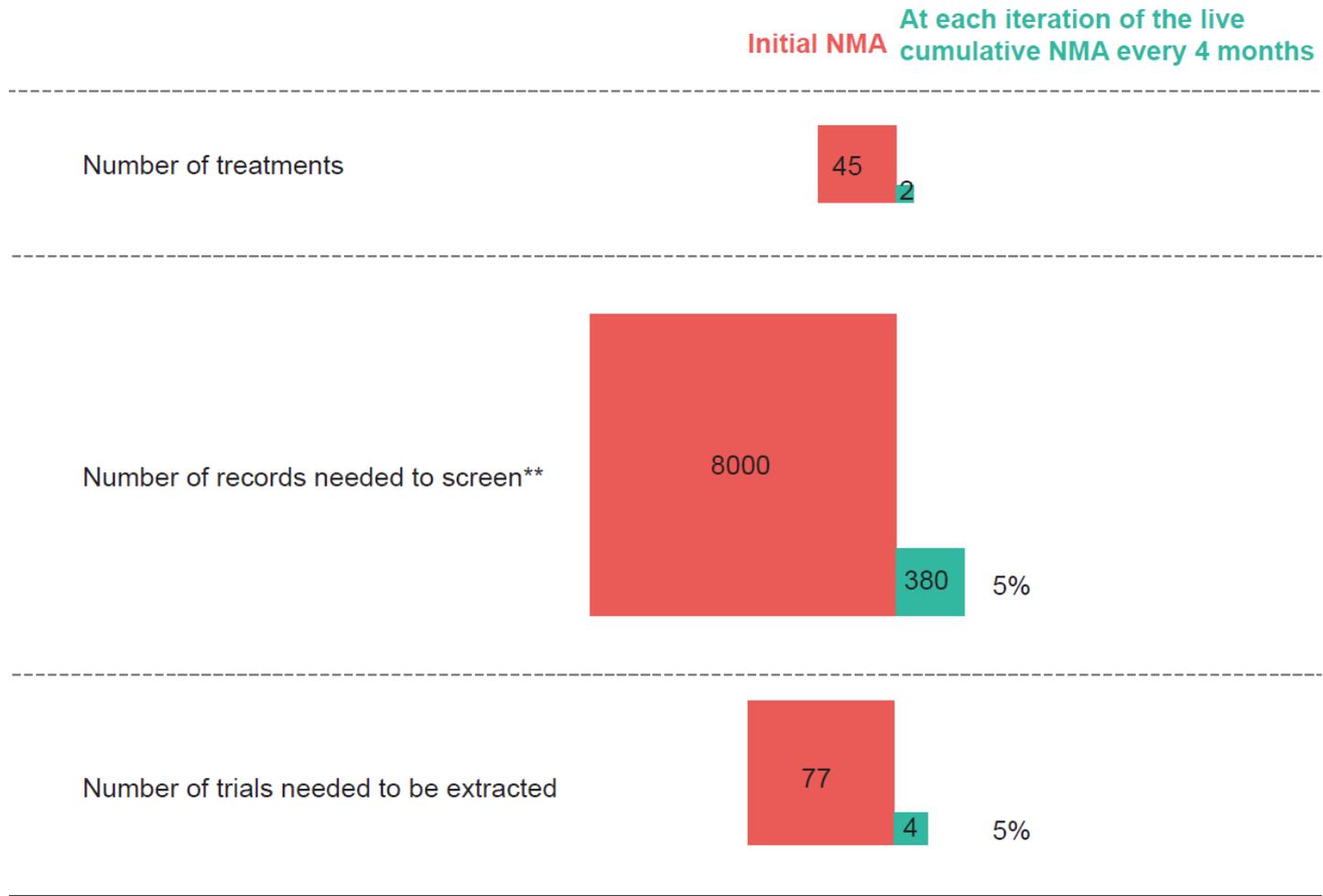


Methodological steps for each update

- Definition of treatments of the network of trials
- Synthesis of all trial results
- Open Data



Work-load for the NSCLC example

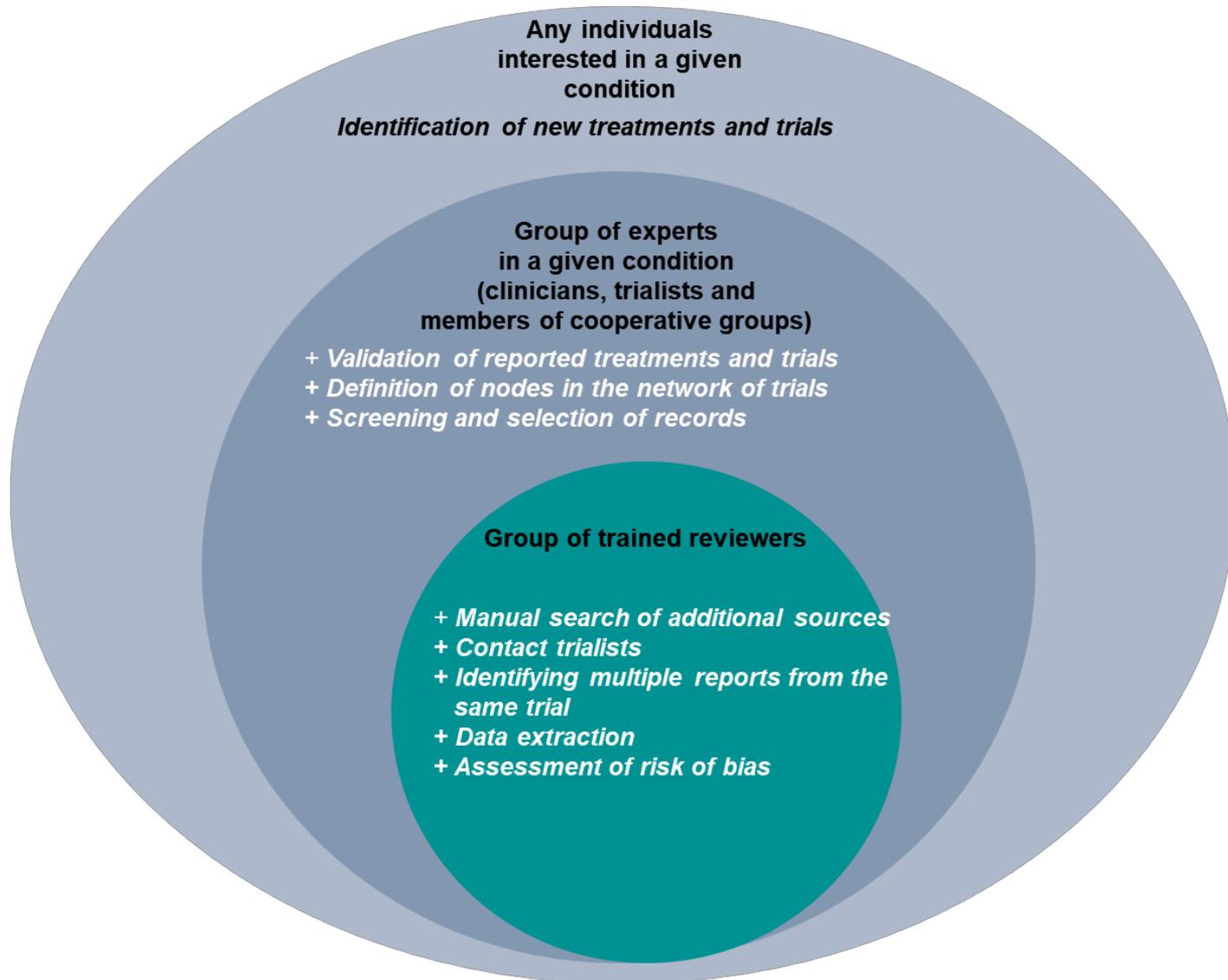


→ Investing a massive amount of resources to produce a NMA and not maintaining it afterwards does not make sense

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

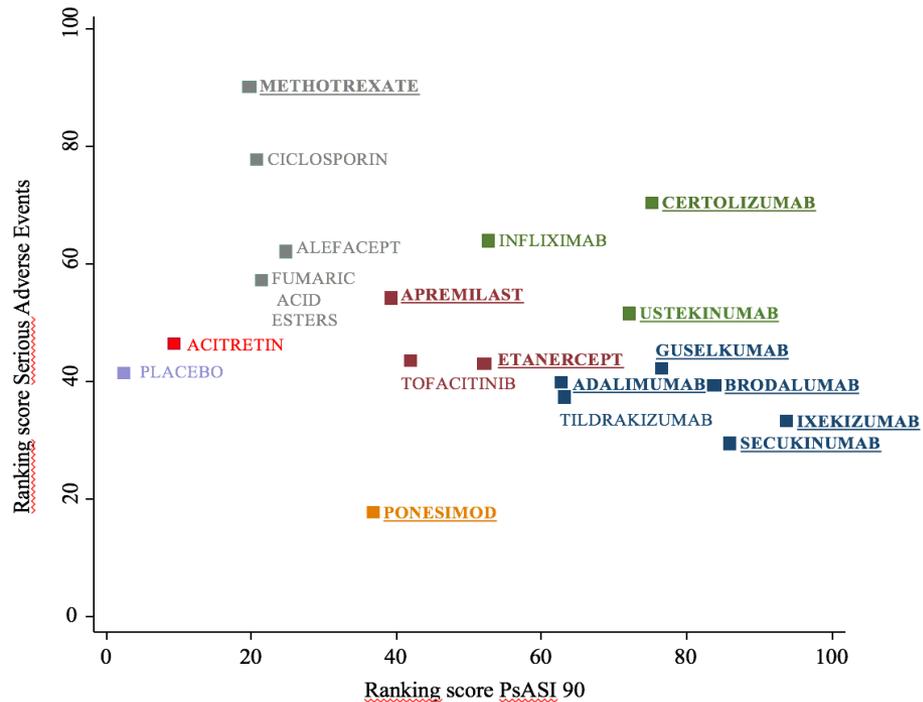
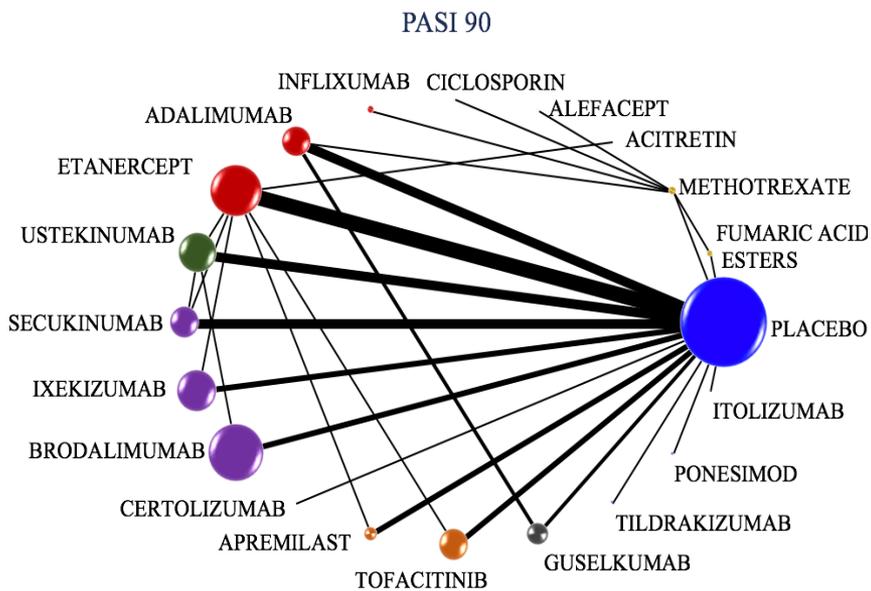


Building a research community

- **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 threatening 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?



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

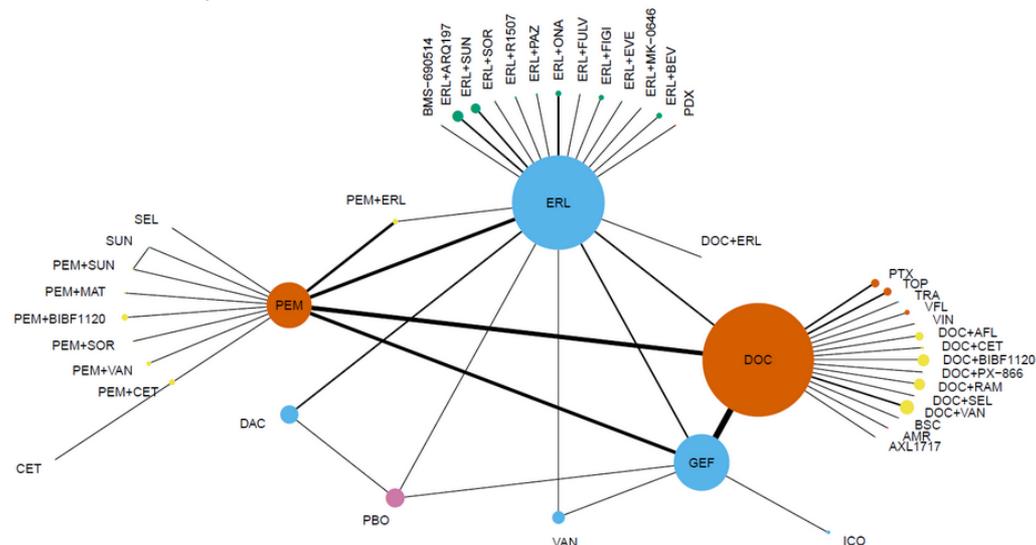
For many conditions, multiple competing treatments are available, many of which have been assessed in randomized trials. Clinicians and patients who are making medical decisions need to know which treatments work best among all treatments available for the condition of interest. They increasingly use 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.

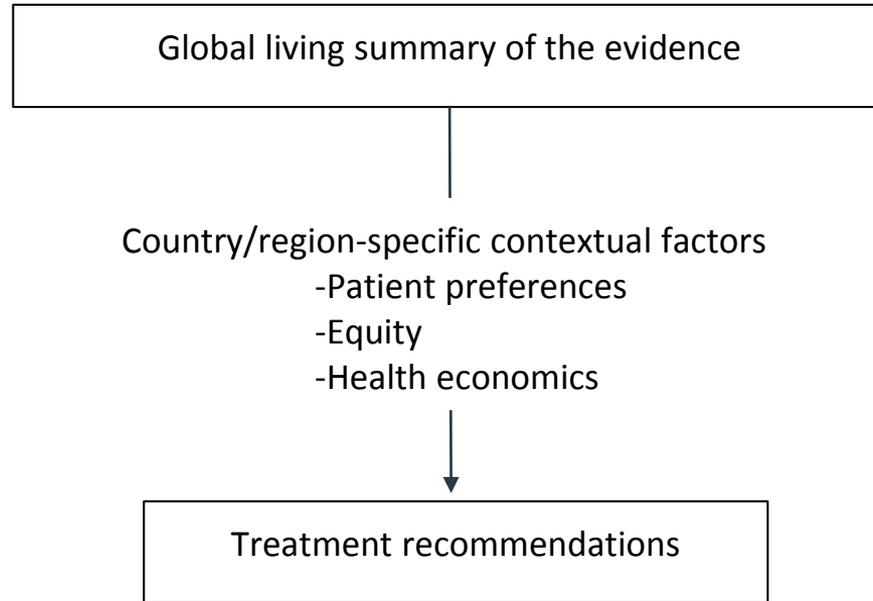
DOI: 10.1002/14651858.CD010227.pub2.

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Living Guidelines Project in Rheumatoid Arthritis

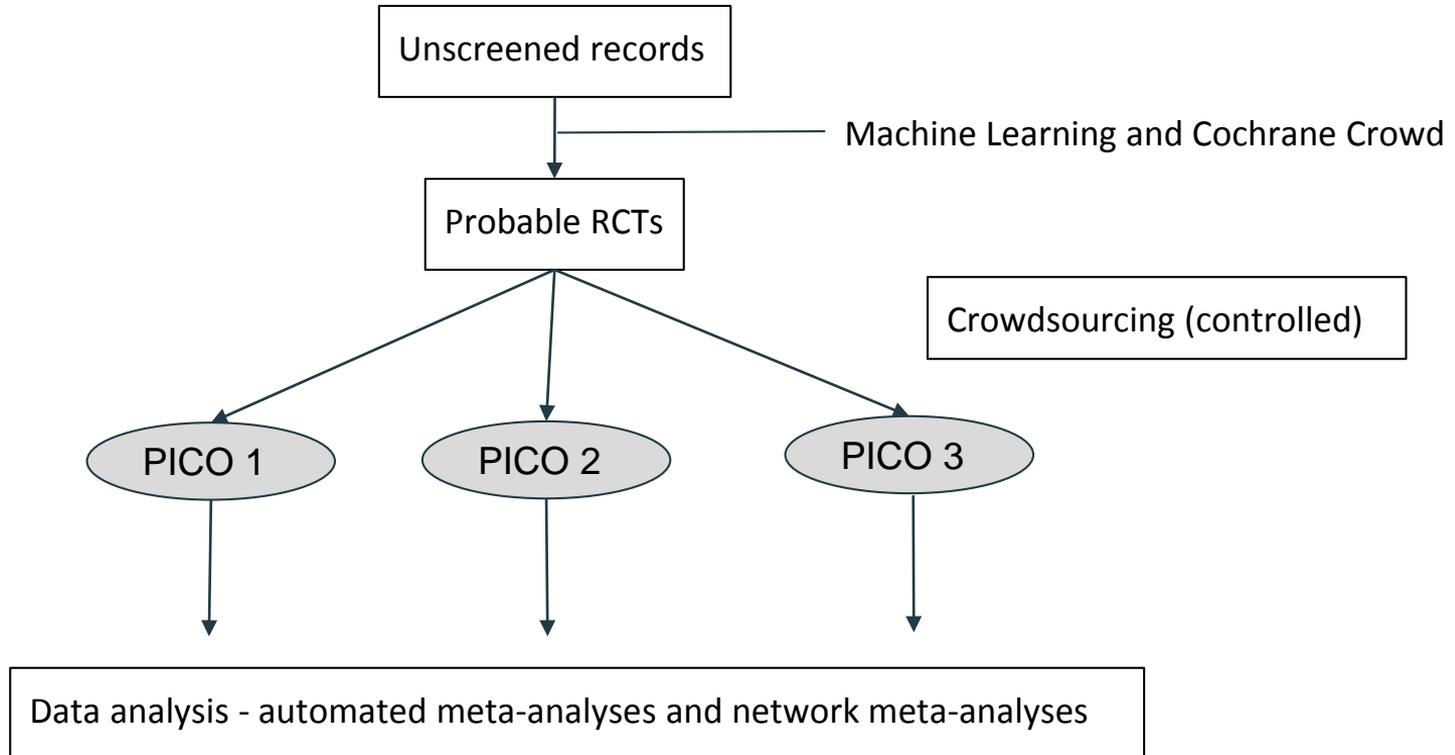
- Collaborative approach to ongoing evidence reviews: CRA, Cochrane, Australia & NZ (ANZMUSC), ACR
- Each group makes their own recommendations
- Opportunity to add other collaborators as project evolves

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



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

Budesonide inhaled via Turbuhaler: a more effective treatment for asthma than beclomethasone dipropionate via Rotahaler [1995261770]

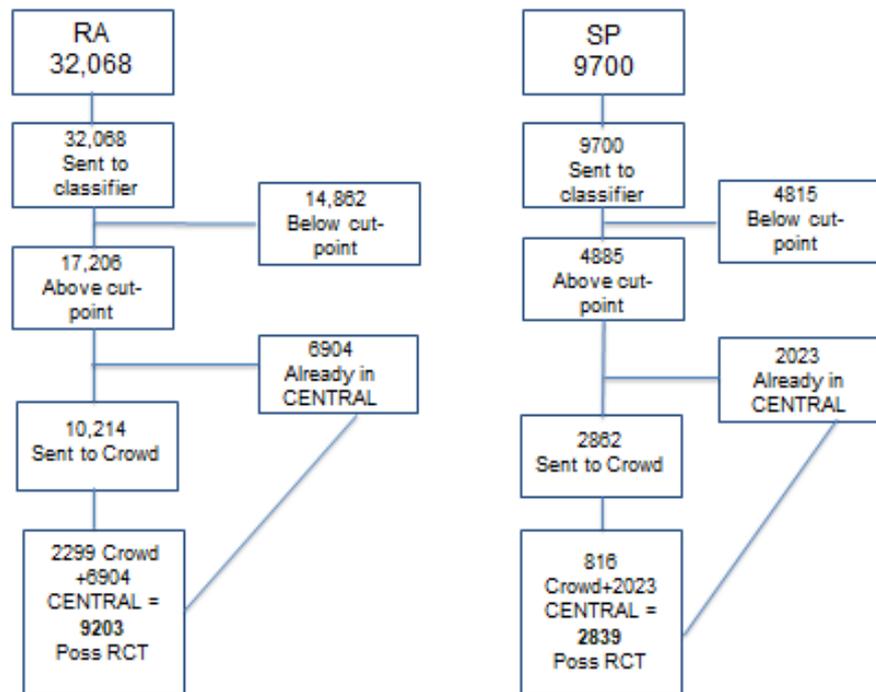
BACKGROUND: Chlorofluorocarbon-propelled metered dose inhalers are facing a worldwide ban. Dry powder inhalers have been developed for the agents used in treatment of asthma. **OBJECTIVE:** Our objective was to compare the effects of two inhaled glucocorticosteroids in dry power inhalers: budesonide (delivered via Turbuhaler) and beclomethasone dipropionate (delivered via Rotahaler). **METHODS:** A randomized, crossover study with two steroid-treatment periods of 8 weeks. At the end of the study, the treatment with the inhaled steroid was stopped for 4 weeks. Sixteen adult patients with moderately severe asthma participated. Before the study all patients were treated with an inhaled steroid in a median dose of 0.60 mg/day (range 0.15-0.80); during the study they received 0.20 mg twice daily. Peak expiratory flow rate was measured twice daily at home throughout the study, lung function was assessed every fourth week and airway responsiveness was measured before and after each period. Preference concerning efficacy and inhaler type was assessed at the end of the study. **RESULTS:** Twelve patients completed the study. Lung function, airway responsiveness, and symptoms deteriorated significantly in the steroid-free washout period; this period had to be shortened in 5/12 patients. Mean morning peak expiratory flow was significantly higher during budesonide treatment than during beclomethasone dipropionate treatment, the difference being 17 L/min (95% C.I.: 2-32 L/min, $P = .026$). Airway responsiveness improved 1.1 doubling concentrations after budesonide treatment, but decreased 0.3 doubling concentrations after beclomethasone dipropionate treatment. The difference between the values after budesonide and beclomethasone dipropionate treatment was 1.4 doubling concentrations (95% C.I.: 0.4-2.4 doubling concentrations, $P = .033$). Forced expiratory flow in one second improved slightly more during budesonide than during beclomethasone treatment. The difference was 4.3% predicted (95% C.I.: -0.7-9.3%). Most patients reported budesonide Turbuhaler to be more effective (10 versus 0) and easier to use (11 versus 1) than beclomethasone dipropionate Rotahaler. **CONCLUSIONS:** As a consequence of the difference in local potency of the steroids and the fact that Turbuhaler deposits more drug particles in the lung than



What is the age of the participants? ⓘ

- Infant**
 - Birth to 1 mo
 - Infant 1 to 23 mo
- Child**
 - Child, Preschool 2-5 years
 - Child 6-12 years
 - Adolescent 13-18 years
- Adult**
 - Young Adult 19-24 years
 - Adult 19-44 years
 - Middle Aged 45-64 years
- Aged**
 - Aged 65-79 years
 - Aged, 80 and over 80+ years

PICO Annotation



Initial Search Results

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:

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The benefits

-  My students are learning by doing and I can monitor their progress
-  My students are rewarded with certificates of achievement
-  We're helping Cochrane find the evidence needed to answer questions about treatments

Automating the analyses

- Planned project for PhD student (Kamsu 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
21			Year 1	Year 2	Year 3	Year 4					
22	Age										
23	Gender										
24											
25	Interventions	Trial 1	Trial 2	Trial 3	Trial 4						
26											
27	Outcomes										
28											
29	MOAE										
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	HAG										
38		Baseline	6 months		12 months						
39		mean	SD	N	SD	N	SD	N			
40	Trial 1	1	2	3	2	3	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 Identifier										
49	Sponsorship										
50	Source										
51	Country										
52	Setting										
53	Comments										
54	Authors name										
55	Institution										
56	Email										
57	Address										
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

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

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			
<ul style="list-style-type: none"> Balanced crystalloid (2 RCT, 846 participants) 	0.75 (0.38 to 1.04) Network estimate	100 per 1000	101 per 1000 (from 100 to 102)	0 per 1000 (from 0 to 0)	⊕○○○ Low Very low certainty	2.00 (1.00 to 3.00)	Probably superior
<ul style="list-style-type: none"> Albumin 	0.75 (0.37 to 1.04) Network estimate	100 per 1000	100 per 1000 (from 99 to 101)	0 per 1000 (from 0 to 0)	⊕○○○ Low Very low certainty	2.00 (1.00 to 3.00)	Probably inferior
<ul style="list-style-type: none"> L-HES 	0.81 (0.42 to 1.01) Network estimate	100 per 1000	104 per 1000 (from 103 to 105)	4 per 1000 (from 3 to 5)	⊕○○○ Low Very low certainty	4.00 (2.00 to 6.00)	Probably superior
<ul style="list-style-type: none"> Saline solution (4 RCT, 7842 participants) 	1.04 (0.67 to 1.04) Network estimate	100 per 1000	100 per 1000 (from 99 to 101)	0 per 1000 (from 0 to 0)	⊕○○○○ Very low Very low certainty	4.00 (2.00 to 6.00)	Probably superior
<ul style="list-style-type: none"> Gelatin 	1.00 (0.48 to 2.27) Network estimate	100 per 1000	100 per 1000 (from 99 to 101)	0 per 1000 (from 0 to 0)	⊕○○○ Low Very low certainty	4.00 (2.00 to 6.00)	Definitely inferior
<ul style="list-style-type: none"> L-HES 	Reference Comparison	No estimate	No estimate	No estimate	Reference Comparison	1.00 (1.00 to 1.00)	Reference comparison

NMA-SoF table definitions

*Number of studies included in the meta-analysis

**Relative effect (95% CrI) estimates are reported as odds ratios (OR), credible intervals (CrI). Results are presented in credible intervals (CrI) since a Bayesian analysis has been conducted.

***Anticipated absolute effects (individuals at risk) are presented as base rates by calculating the difference between the rate of the intervention group with the rate of the control group.

****Odds ratios and credible intervals are presented. Risk ratios (RR) are defined as the probability that a treatment will result in a certain event (e.g., mortality) in a random meta-analysis in the best, the worst, the third and so on until the least effective treatment.

*****Interventions are reported from studies included in the network meta-analysis for the comparison of interest.

⊕○○○○○: Moderate to high certainty evidence; ⊕○○○○: Moderate certainty evidence; ⊕○○○: Low certainty evidence; ⊕○○: Very low certainty evidence; ⊕○: Very low certainty evidence; ○: Very low certainty evidence.

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

Intervention	Comparator	Number of trials for direct comparison	Treatment effect (95 % CrI)	DIRECT EVIDENCE						INDIRECT EVIDENCE			NETWORK META-ANALYSIS	
				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	Publication 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 & Considerations

- 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 & Considerations

- 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, Kamsu 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



This webinar was presented on behalf of the
Living Evidence Network

To join the Living Evidence Network
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