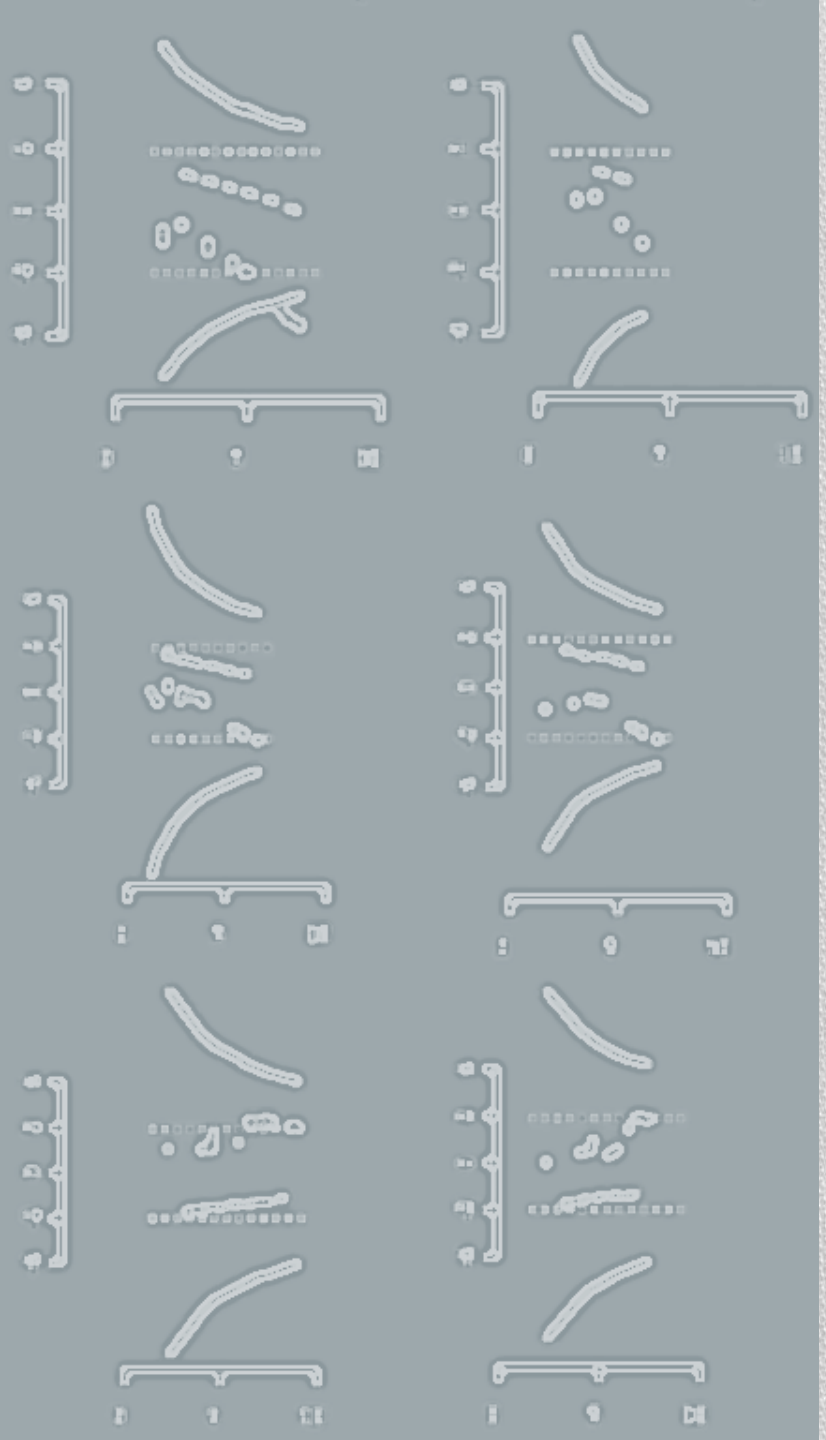


The emerging evidence synthesis tools: Actively Living Network Meta-Analysis

Adriani Nikolakopoulou, Sven Trelle, Matthias Egger, Georgia Salanti

Institute of Social and Preventive Medicine & CTU Bern
University of Bern

Cochrane Colloquium Edinburgh
16-18 September 2018
Edinburgh, UK

I have no actual or potential conflict of interest in relation to this presentation

Network meta-analysis

synthesises both **direct and indirect evidence** in a network of trials that contain multiple interventions

Living systematic reviews

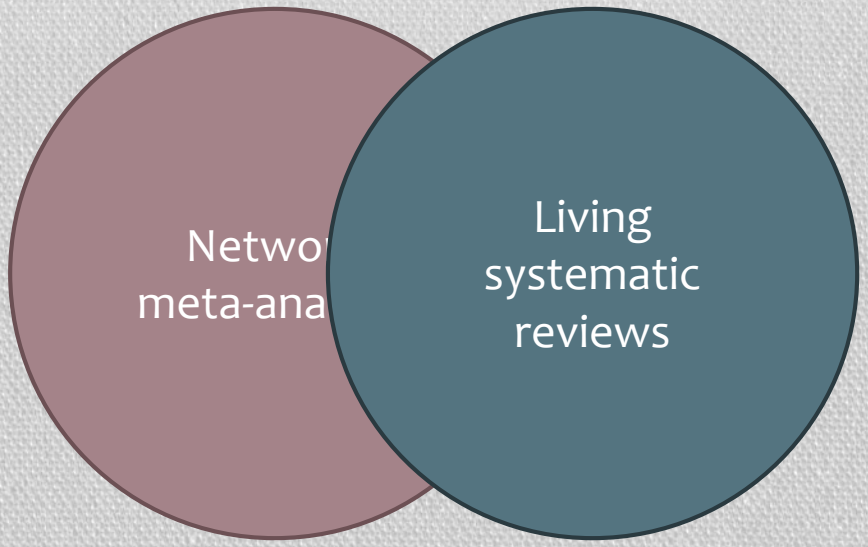
*"high quality, **up-to-date online summaries**, updated as new research becomes available"*

Eliot et al. PLoS Medicine 2014

Evidence based sample size calculations

*"Embarking on additional primary research without reviewing systematically what is already known is **unethical, unscientific and wasteful**"*

Chalmers I, RSM, 2015



*"This waste of research might be reduced by the development of **live cumulative network meta-analyses.**"*

Créquit *et al. BMC Medicine* (2016) 14:8
DOI 10.1186/s12916-016-0555-0

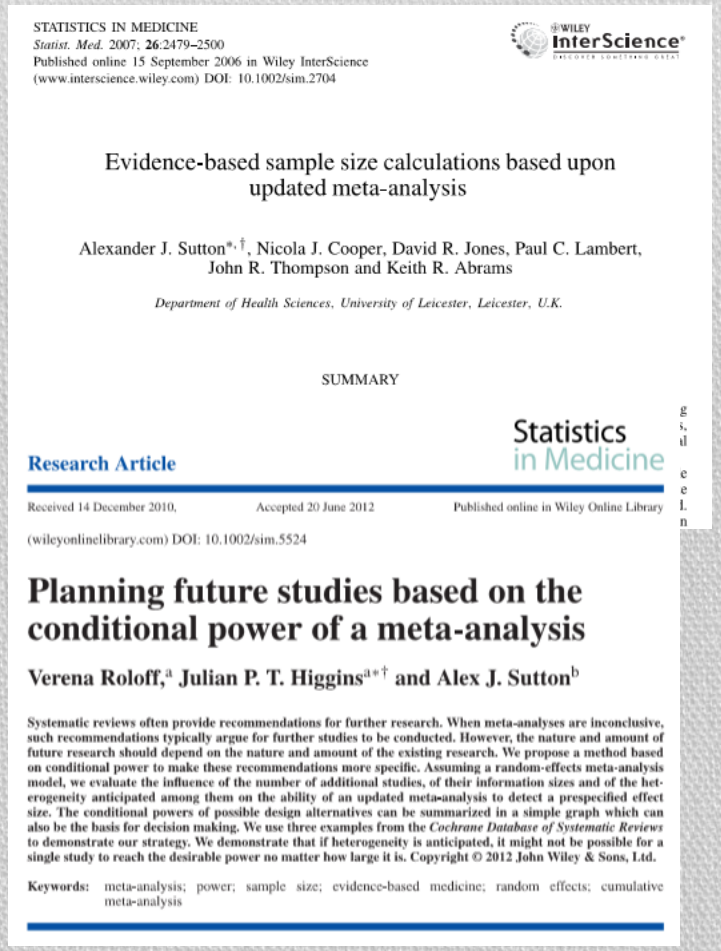
BMC Medicine

RESEARCH ARTICLE Open Access

Wasted research when systematic reviews fail to provide a complete and up-to-date evidence synthesis: the example of lung cancer

Perrine Créquit[1,2†], Ludovic Trinquart[1,2,3,4*†], Amélie Yavchitz[1,2,3] and Philippe Ravaud[1,2,3,4,5]

Network meta-analysis



STATISTICS IN MEDICINE
Statist. Med. 2007; **26**:2479–2500
Published online 15 September 2006 in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/sim.2704

Evidence-based sample size calculations based upon updated meta-analysis

Alexander J. Sutton*,†, Nicola J. Cooper, David R. Jones, Paul C. Lambert, John R. Thompson and Keith R. Abrams

Department of Health Sciences, University of Leicester, Leicester, U.K.

SUMMARY

Research Article

Statistics in Medicine

Received 14 December 2010, Accepted 20 June 2012 Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.5524

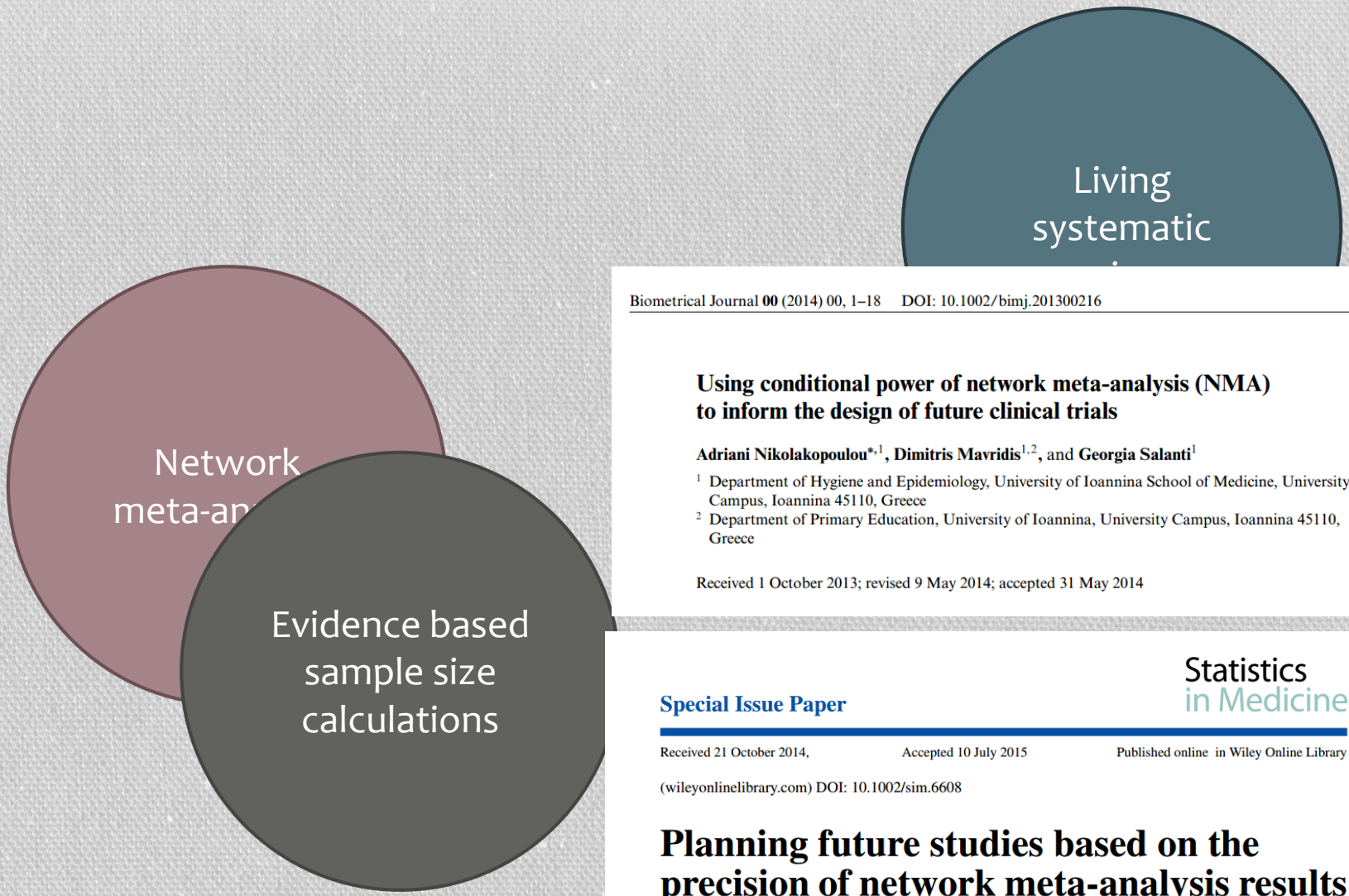
Planning future studies based on the conditional power of a meta-analysis

Verena Roloff,[a] Julian P. T. Higgins[a]*† and Alex J. Sutton[b]

Systematic reviews often provide recommendations for further research. When meta-analyses are inconclusive, such recommendations typically argue for further studies to be conducted. However, the nature and amount of future research should depend on the nature and amount of the existing research. We propose a method based on conditional power to make these recommendations more specific. Assuming a random-effects meta-analysis model, we evaluate the influence of the number of additional studies, of their information sizes and of the heterogeneity anticipated among them on the ability of an updated meta-analysis to detect a prespecified effect size. The conditional powers of possible design alternatives can be summarized in a simple graph which can also be the basis for decision making. We use three examples from the *Cochrane Database of Systematic Reviews* to demonstrate our strategy. We demonstrate that if heterogeneity is anticipated, it might not be possible for a single study to reach the desirable power no matter how large it is. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: meta-analysis; power; sample size; evidence-based medicine; random effects; cumulative meta-analysis

Evidence based sample size calculations



Biometrical Journal **00** (2014) 00, 1–18 DOI: 10.1002/bimj.201300216 1

Using conditional power of network meta-analysis (NMA) to inform the design of future clinical trials

Adriani Nikolakopoulou[*,1], **Dimitris Mavridis**[1,2], and **Georgia Salanti**[1]

[1] Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, University Campus, Ioannina 45110, Greece
[2] Department of Primary Education, University of Ioannina, University Campus, Ioannina 45110, Greece

Received 1 October 2013; revised 9 May 2014; accepted 31 May 2014

Special Issue Paper

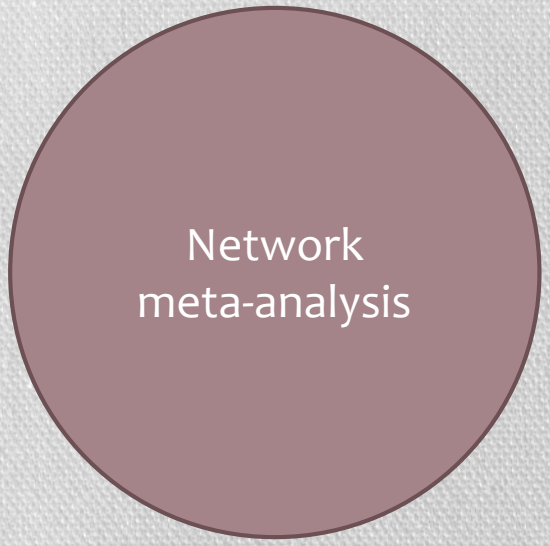
Statistics in Medicine

Received 21 October 2014, Accepted 10 July 2015 Published online in Wiley Online Library

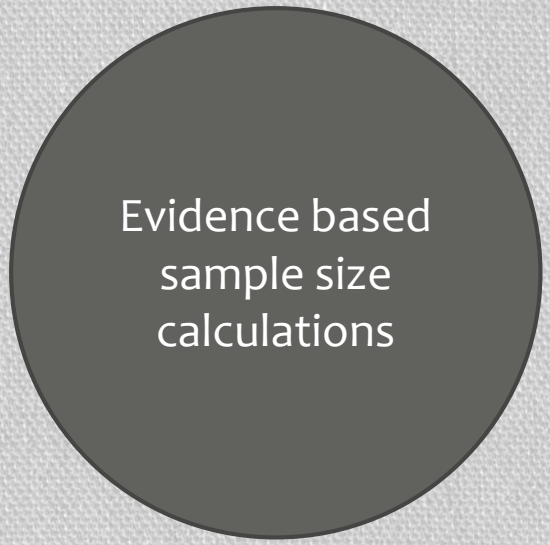
(wileyonlinelibrary.com) DOI: 10.1002/sim.6608

Planning future studies based on the precision of network meta-analysis results

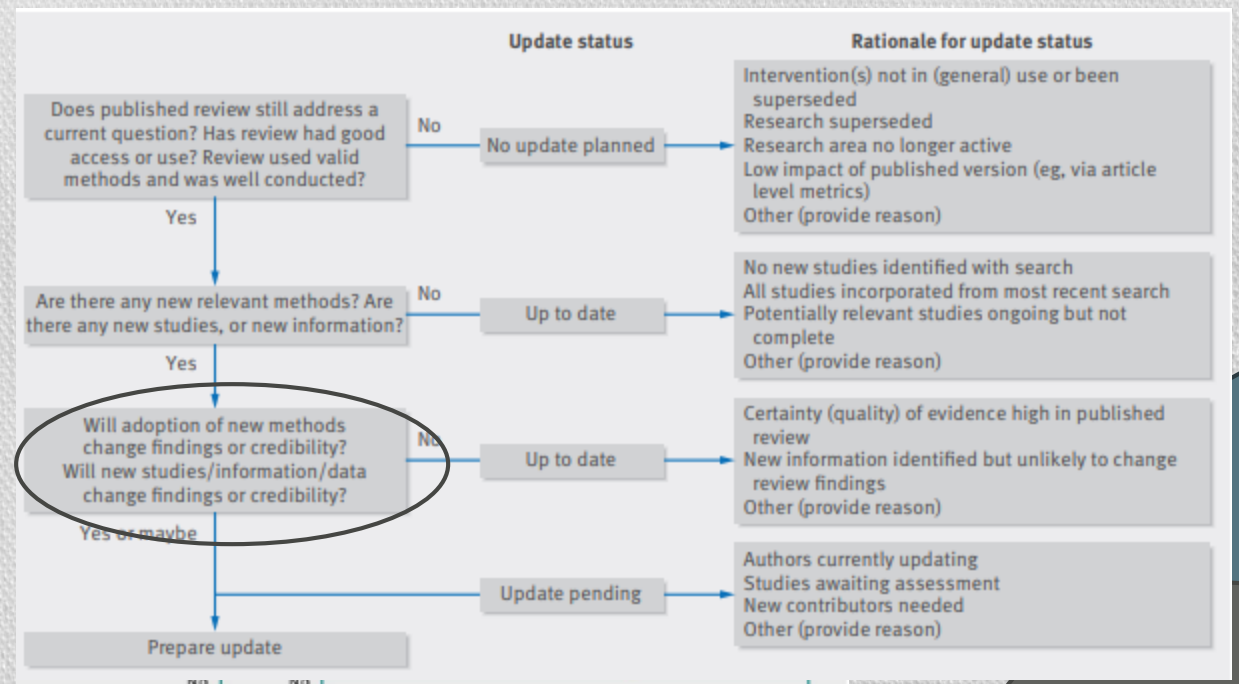
Adriani Nikolakopoulou,[a] **Dimitris Mavridis**[a,b] **and Georgia Salanti**[a*†]

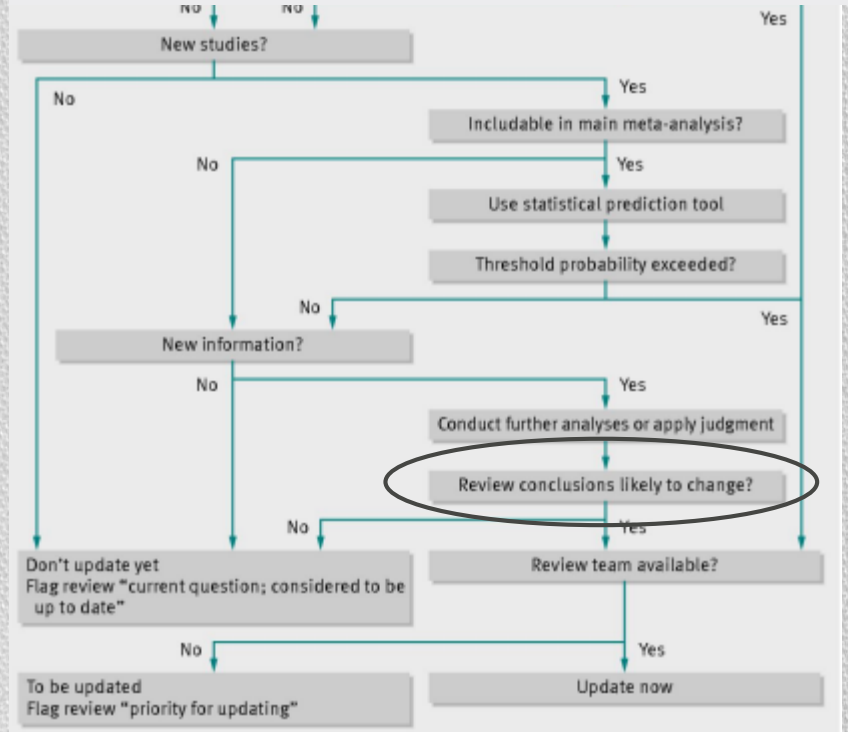

Network
meta-analysis

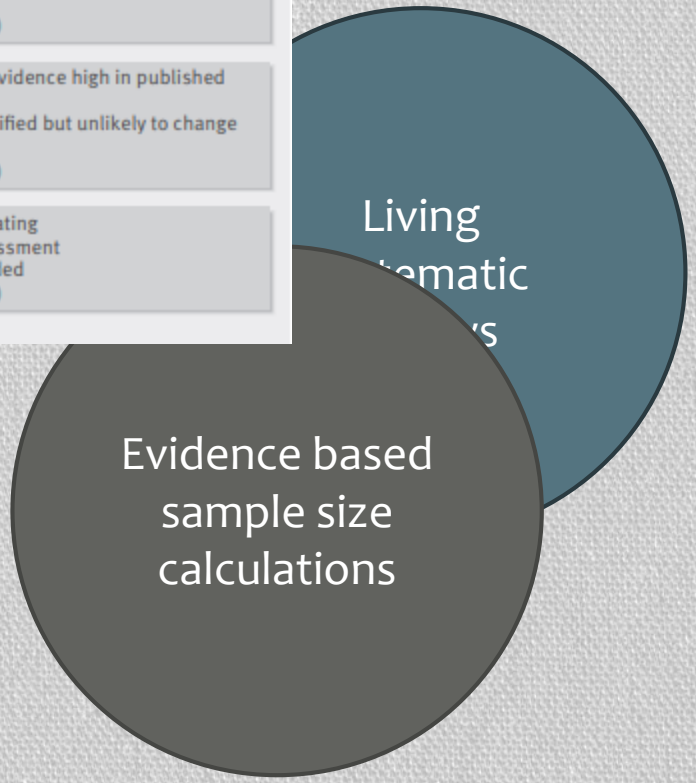

Living
systematic
reviews


Evidence based
sample size
calculations

Garner et al., BMJ, 2016

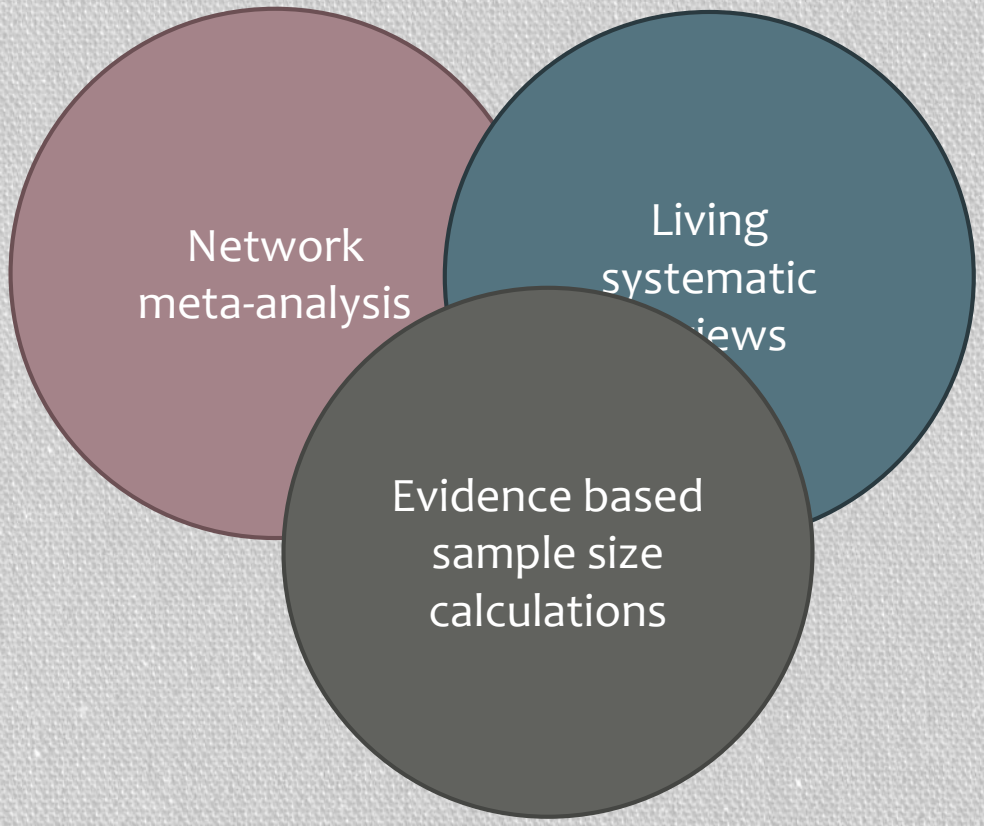




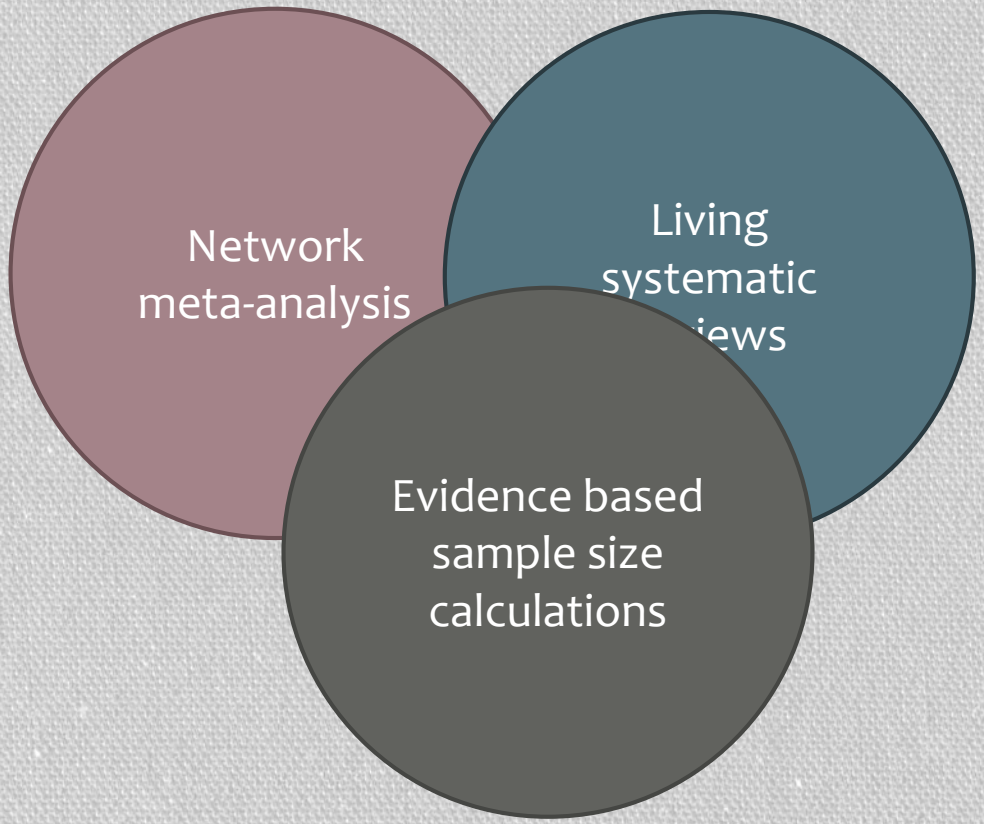


Takwoingi et al. BMJ, 2013

A general framework



Actively Living Network Meta-Analyses



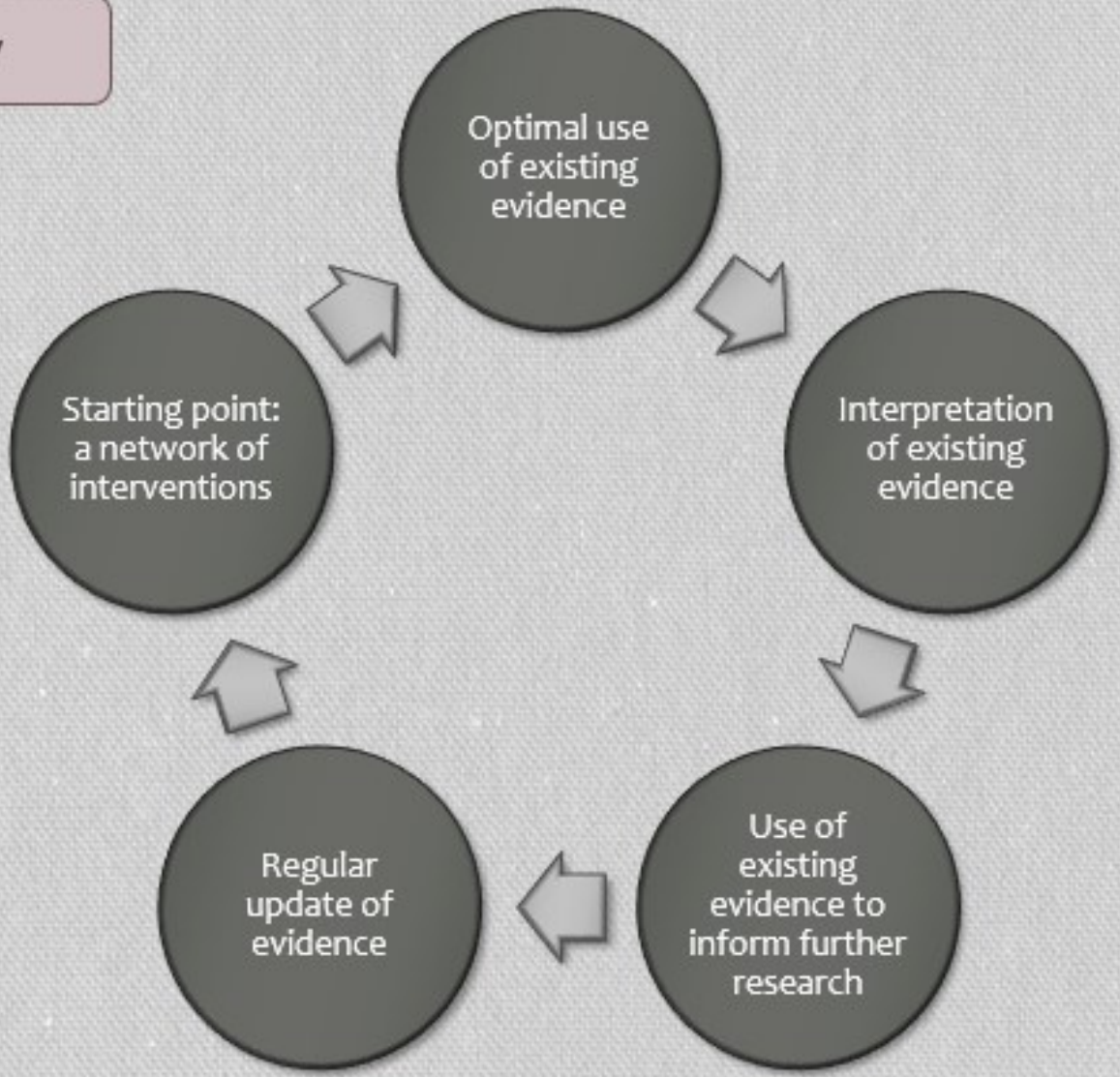
A living network meta-analysis that actively makes **specific suggestions about the need of further studies** to answer the research question they address.

framework

application

acceptability

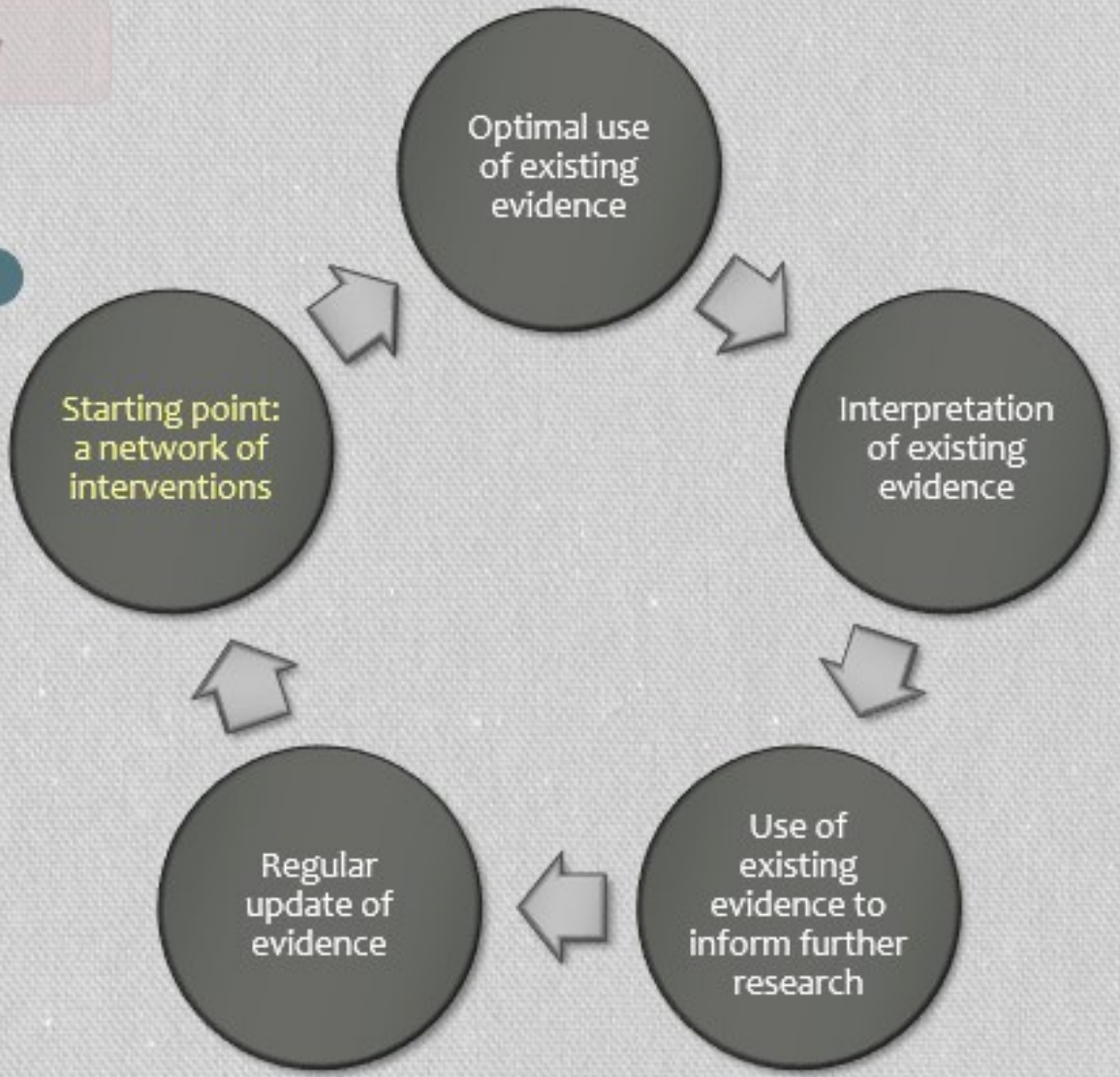
The lifecycle of an y Living Network Meta-Analysis



framework

application

acceptability



framework

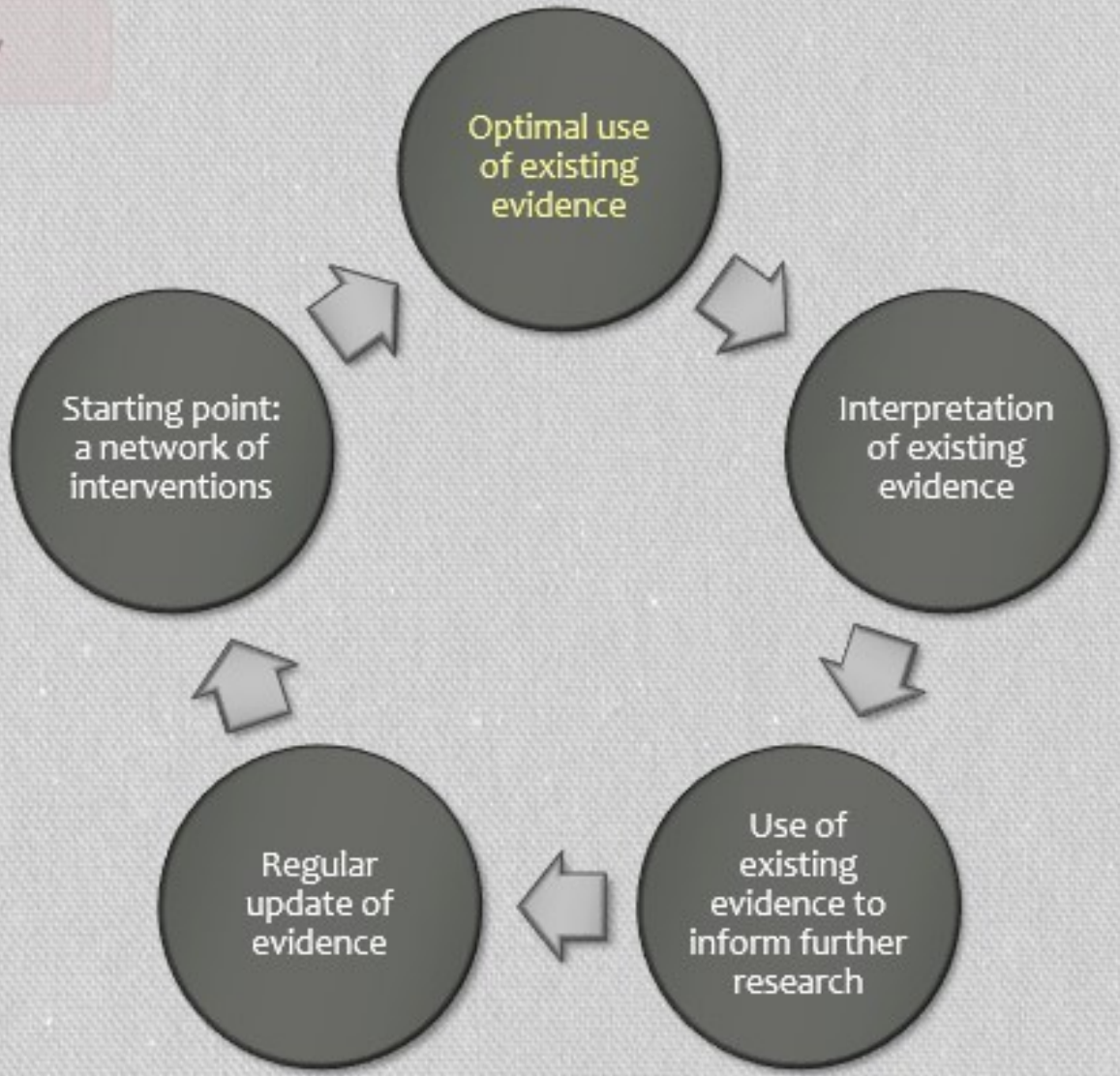
application

acceptability

Network meta-analysis

Improvement in precision of treatment effects

Insight into comparative benefits and harms



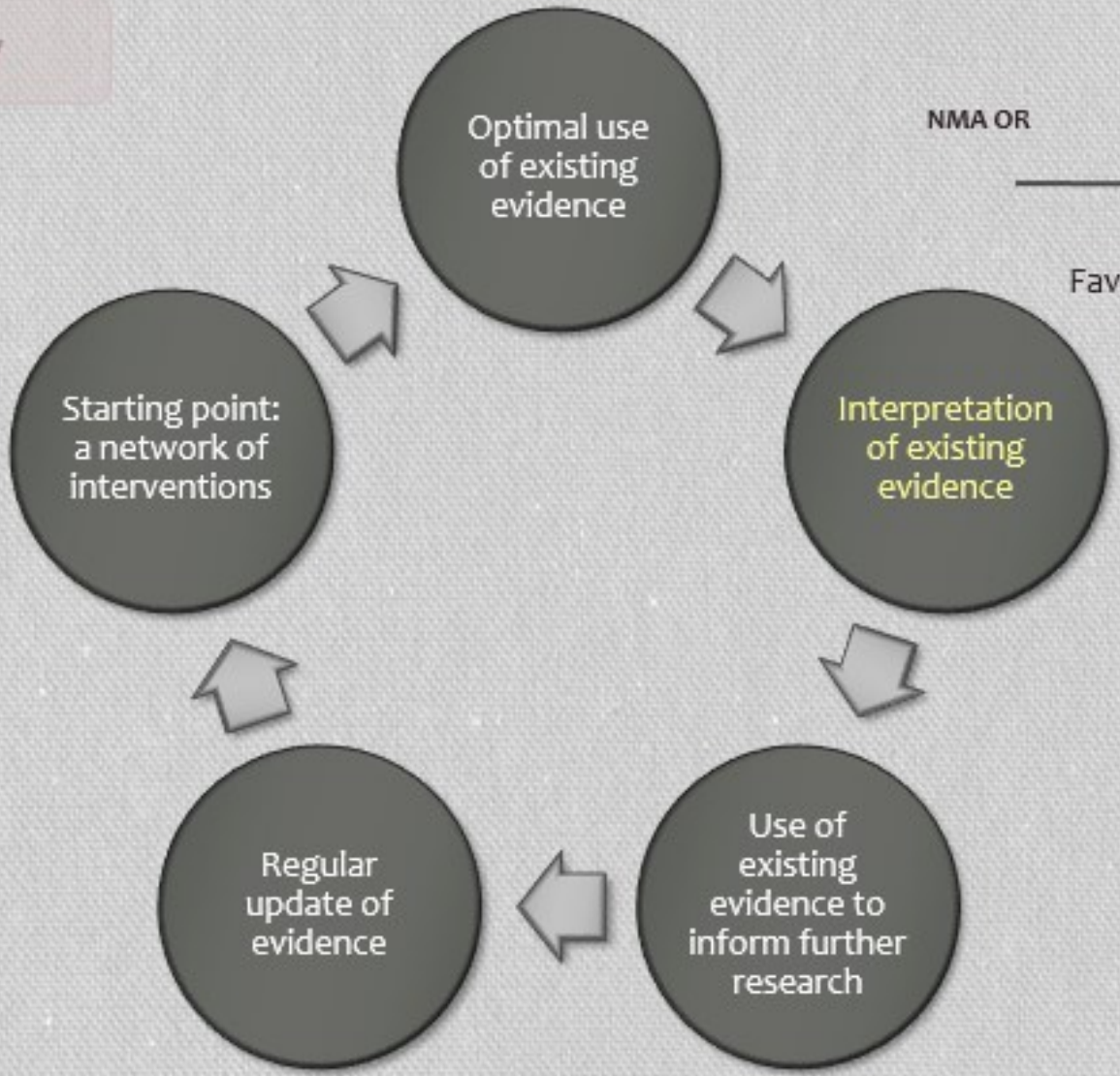
framework

application

acceptability

Is the current evidence conclusive?

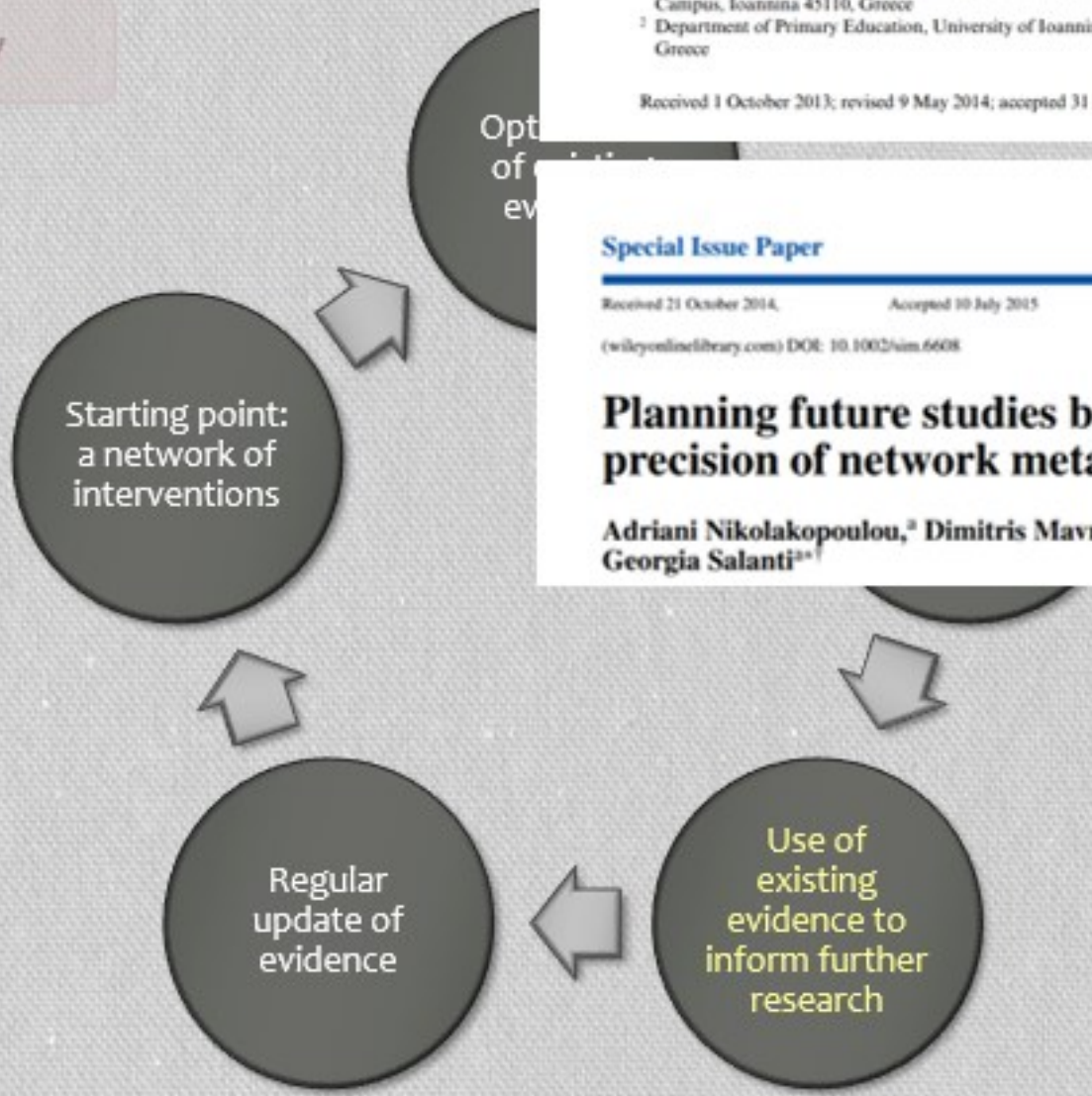
Does the confidence interval include values that would lead to different clinical decisions?



framework

application

acceptability



Biometrical Journal 00 (2014) 00, 1–18 DOI: 10.1002/bimj.201300216 1

Using conditional power of network meta-analysis (NMA) to inform the design of future clinical trials

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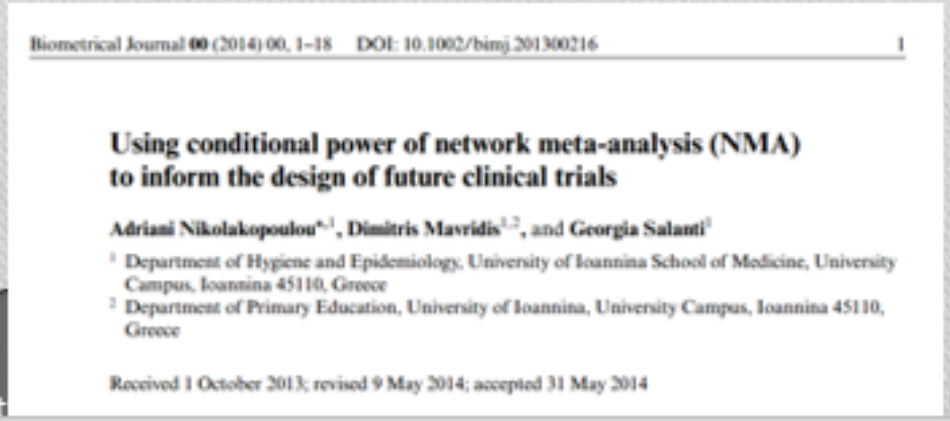
Planning future studies based on the precision of network meta-analysis results

Adriani Nikolakopoulou,[a] Dimitris Mavridis[a,b] and Georgia Salanti[a]*

framework

application

acceptability



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Methodology to design a new study based on a NMA

Based on

The **conditional power** of the updated NMA model

conditional power

The power to detect a specified overall mean effect size in a future meta-analysis given the observed result of the existing meta-analysis

and

The relative **improvement in precision in NMA effects** from the updated model

research

framework

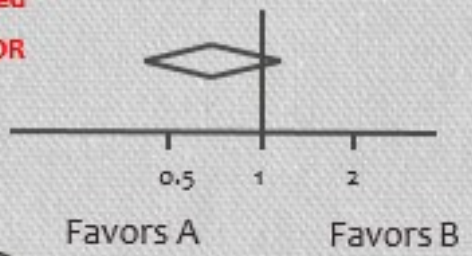
application

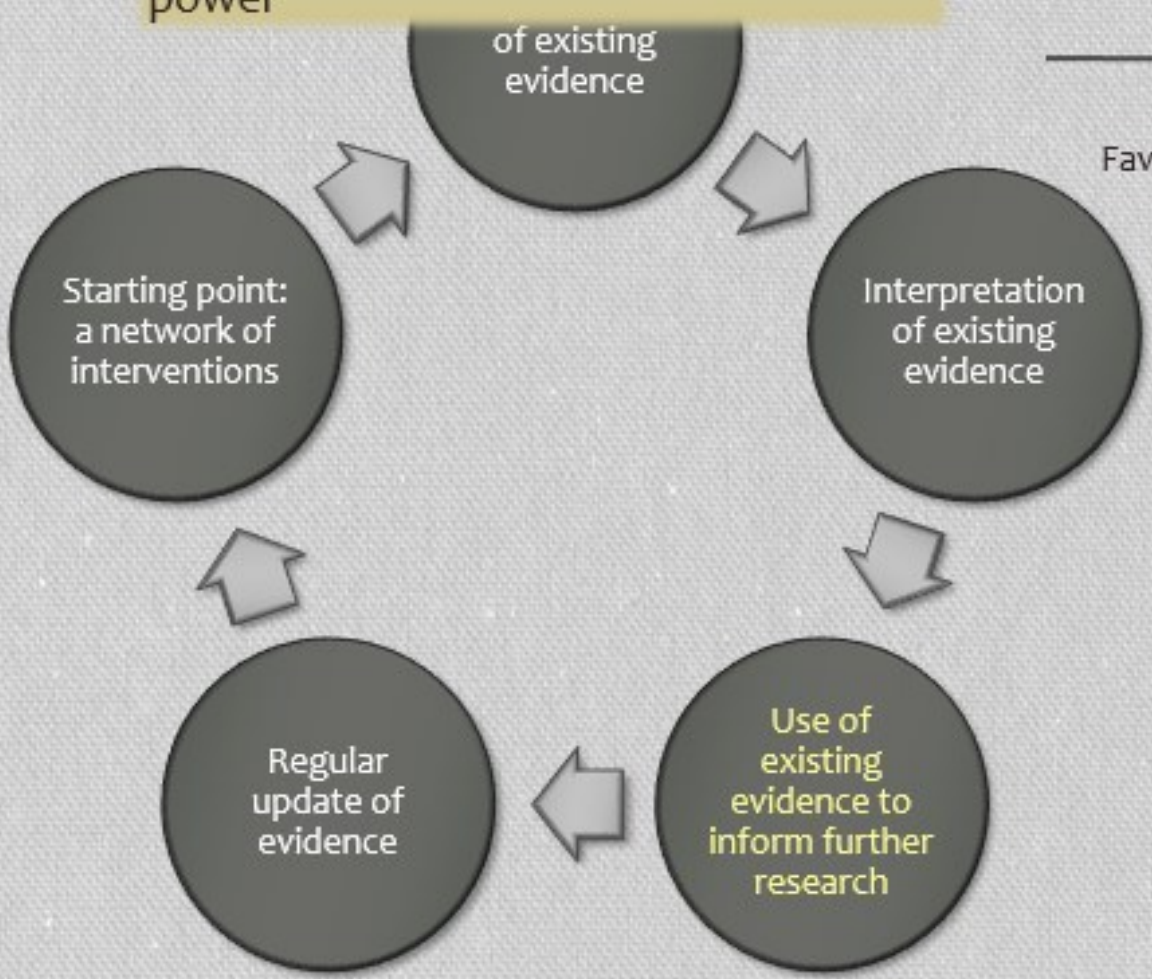
acceptability

We need less sample size (compared to pairwise meta-analysis)

We can investigate alternative designs: If the direct comparison of the treatments of interest is impractical, planning indirect evidence will add power

Updated NMA OR





framework

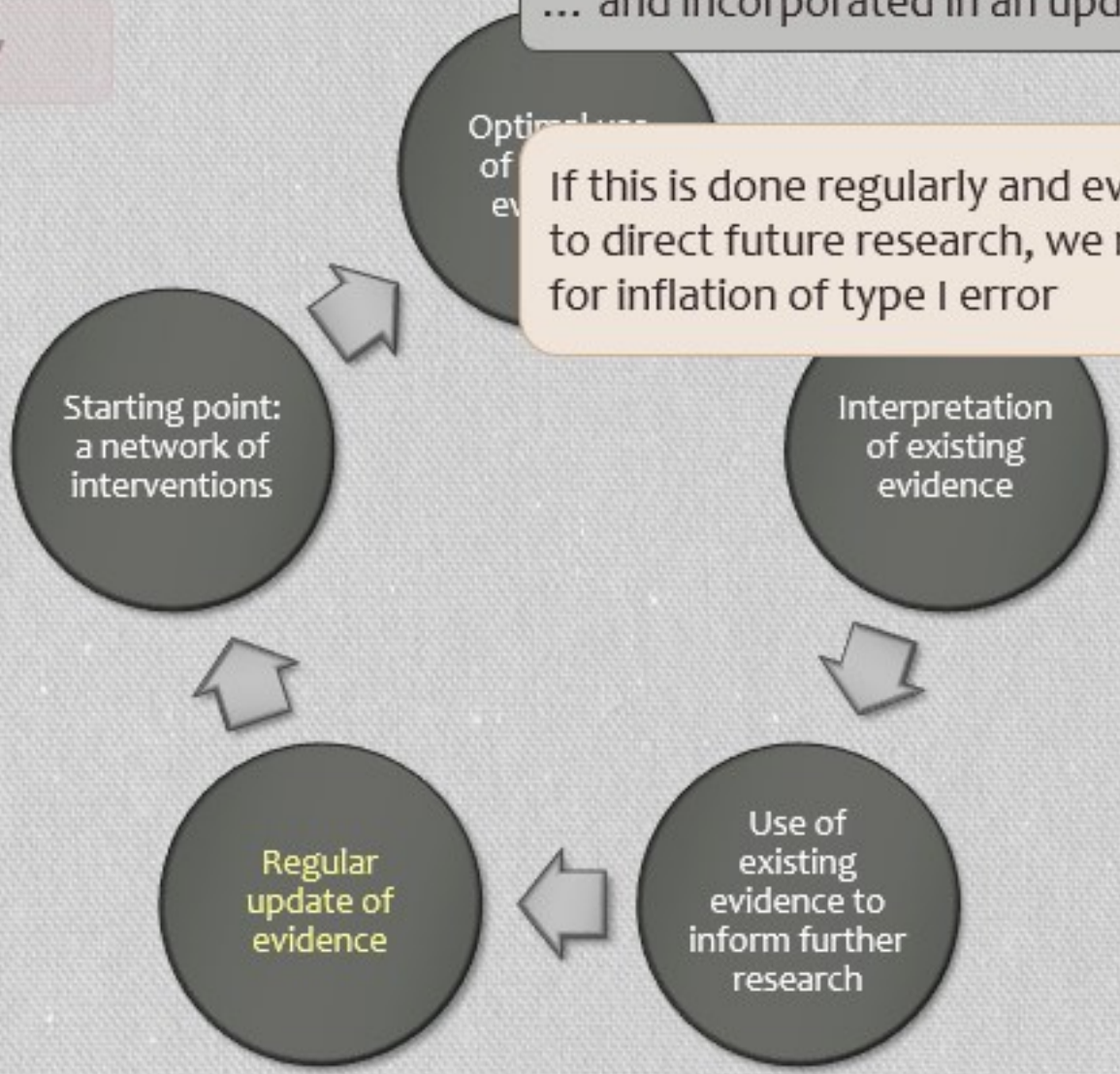
application

acceptability

The new study has designed…

… implemented …

… and incorporated in an updated NMA



If this is done regularly and evidence is used to direct future research, we need to adjust for inflation of type I error

Example: olanzapine versus haloperidol in schizophrenia

Articles

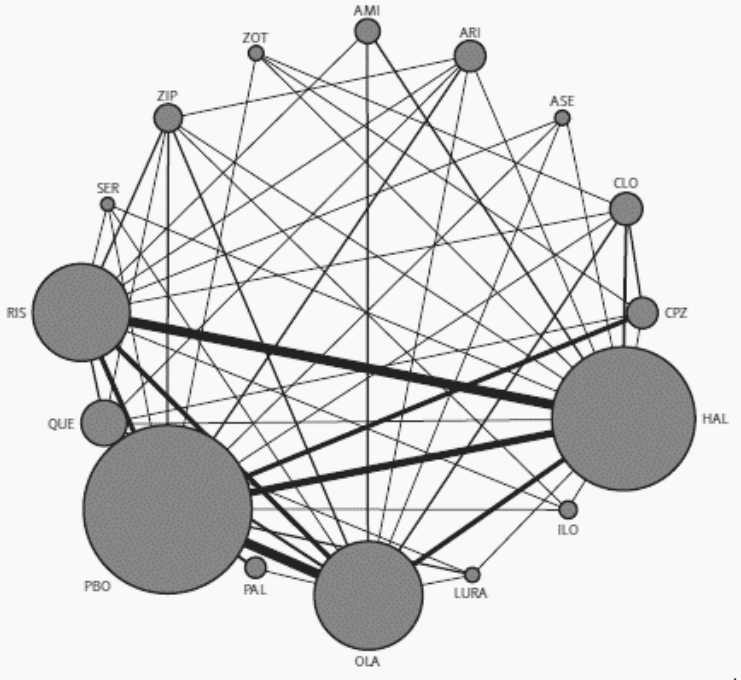
Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

Stefan Leucht, Andrea Cipriani, Loukia Spineli, Dimitris Mavridis, Deniz Örey, Franziska Richter, Myrto Samara, Corrado Barbui, Rolf R Engel, John R Geddes, Werner Kissling, Marko Paul Stapf, Bettina Lässig, Georgia Salanti, John M Davis

Summary

Background The question of which antipsychotic drug should be preferred for the treatment of schizophrenia is controversial, and conventional pairwise meta-analyses cannot provide a hierarchy based on the randomised evidence. We aimed to integrate the available evidence to create hierarchies of the comparative efficacy, risk of all-cause discontinuation, and major side-effects of antipsychotic drugs.

Lancet 2013; 382: 951–62
Published Online
June 27, 2013
http://dx.doi.org/10
S0140-6736(13)607

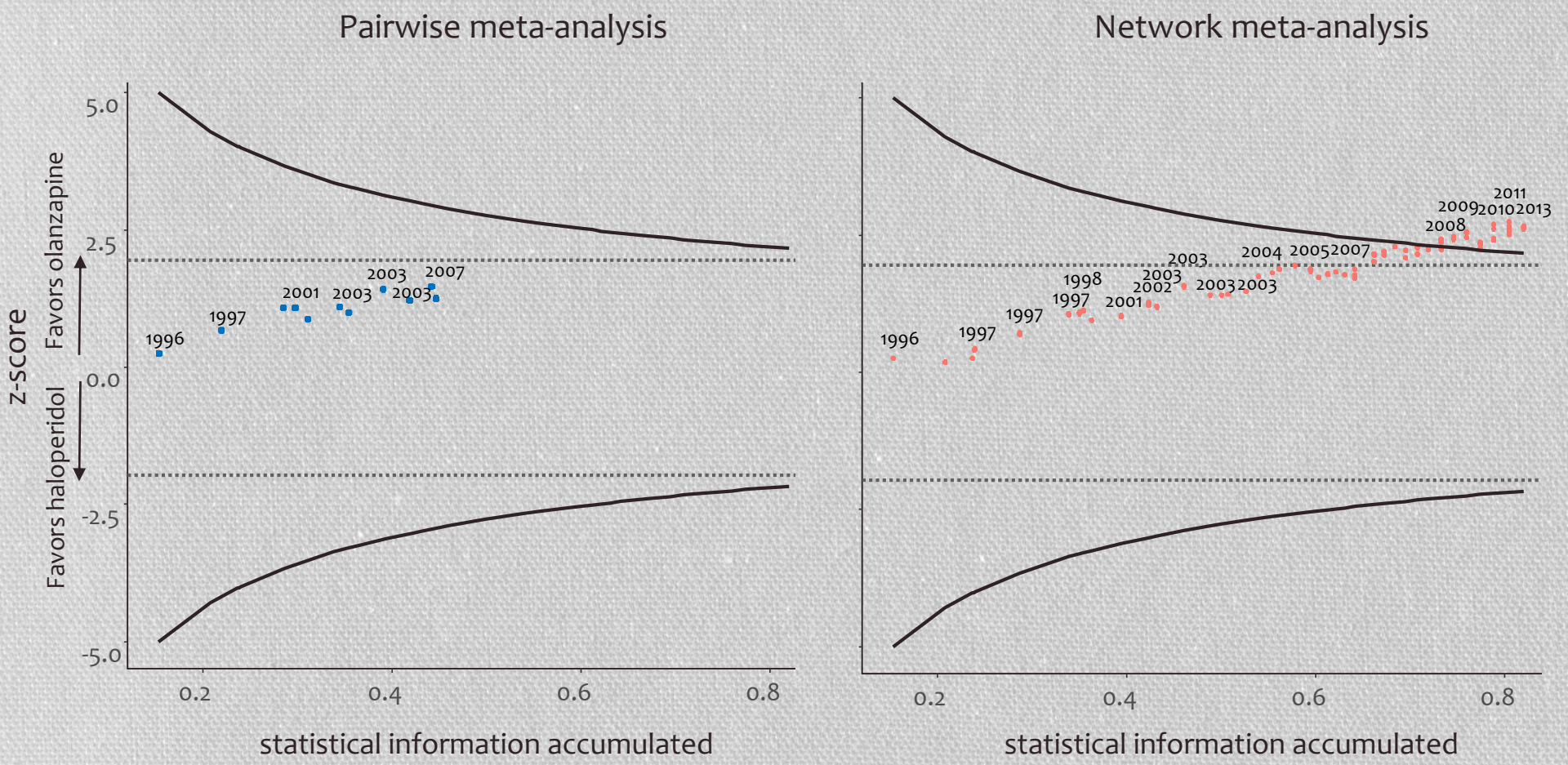


Outcome: overall change in symptoms

Type I and II errors: 5% and 10%

SMD of 0.13 favouring olanzapine as alternative effect

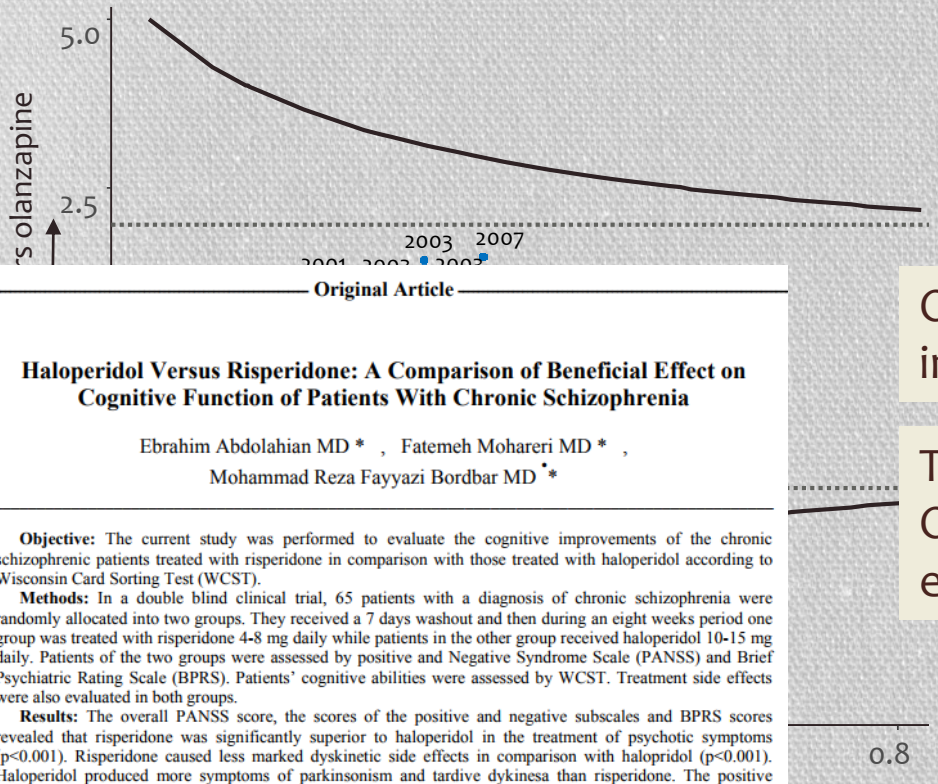
Example: olanzapine versus haloperidol in schizophrenia

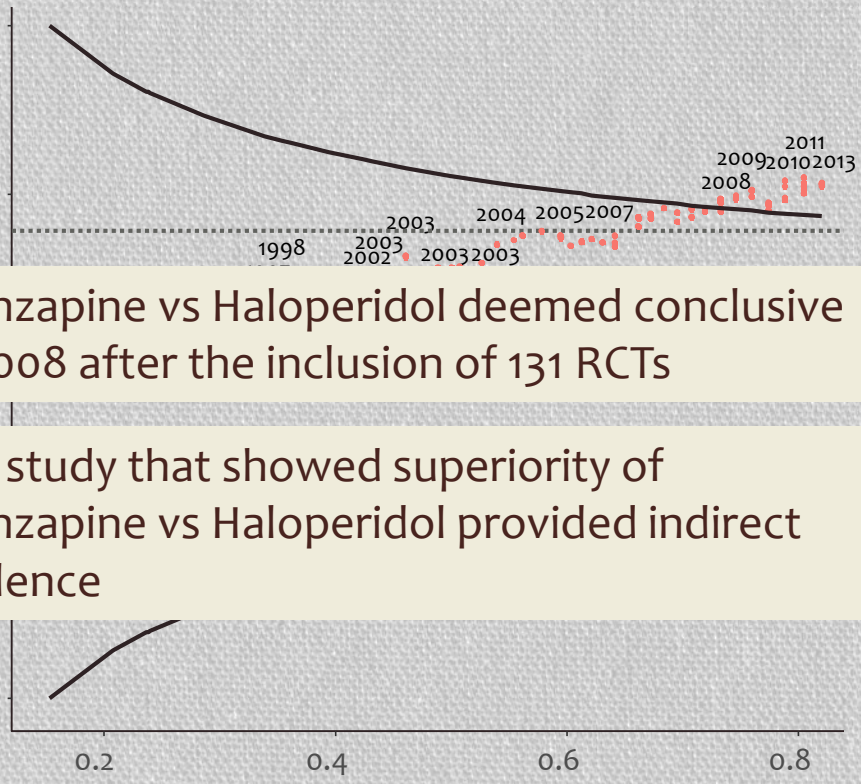


Example: olanzapine versus haloperidol in schizophrenia

Pairwise meta-analysis

Network meta-analysis





Original Article

Haloperidol Versus Risperidone: A Comparison of Beneficial Effect on Cognitive Function of Patients With Chronic Schizophrenia

Ebrahim Abdolahian MD * , Fatemeh Mohareri MD * ,
Mohammad Reza Fayyazi Bordbar MD *

Objective: The current study was performed to evaluate the cognitive improvements of the chronic schizophrenic patients treated with risperidone in comparison with those treated with haloperidol according to Wisconsin Card Sorting Test (WCST).

Methods: In a double blind clinical trial, 65 patients with a diagnosis of chronic schizophrenia were randomly allocated into two groups. They received a 7 days washout and then during an eight weeks period one group was treated with risperidone 4-8 mg daily while patients in the other group received haloperidol 10-15 mg daily. Patients of the two groups were assessed by positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS). Patients' cognitive abilities were assessed by WCST. Treatment side effects were also evaluated in both groups.

Results: The overall PANSS score, the scores of the positive and negative subscales and BPRS scores revealed that risperidone was significantly superior to haloperidol in the treatment of psychotic symptoms ($p<0.001$). Risperidone caused less marked dyskinetic side effects in comparison with halopridol ($p<0.001$). Haloperidol produced more symptoms of parkinsonism and tardive dykinesa than risperidone. The positive cognitive effect of risperidone was significantly better than haloperidol at 4th ($p<0.001$) and 8th ($p<0.001$) weeks.

Conclusion: Apart from being more effective in improving positive and negative symptoms of psychotic disorders, risperidone is also more beneficial in reducing the symptoms of cognitive impairment in chronic and long standing form of schizophrenia. It also seems to be better tolerated than haloperidol.

Iranian Journal of Psychiatry and Behavioral Sciences (IJPBS), Volume 2, Number 1, Spring and Summer 2008: 14-20.

Keywords: Haloperidole • Risperidone • Schizophrenia • Cognition • WCST

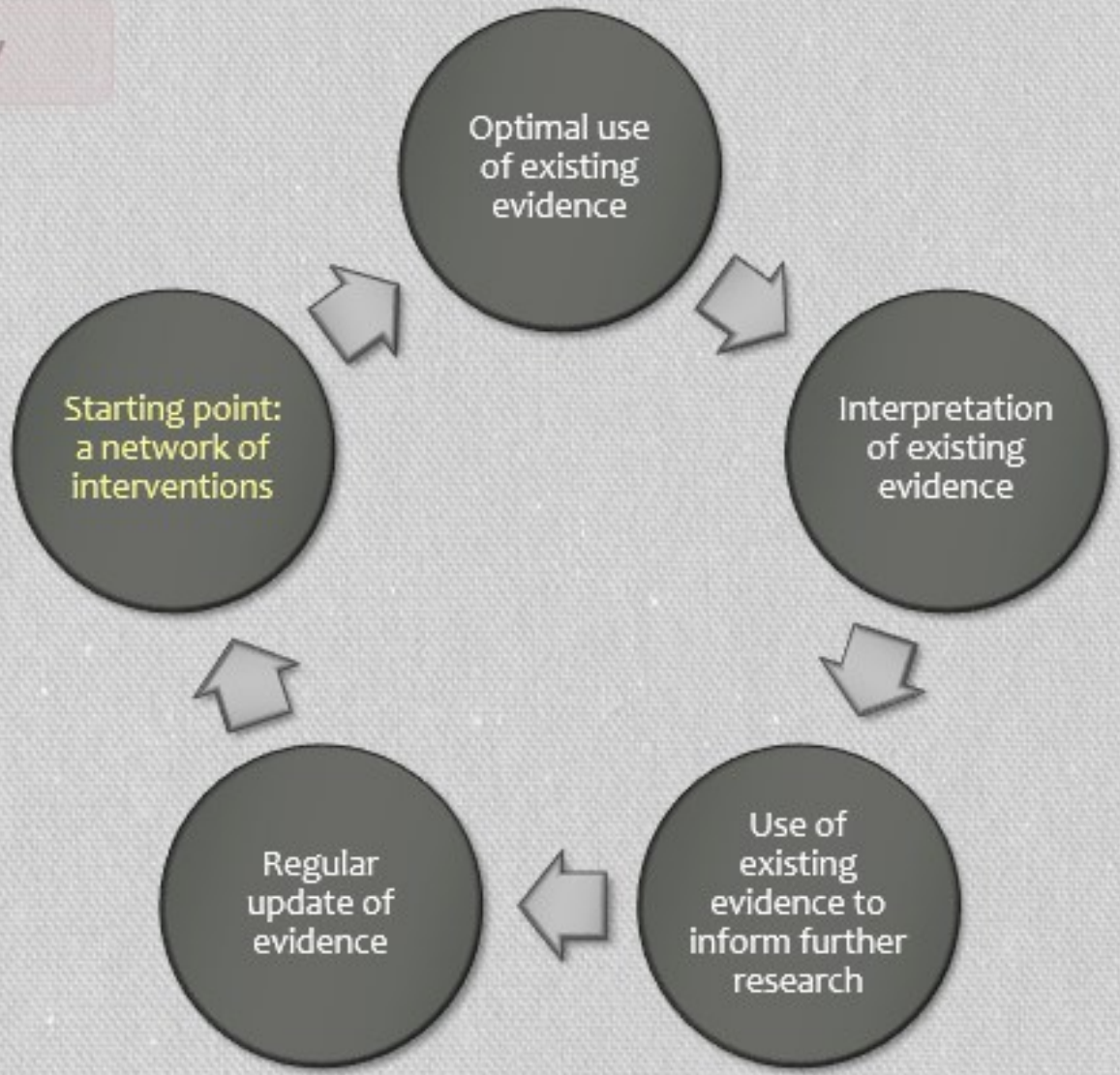
Olanzapine vs Haloperidol deemed conclusive in 2008 after the inclusion of 131 RCTs

The study that showed superiority of Olanzapine vs Haloperidol provided indirect evidence

framework

application

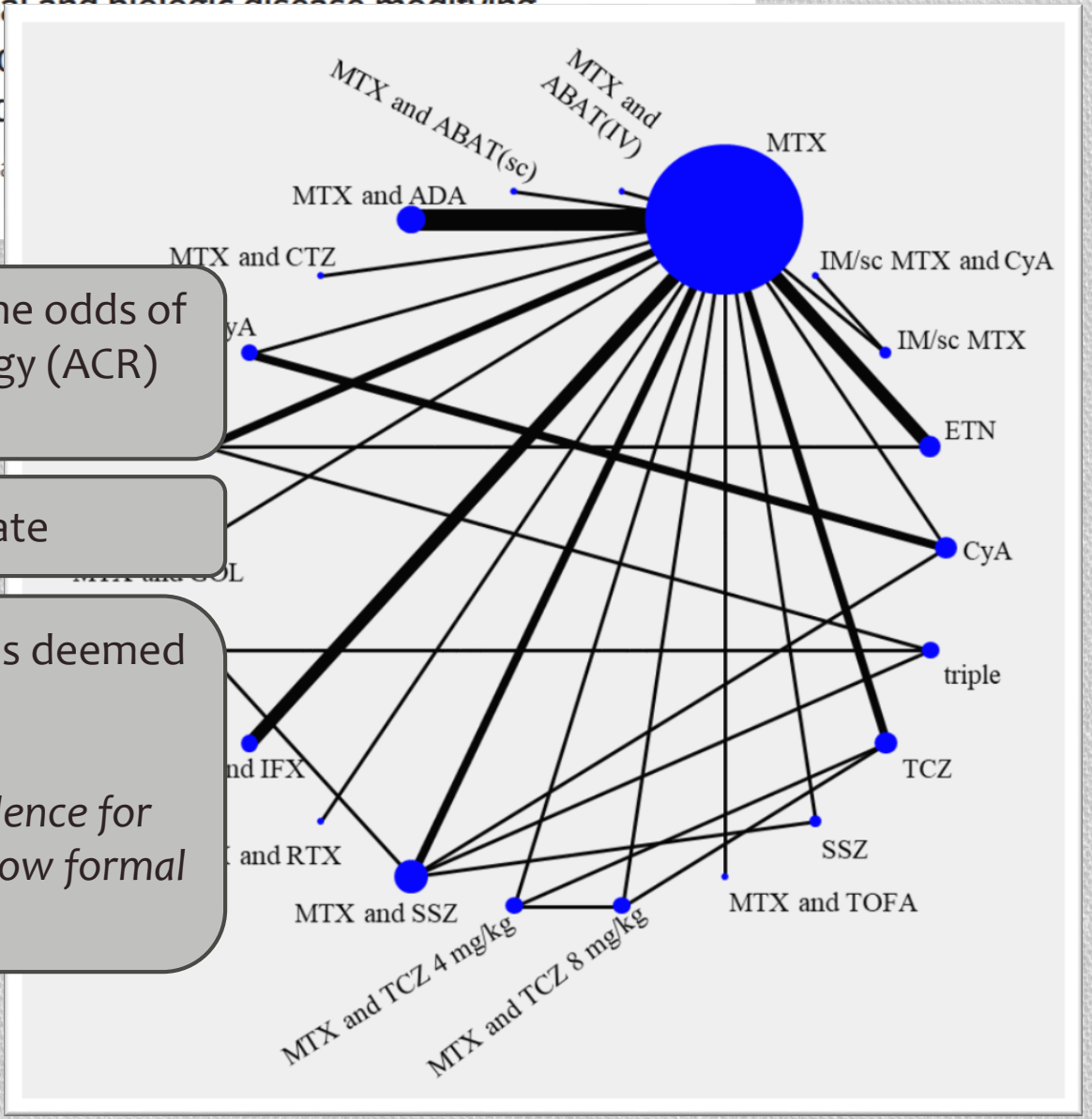
acceptability



RESEARCH

Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying antirheumatic drugs f… systematic review and…

Glen S Hazlewood,[1, 2, 3, 4] Cheryl B…
Claire Bombardier[5, 6, 7]



Outcome: efficacy measured as the odds of American College of Rheumatology (ACR) 50 response

Heterogeneity was low to moderate

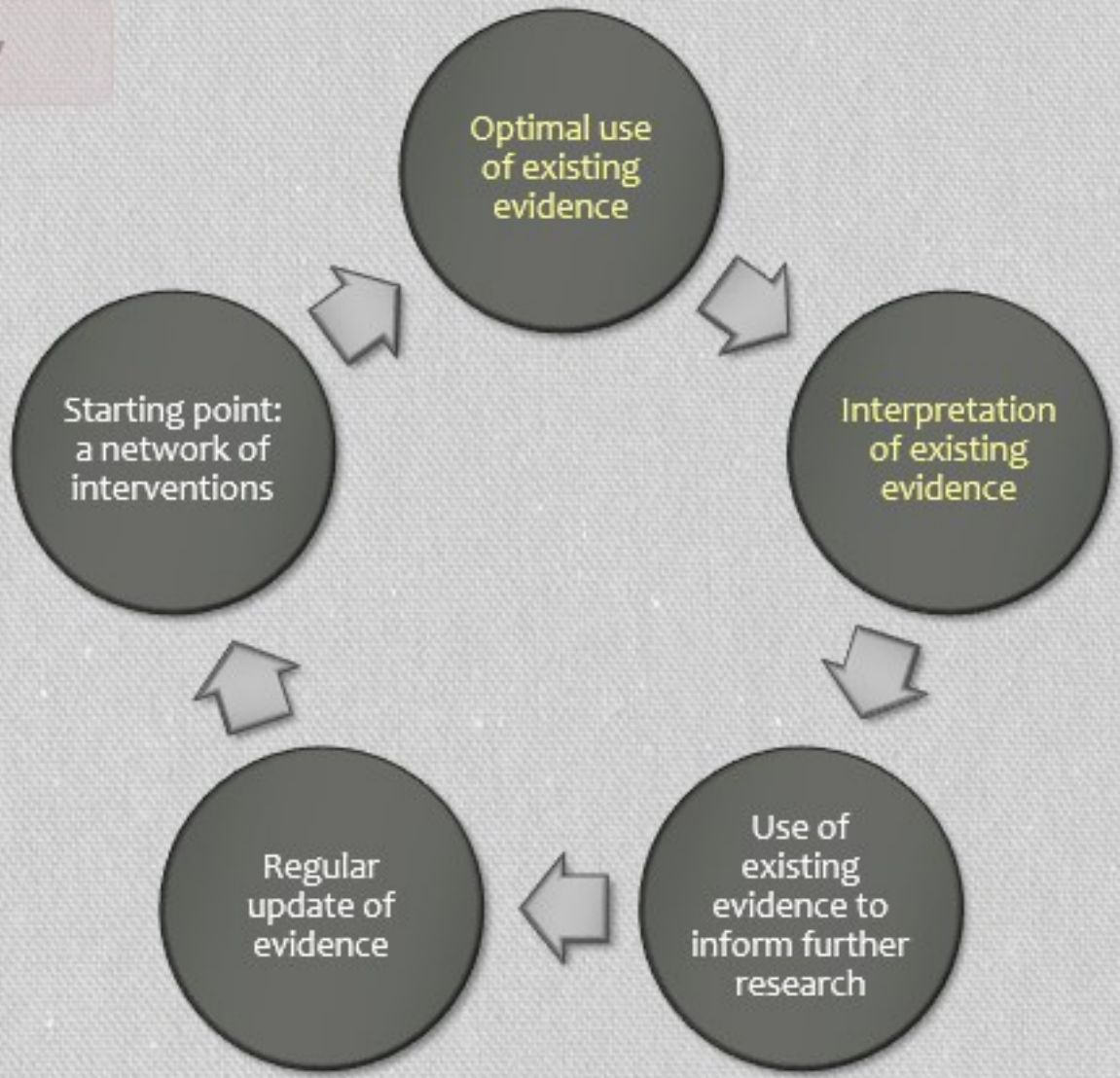
The assumption of coherence was deemed plausible after considering trial characteristics

- *although the lack of direct evidence for many comparisons does not allow formal statistical evaluation*

framework

application

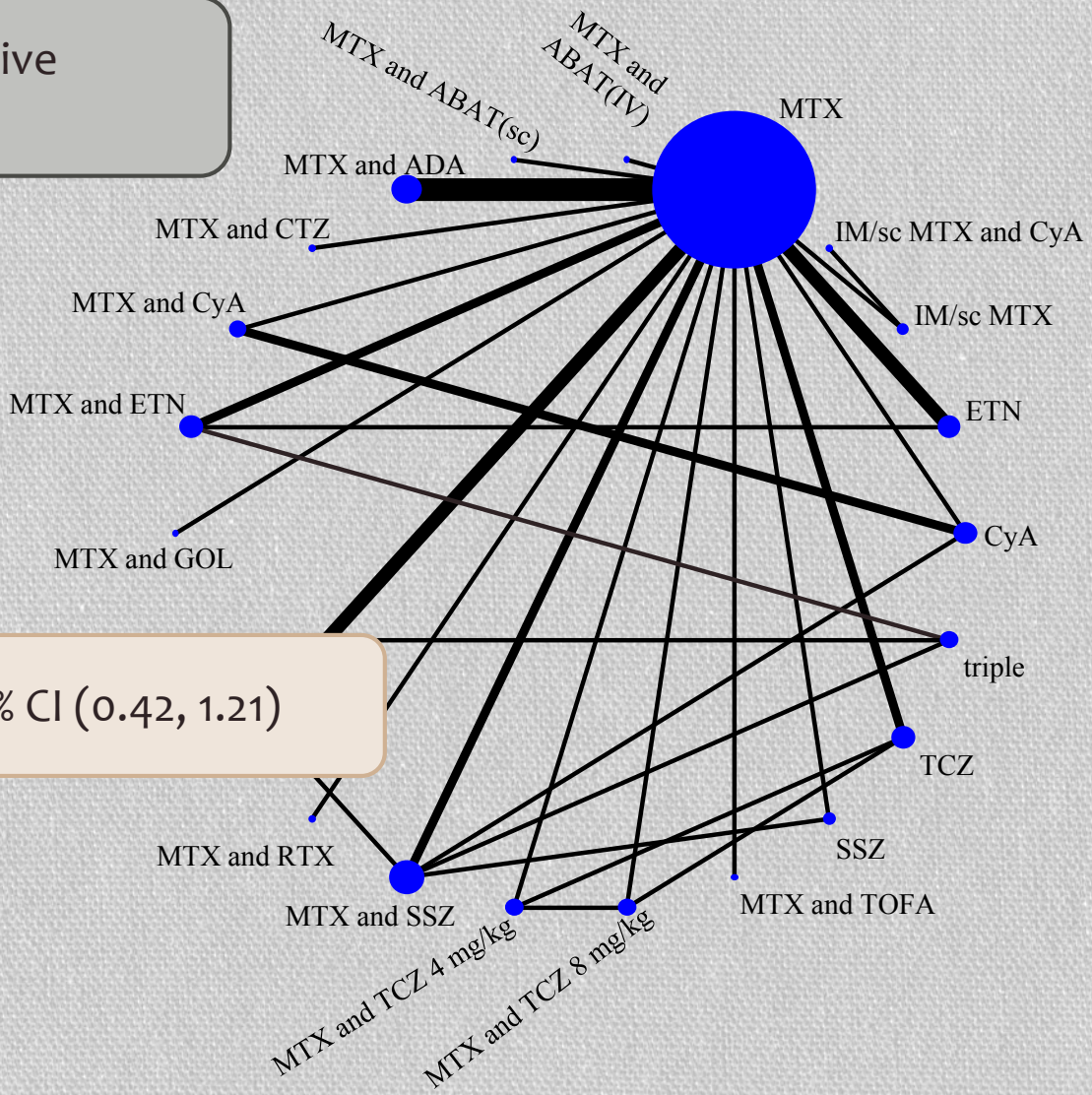
acceptability



Methotrexate is recommended as the first disease-modifying anti-rheumatic drugs

NMA results showed that combining methotrexate with biologic drugs was similarly effective with a triple therapy of conventional drugs (less costly)

MTX and ETN was the most effective treatment in the network



OR 0.71 favoring MTX and ETN, 95% CI (0.42, 1.21)

Evidence is inconclusive

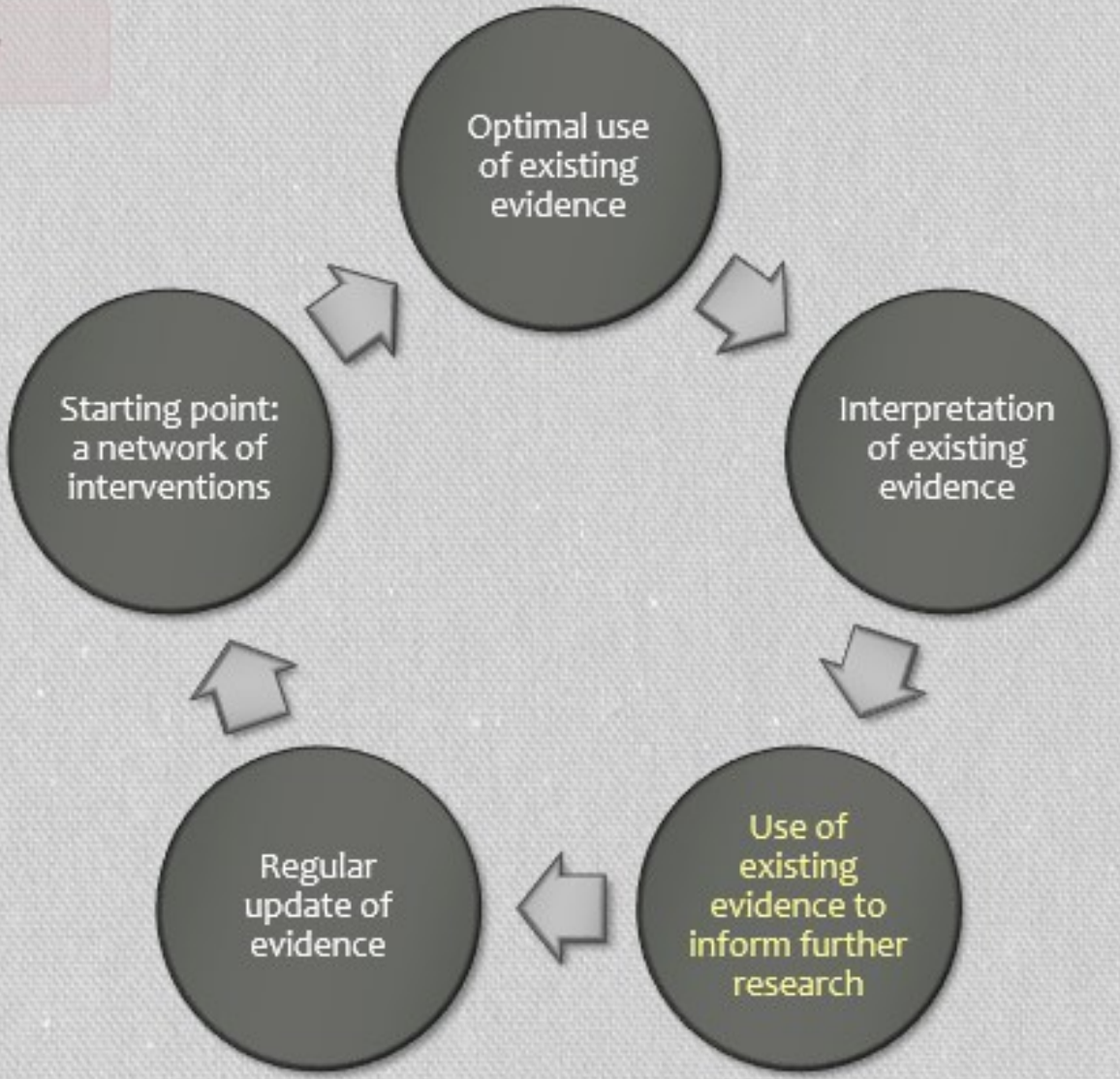
framework

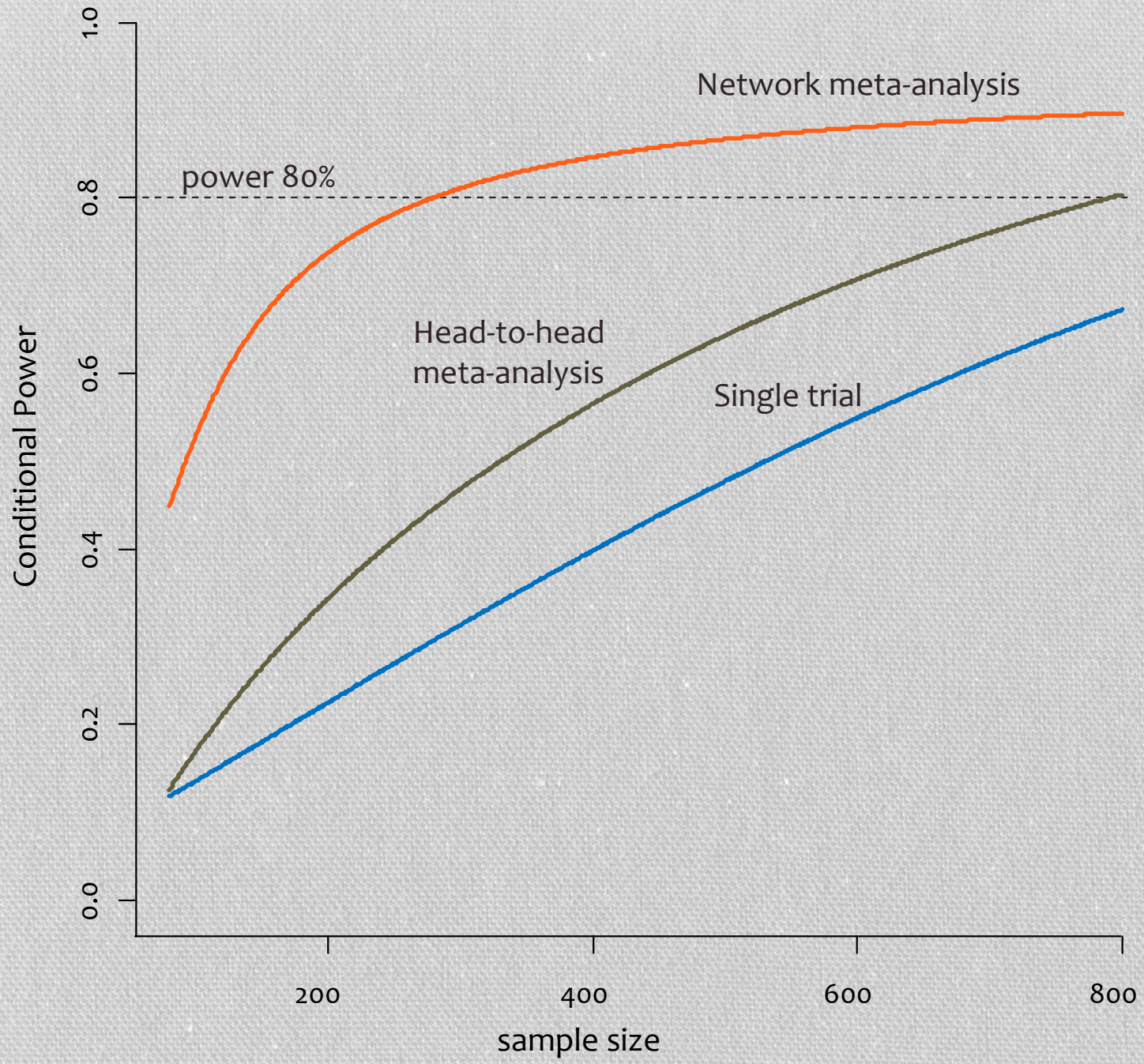
application

acceptability

Plan a new MTX and ETN versus triple therapy trial

Conditional power to detect an OR of 0.71

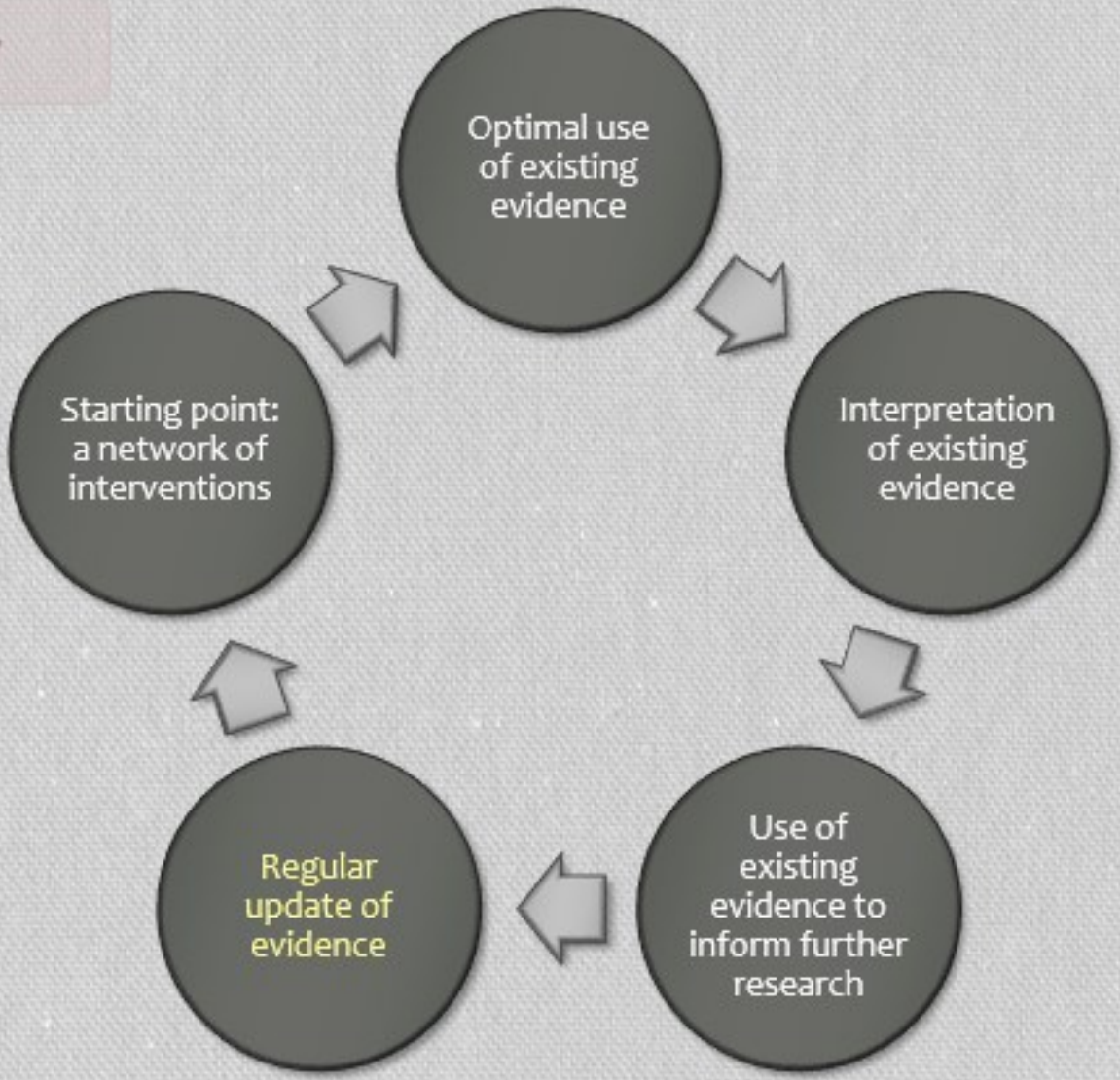



Conditional Power
0.0
0.2
0.4
0.6
0.8
1.0
power 80%
Network meta-analysis
Head-to-head
meta-analysis
Single trial
200
400
600
800
sample size

framework

application

acceptability



NMAs published **after 2012** with at least
5 treatments, 20 trials and within at least **10 years**

One treatment comparison per network
– the one most **relevant to guideline development**

	Network meta-analysis		
Pairwise meta-analysis	Yes	No	Total
Yes	7 (14%)	0 (0%)	7 (14%)
No	10 (20%)	32 (65%)	42 (86%)
Total	17 (35%)	32 (65%)	49 (100%)

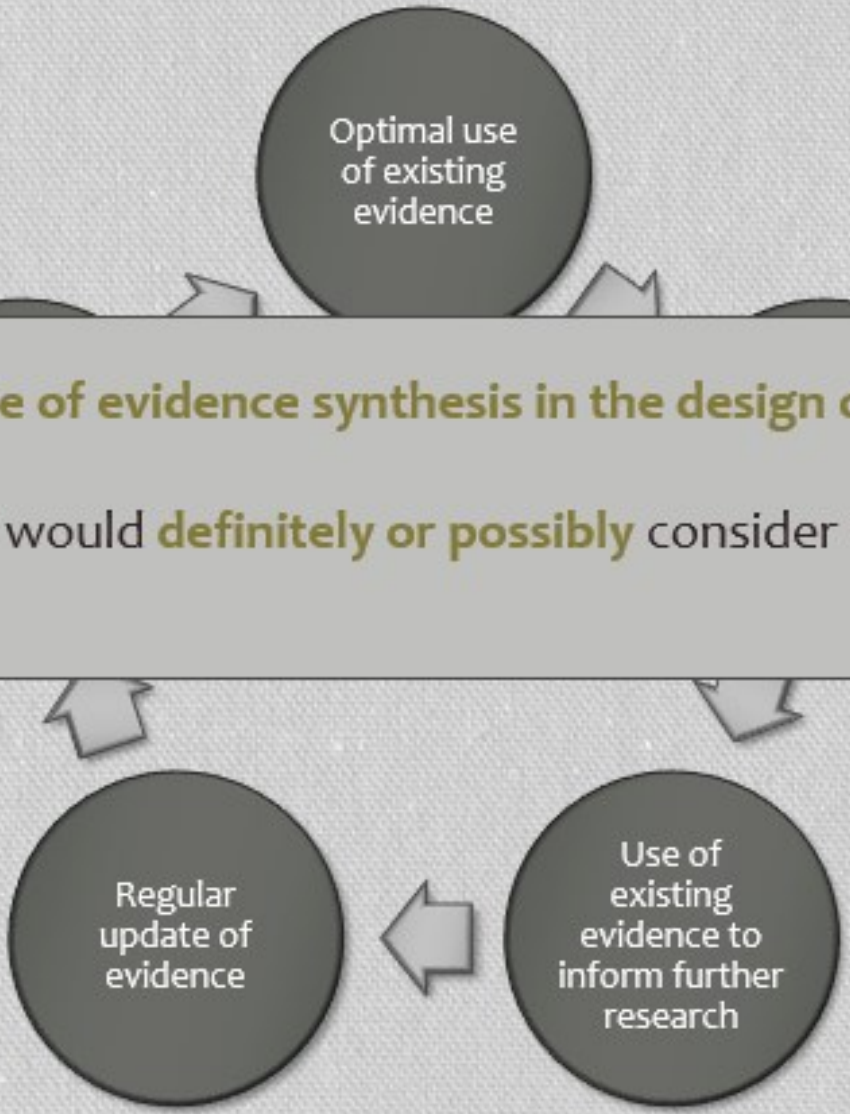
Nikolakopoulou et al., BMJ, 2018

framework

application

acceptability

Online survey among 76 methodologists in Europe



Low to moderate use of evidence synthesis in the design of future trials

65% stated that they would **definitely or possibly** consider it when planning a trial in the future

Discussion

Limitations

Heterogeneity and **incoherence** might pose barriers in the realisation of actively living network meta-analysis

Methodology to

-determine what sort of studies are needed based on a NMA

-continuously update an existing NMA

actively direct future research

Thank you!