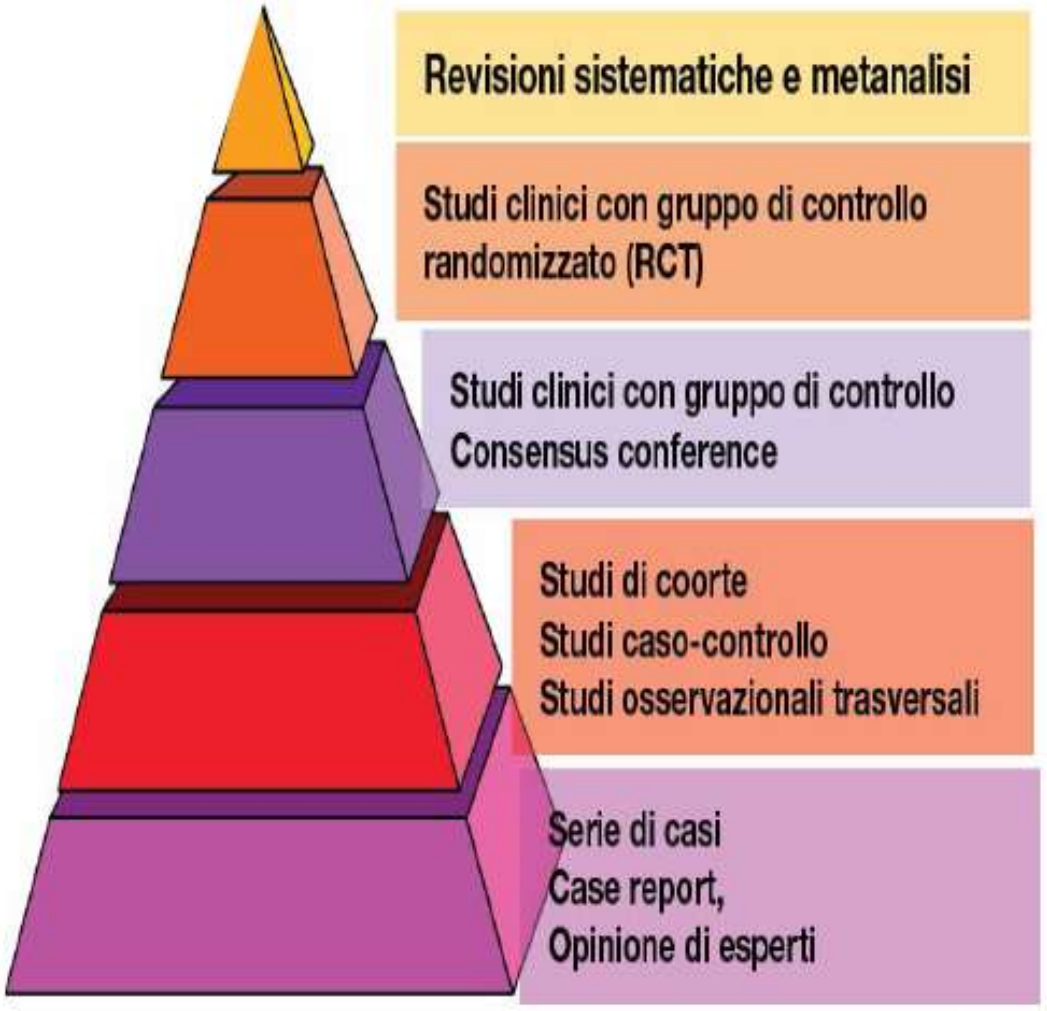
Tipologia delle Revisioni della Letteratura Scientifica.

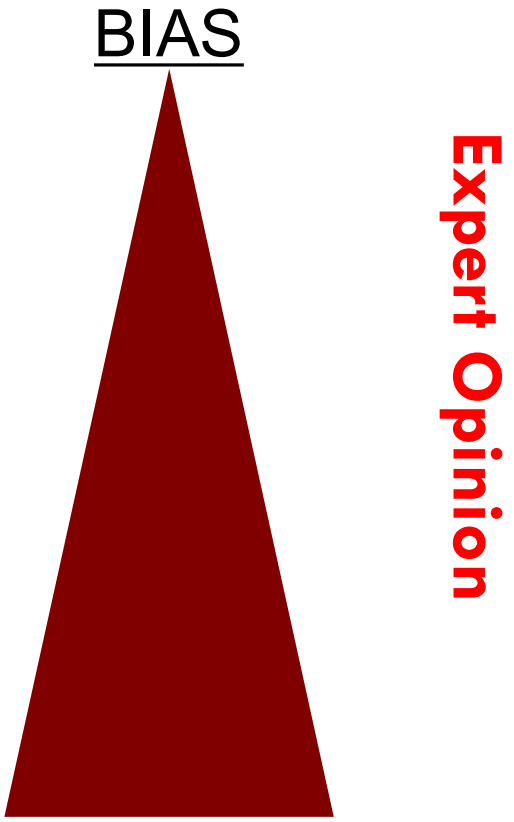
Obiettivi di una Revisione Sistematica.

La Piramide delle evidenze



STUDY DESIGN

- Randomized Controlled Trials
- Cohort Studies and Case Control Studies
- Case Reports and Case Series, Non-systematic observations
- Expert Opinion (personal clinical experience)



Revisioni sistematiche …

controlled trials of parachute intervention.

Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

not been proved with randomised controlled trials

Cosa è una revisione sistematica (RS)? (1)

- Un tentativo di sintetizzare i risultati e le conclusioni di due o più pubblicazioni (articoli primari) su una determinata problematica sanitaria.
- Vero e proprio progetto di ricerca

Cosa è una RS? (2)

Una valutazione *complessiva ed esaustiva*

- della *qualità*
- della *rilevanza clinica* e
- *eterogeneità*

Di tutte le informazioni disponibili su una determinata problematica sanitaria.

Cosa è una RS? (3)

- Una revisione che è stata realizzata attraverso un approccio scientifico rigoroso, per ridurre gli errori sistematici e casuali, in un modo documentato nei materiali e metodi.

- Una revisione sistematica può includere, o meno, una metanalisi: un'analisi statistica dei risultati degli studi indipendenti che ha, generalmente, come obiettivo di produrre una singola stima numerica dell'effetto del trattamento.

Chalmers I and Altman DG, 1995

Principi di una meta-analisi

Una meta-analisi può:

- Combinare i risultati dei singoli studi per ottenere una stima complessiva dell'effetto del trattamento;
- Esplorare l'eterogeneità tra gli studi (e le relative fonti di eterogeneità).

  NB: una revisione sistematica non si conclude forzatamente con una meta-analisi.

Una visione insiemistica

Revisione tradizionale

- Paragonabile al **capitolo** di un libro
- **Non esplicita** il metodo di **selezione**, **sintesi** ed **interpretazione** delle evidenze
- Complicato fare una valutazione critica riproducibile
- Obiettivi molto **ampi**
- Spesso fatte su commissione (conflitto Int.)

Revisioni sistematiche vs Revisioni narrative

Le revisioni tradizionali vs le revisioni sistematiche

CARATTERISTICHE	REVISIONE TRADIZIONALE	REVISIONE SISTEMATICA
Domanda	Ampia	Focalizzata su un unico quesito clinico
Fonti e ricerca	Non specificate	Complete ed esplicita
Selezione	Solitamente non specificata	Basata su criteri specifici
Valutazione critica	Variabile	Rigorosa
Sintesi	Qualitativa	Qualitativa/quantitativa (meta-analisi)

Caratteristiche delle RS (1)

- Chiara definizione del titolo e dell'obiettivo;
- Strategia di ricerca esaustiva che risponda agli obiettivi della RS (studi rilevanti) per includere sia gli studi pubblicati che i non pubblicati;
- Criteri di inclusione/esclusione adottati esplicitati e motivati;
- Lista esaustiva di tutti gli studi identificati;
- Presentazione chiara delle caratteristiche di ogni studio incluso e analisi della loro qualità metodologica;

Caratteristiche delle RS (2)

- Lista degli studi esclusi e motivazione dell'esclusione;
- Analisi trasparente dei risultati degli studi eleggibili utilizzando tecniche di sintesi statistica (meta-analisi) se appropriato e possibile;
- Analisi di sensibilità dei dati se appropriate e possibili;
- Stesura di un rapporto finale che presenti chiaramente l'obiettivo, descriva i materiali e metodi e riporti i risultati.

Perché sono necessarie le revisioni sistematiche?

- Perché il numero di pubblicazioni e di ricerche su un determinato argomento è troppo grande
- Perché considerare solo parte delle informazioni disponibili può determinare errori (publication bias)
- Perché la qualità metodologica degli studi è variabile
- Perché i risultati di studi diversi condotti sullo stesso argomento spesso differiscono tra loro

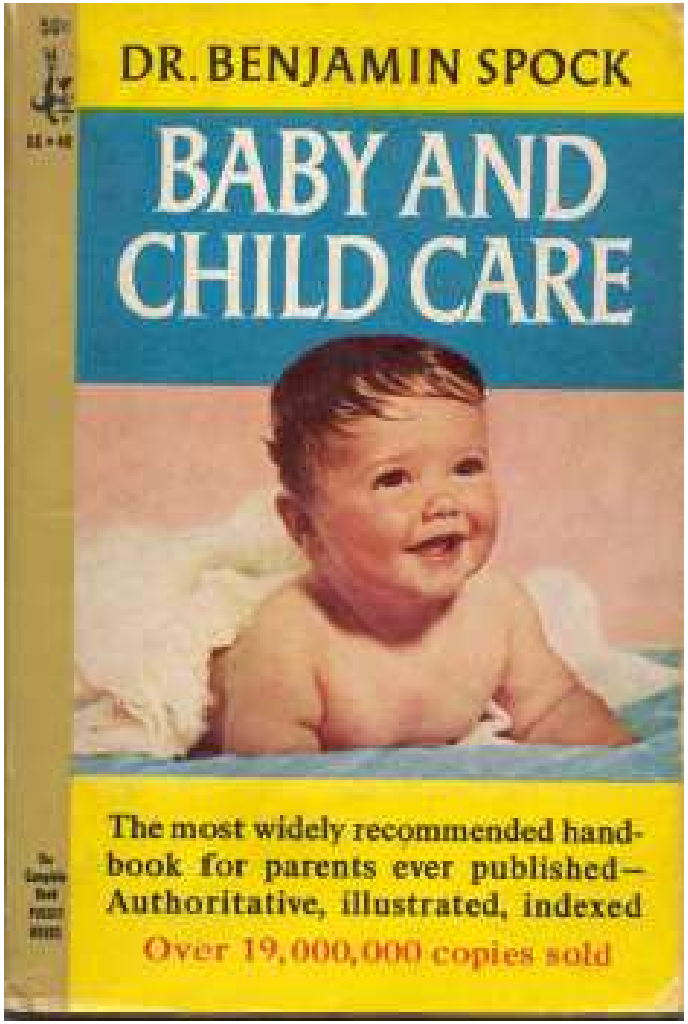
Perché sono utili le
revisioni sistematiche?

‘In God we trust, all others (must) bring data’

W Edwards Deming

Situazioni di particolare utilità

- Quando risultati conflittuali si accumulano rapidamente con risultati incerti
- Quando una patologia è percepita in modo "drammatico" dalla popolazione
- Quando un trattamento potenzialmente efficace rischia di essere abbandonato
- Quando la ricerca clinica deve essere "ri-orientata"
- Quando bisogna esplicitare la limitazione delle informazioni scientifiche disponibili per le decisioni sanitarie
- Ogni volta che si deve costruire un progetto di ricerca


DR. BENJAMIN SPOCK
BABY AND CHILD CARE
The most widely recommended handbook for parents ever published—Authoritative, illustrated, indexed
Over 19,000,000 copies sold

Benjamin McLane Spock (New Haven, 2 maggio 1903 – La Jolla, 15 marzo 1998) - pediatra statunitense
- fama con la pubblicazione del libro: ***Common Sense Book of Baby and Child Care*.**
Il libro venne **pubblicato** per la prima volta nel **1946** e fu tradotto in tutte le principali lingue del mondo; fu uno dei maggiori successi editoriali dell'immediato dopoguerra, vendendo per circa un decennio un milione di copie all'anno e raggiungendo, nel 2011, un volume complessivo di vendite di circa **50 milioni** di copie. Spock aveva avuto l'abilità di trattare temi molto popolari (soprattutto presso le donne), come la gravidanza, il parto, l'alimentazione e le cure del bambino, con un linguaggio semplice e brillante, spregiudicato e anticonformista, presentando progressi e orientamenti della ginecologia e della pediatria come novità rivoluzionarie derivanti anche dalla sua esperienza professionale.

Scenario: 1970 – reparto di ostetricia

Madre primipara, spaventata dalla “**morte in culla”**, alla dimissione dal reparto dopo il parto, **chiede**:

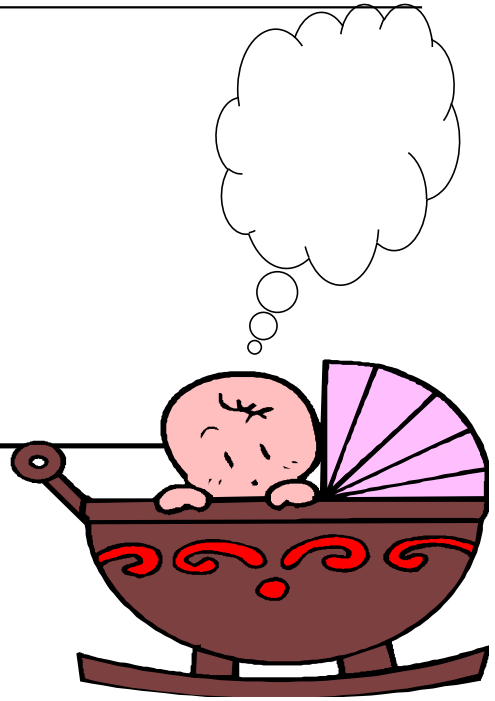
Qual è la posizione migliore in cui porre il neonato durante il sonno ?

Il medico di stanza scrupoloso commissiona allo specializzando una **ricerca bibliografica …**

Scenario: 1970 – reparto di ostetricia

Ricerca Bibliografica:

Testo	Posizione consigliata
Mollon 1967 1° ed.	Supina
Potts 1967 1° ed.	Prona o fianco
Illingworth & Illingworth 1968 4° ed.	Indifferente
Illingworth 1968 4° ed.	Prona
Mollon 1968 2° ed.	Supina
Spock 1969 3° ed.	Prona

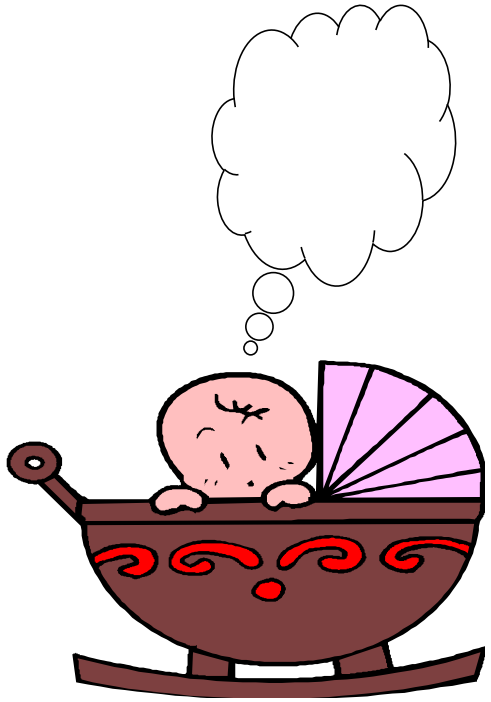


… nella lettera di dimissione, tra le raccomandazioni, viene riportato che *la posizione migliore del neonato nella culla, durante il sonno, è quella* ***prona (pancia in giù)***

...ancora sulla posizione del lattante:

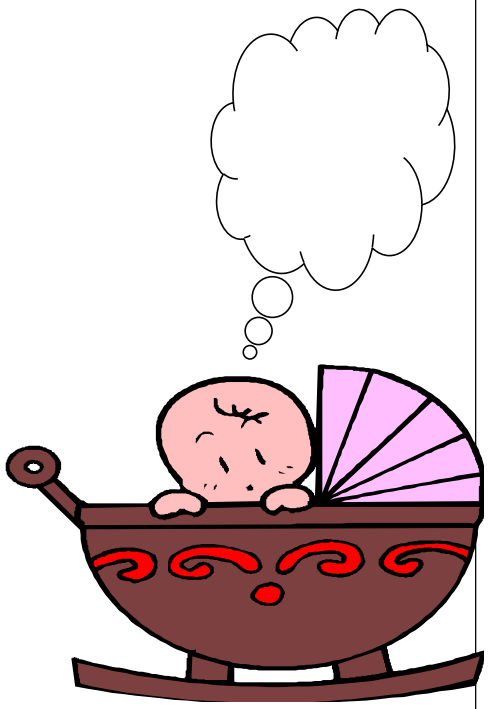
Facoltà di Medicina

Anni 90



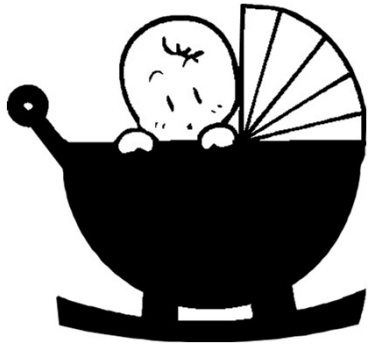
Dal testo consigliato per l'esame di pediatria

- Dalla edizione 1990 e dalla edizione 1997:
  - Sulla morte in culla: 5 (cinque) righe
    - Possibile causa: shock anafilattico da latte vaccino
    - 1-2 casi per 1000 nati vivi
    - Prima causa di morte tra 1 e 12 mesi
  - Sulla posizione dei lattanti nel sonno, riportata per terapia del reflusso gastro-esofageo:
    - "Corretta posizione: prona e su un letto tenuto leggermente inclinato"



Alcune possibile conseguenze di questo modo di procedere:

una strage silenziosa



Int. J. Epidemiol. Advance Access published April 20, 2005

Published by Oxford University Press on behalf of the International Epidemiological Association

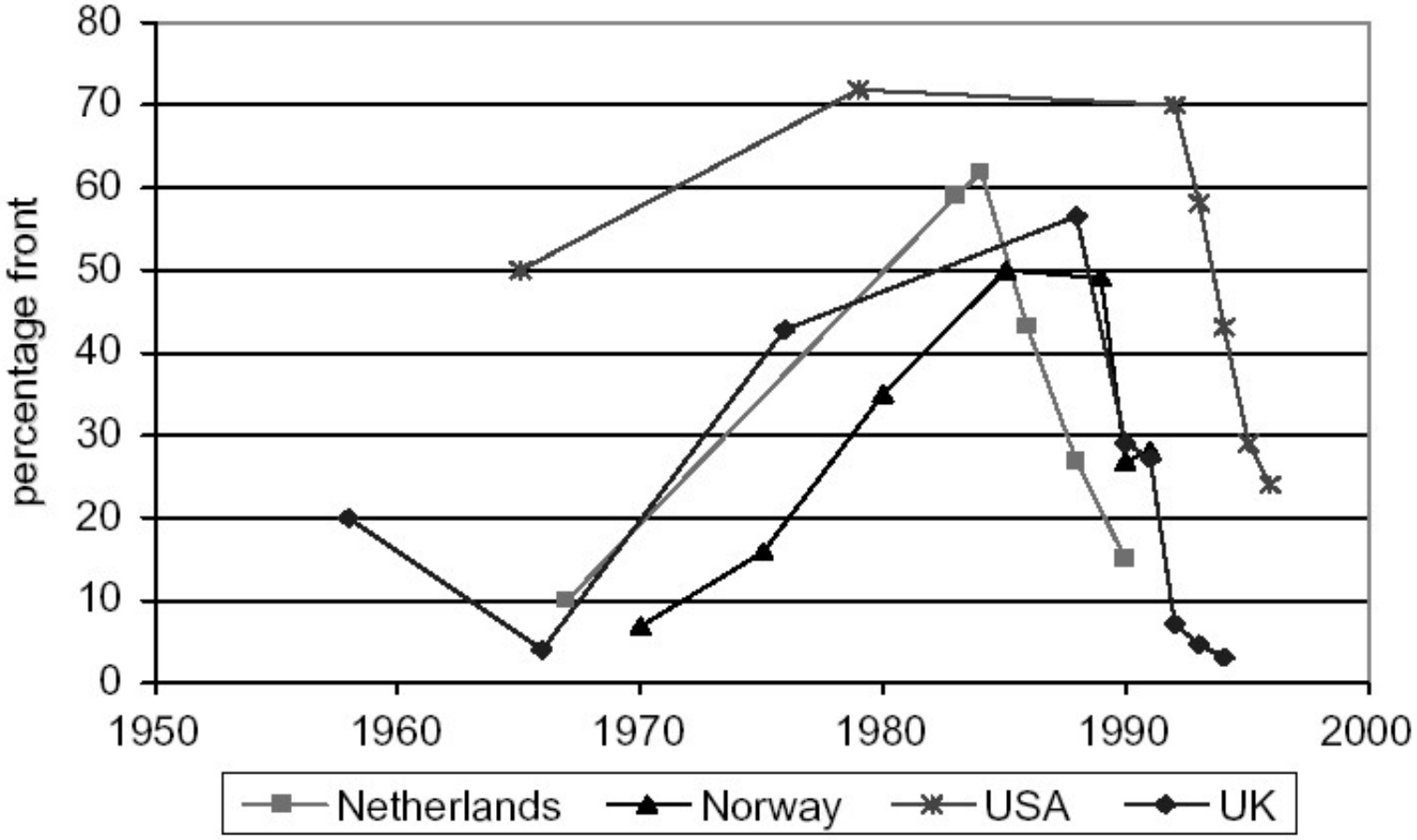
International Journal of Epidemiology
doi:10.1093/ije/dyi088

Infant sleeping position and the sudden infant death syndrome: systematic review of observational studies and historical review of recommendations from 1940 to 2002

Ruth Gilbert,[1]* Georgia Salanti,[2] Melissa Harden[1] and Sarah See[1,3]

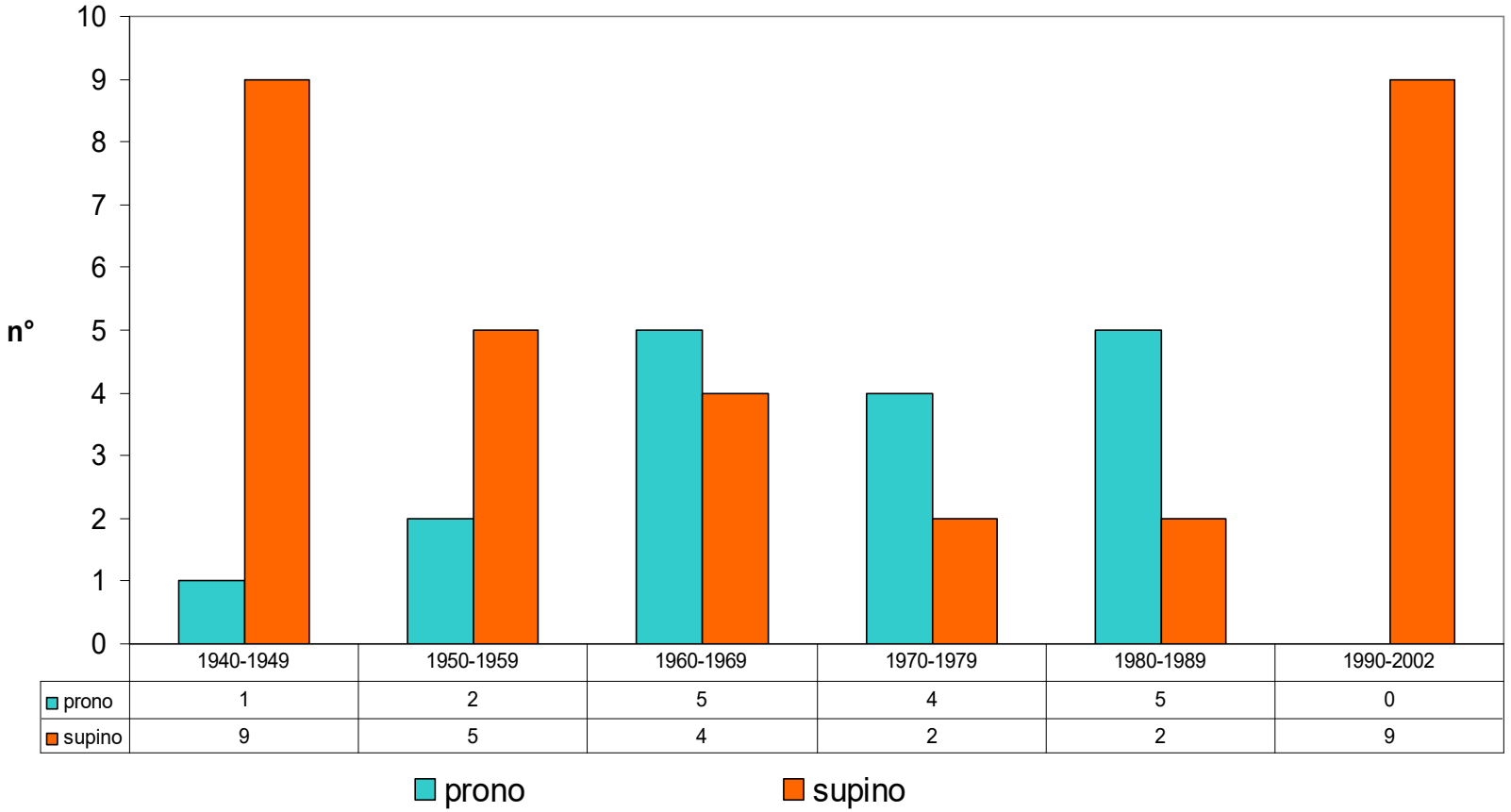
- Morte in culla

Frequenza della posizione prona del lattante nel sonno



(Gilbert 2005)

Raccomandazioni sulle posizioni del sonno nel lattante: letteratura inglese

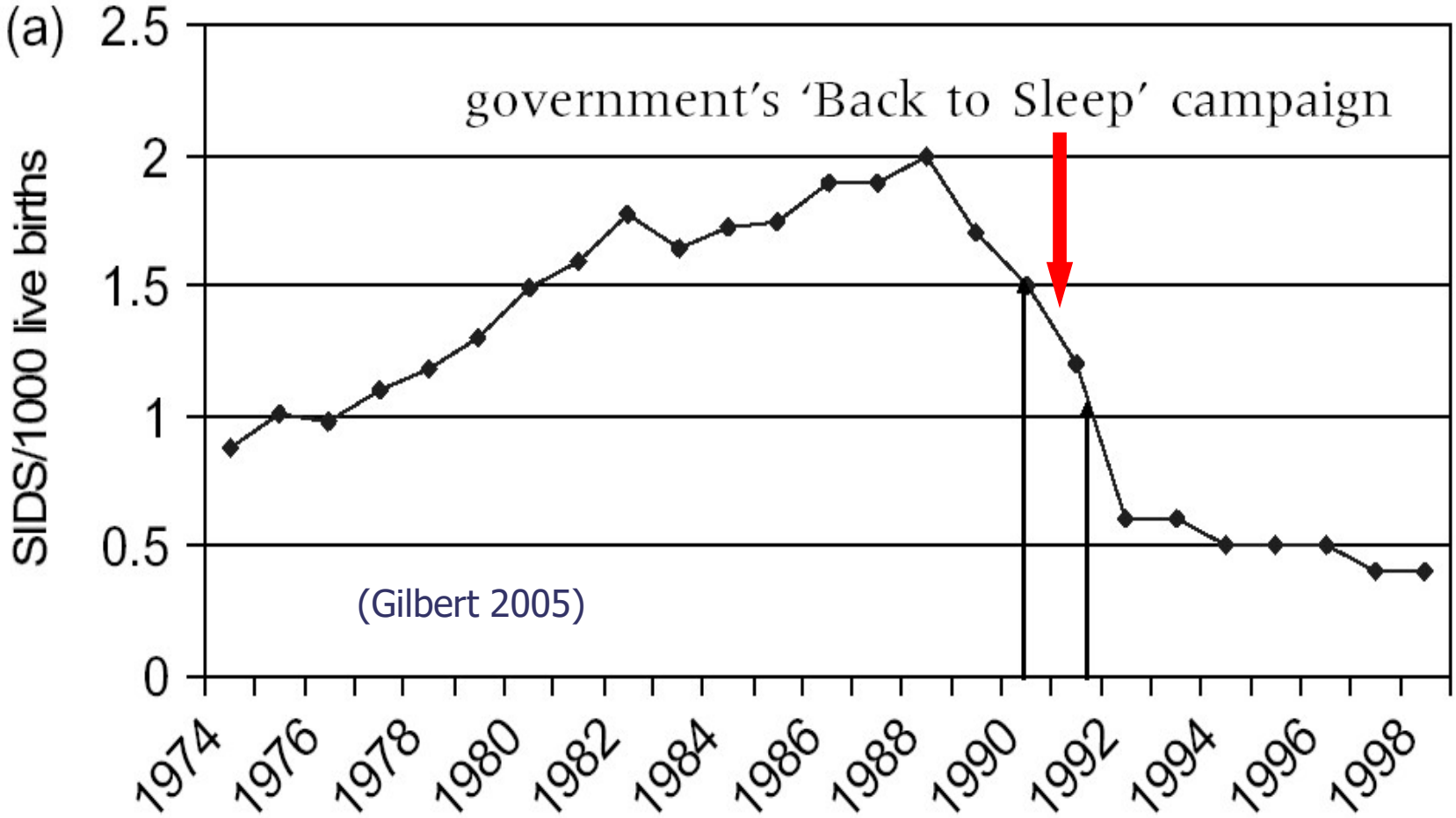


	1940-1949	1950-1959	1960-1969	1970-1979	1980-1989	1990-2002
prono	1	2	5	4	5	0
supino	9	5	4	2	2	9

(Gilbert 2005)

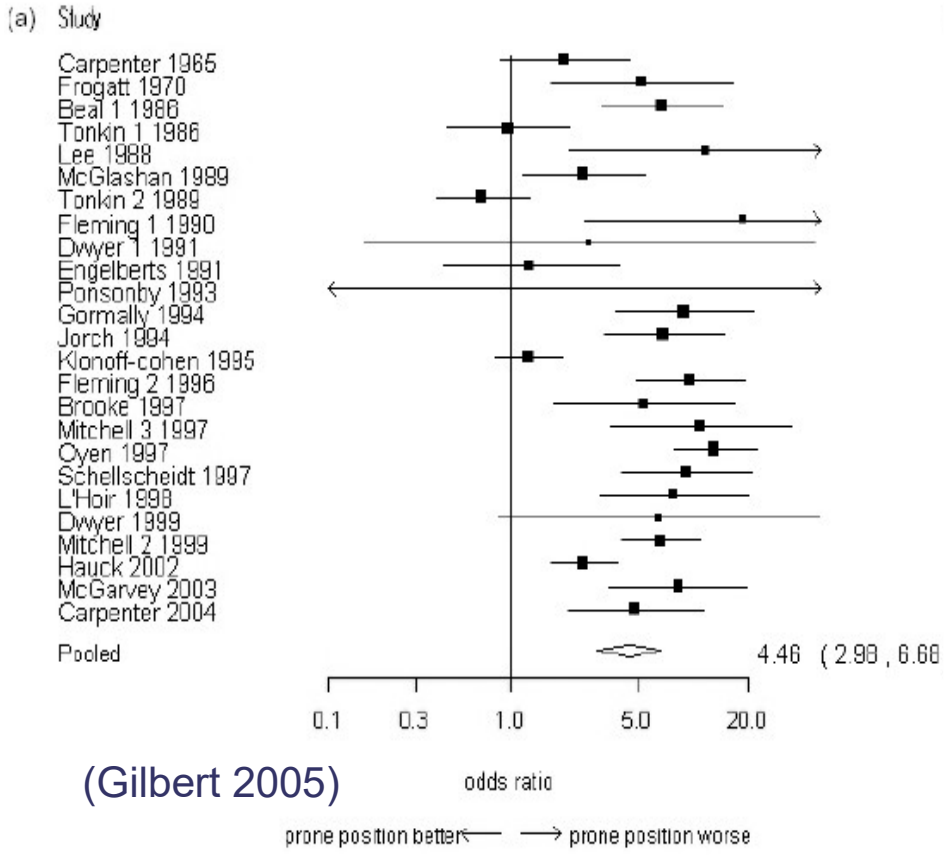
Morte in culla

Incidenza della morte in culla: Time trend in UK



Morte in culla

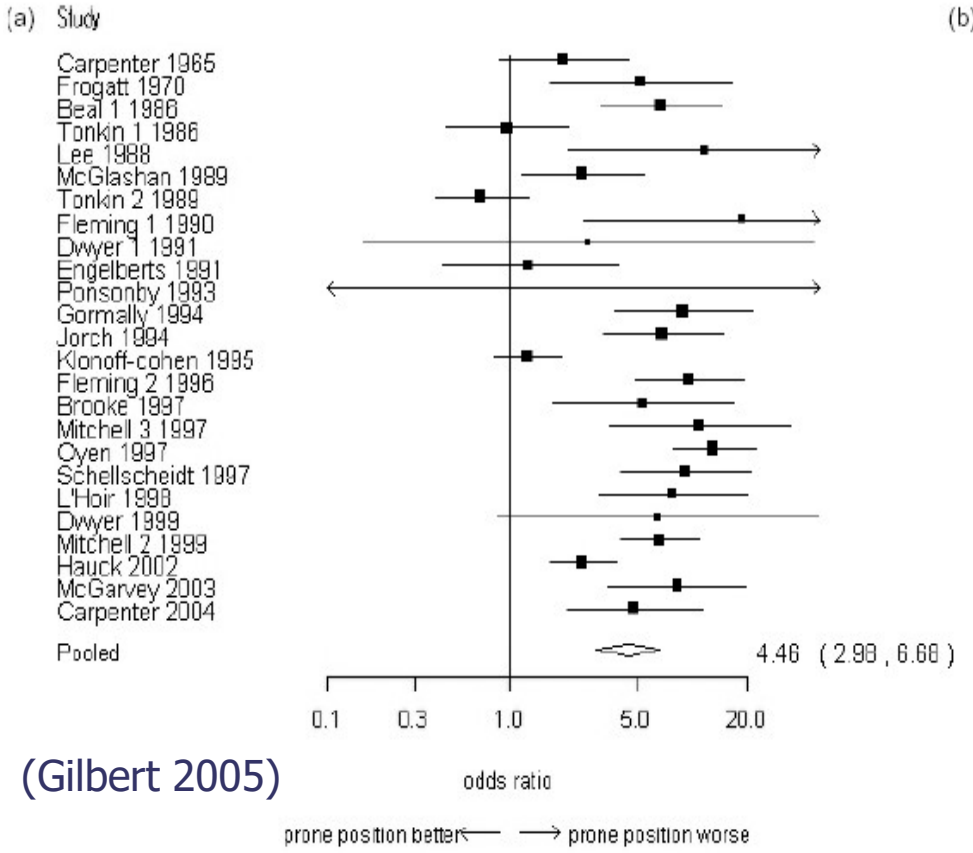
Metanalisi degli studi epidemiologici sulla posizione prona e rischio di morte del lattante nel sonno

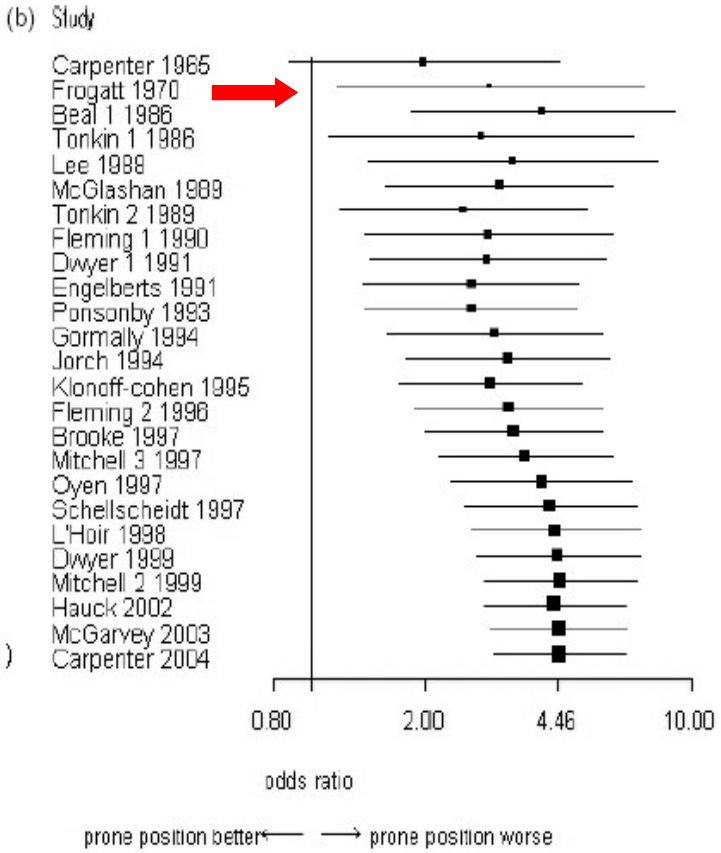


(Gilbert 2005)

Morte in culla

Meta analisi CUMULATIVA





(Gilbert 2005)

Morte in culla

Gilbert 2005:

- La raccomandazione di **tenere il neonato in culla in posizione prona è proseguita per circa 50 anni** senza tener conto dell'**evidenza disponibile** già dal **1970** che la posizione prona era dannosa

- **Una revisione sistematica** dei fattori di rischio prevenibili per evitare la morte in culla avrebbe permesso a partire **dal 1970** di **conoscere** che la posizione prona era dannosa e avrebbe **evitato** più di **10.000 morti in Gran Bretagna e almeno 50.000 tra Europa**, Stati Uniti e Australia.

Fasi di produzione di una LG

- Scelta dell'argomento
- Composizione di un gruppo multidisciplinare
- Definizione dei quesiti clinici
- **Revisione sistematica della letteratura**
- Valutazione critica dei risultati della ricerca (qualità dell'evidenza)
- Formulazione delle raccomandazioni
- Esplicitazione della forza delle raccomandazioni
- Peer review
- Diffusione e implementazione

CON CHI?

- Non da soli!
- Multidisciplinare
- Esperti dell'argomento bilanciati da 'ignari'
- Metodologi, epidemiologi clinici o statistici
- Un po' di esperienza e un po' di training non guastano (ecco perché siete qui)
- Coinvolgere pazienti/users (molto Cochrane)

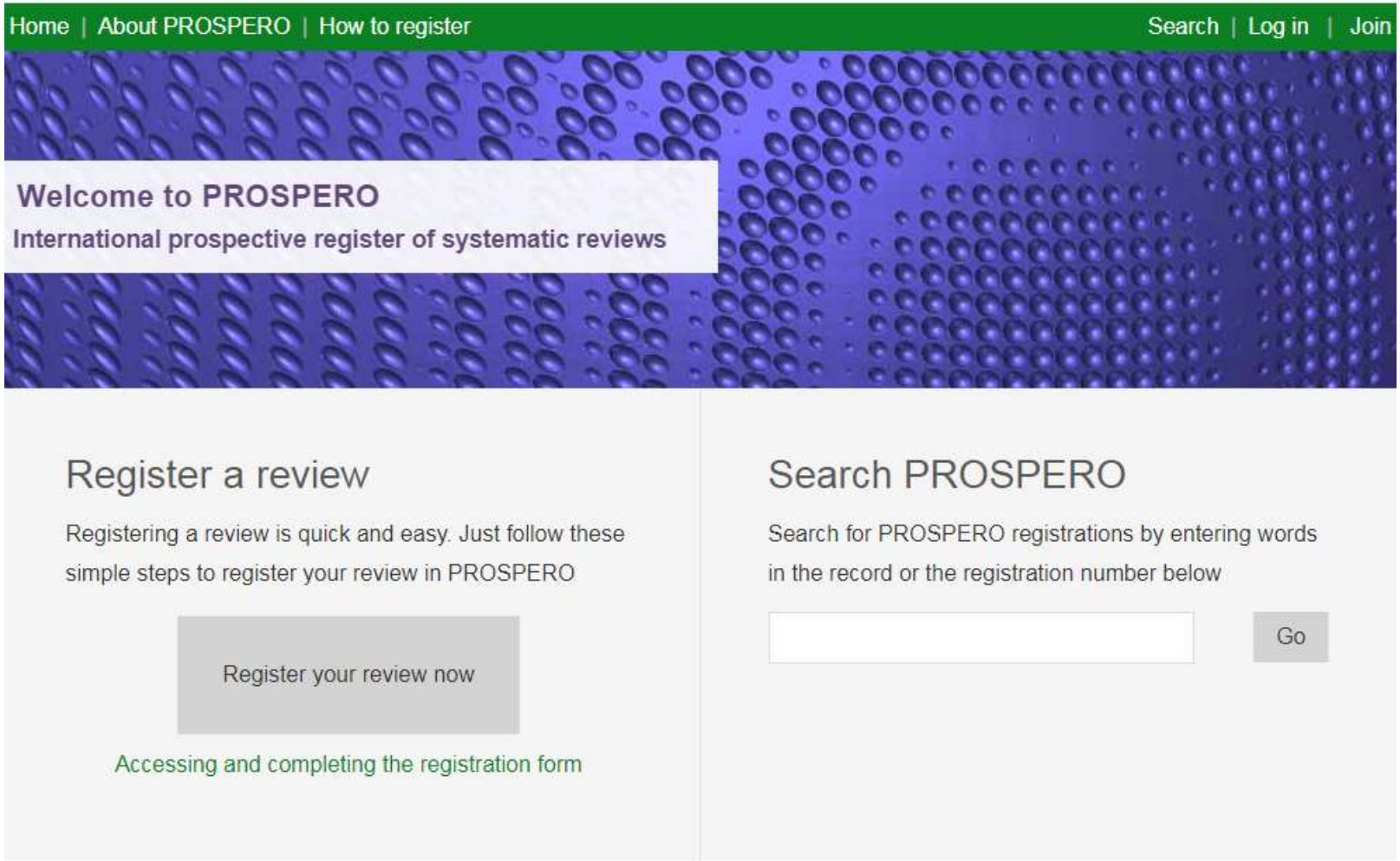
Il protocollo di una revisione sistematica

Protocollo -contenuti

- Background
- Obiettivi della revisione
- Metodi
  - ✓ I criteri di inclusione degli studi
  - ✓ La strategia di ricerca bibliografica
  - ✓ I metodi con cui verranno estratti i dati
  - ✓ I criteri di valutazione di qualità metodologica degli studi che verranno usati
  - ✓ Il metodo usato per l'eventuale sintesi statistica
  - ✓ Eventuali analisi per sottogruppi
  - ✓ Metodo per valutare la qualità dell'evidenza (GRADE)

Protocollo

- Scriverlo: fondamentale
  - ✓più revisori
  - ✓avere idee chiare di quello che si vuole fare
  - ✓evitare il selection bias (criteri di inclusione)
  - ✓evitare il reporting bias (solo i risultati significativi)
- Pubblicarlo: raccomandato



What you will find in PROSPERO

http://www.crd.york.ac.uk/prospero/aboutreg.php?reg=help

Help with registration

Download the guidance notes for registering a systematic review on PROSPERO.

COSA VOGLIAMO FARE?

- The ‘splitting’ rationale is that it is only appropriate to combine trials which are very similar in design, patient selection, intervention characteristics and outcome recording.
- Split reviews avoid combining ‘apples and oranges’
- Reviews can be split by participants, interventions or outcome
- Very narrowly focused reviews are de facto subgroup analyses

Il Quesito/obiettivo della vostra revisione sistematica detta titolo e criteri di inclusione/esclusione (i.e. PICO)

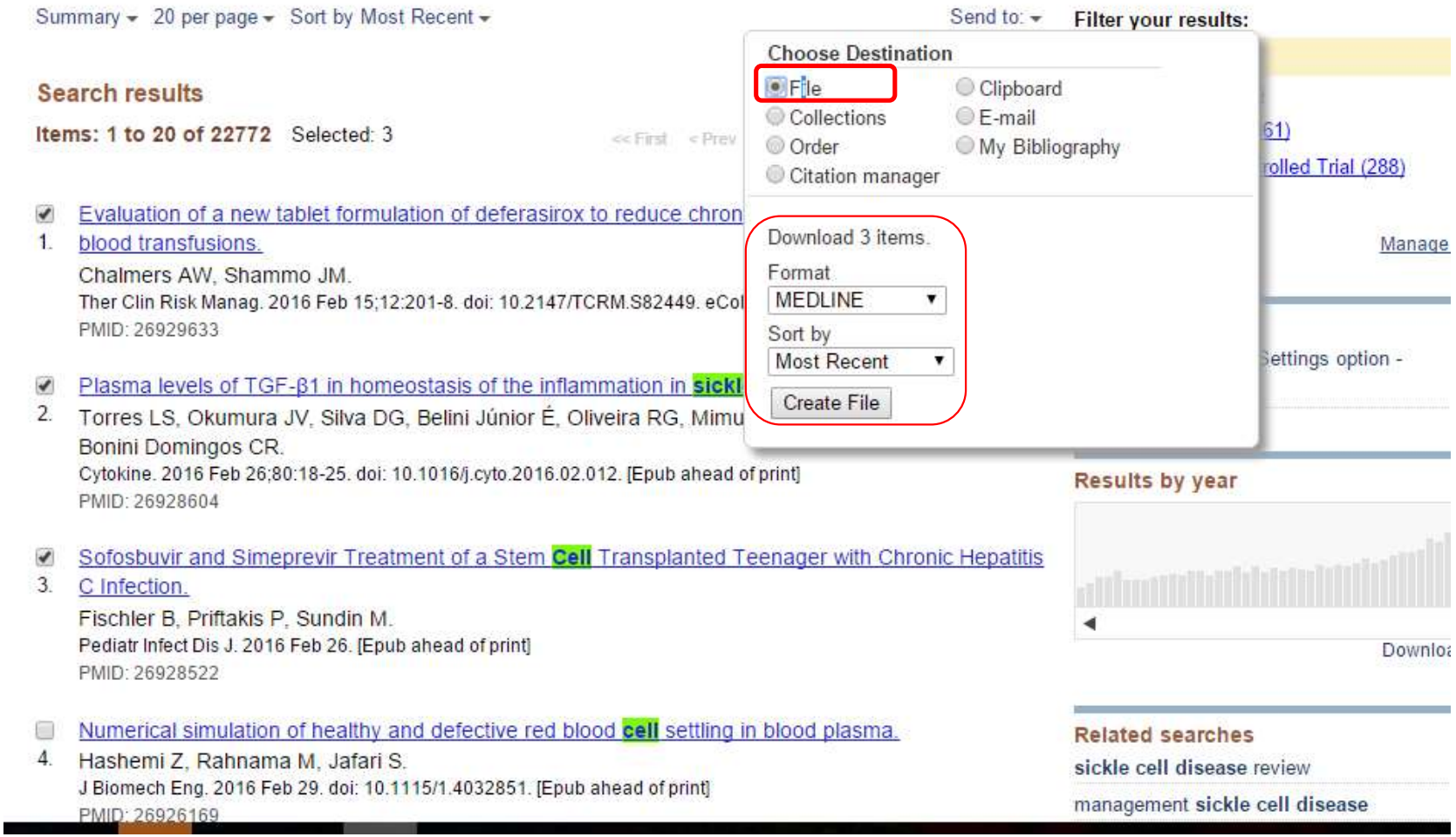
A clearly defined, focused review begins with a well framed question

Output della strategia di ricerca

RISULTATO

Lista di studi potenzialmente includibili

List of records



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DCOM- 20160301
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IS  - 1176-6336 (Linking)
VI  - 12
DP  - 2016
TI  - Evaluation of a new tablet formulation of deferasirox to reduce chronic iron
      overload after long-term blood transfusions.
PG  - 201-8
LID - 10.2147/TCRM.S82449 [doi]
AB  - Transfusion-dependent anemia is a common feature in a wide array of hematological
      disorders, including thalassemia, sickle cell disease, aplastic anemia,
      myelofibrosis, and myelo-dysplastic syndromes. In the absence of a physiological
      mechanism to excrete excess iron, chronic transfusions ultimately cause iron
      overload. Without correction, iron overload can lead to end-organ damage,
      resulting in cardiac, hepatic, and endocrine dysfunction/failure. Iron chelating
      agents are utilized to reduce iron overload, as they form a complex with iron,
      leading to its clearance. Iron chelation has been proven to decrease organ
      dysfunction and improve survival in certain transfusion-dependent anemias, such
      as beta-thalassemia. Several chelating agents have been approved by the United
      States Food and Drug Administration for the treatment of iron overload, including
      deferoxamine, deferiprone, and deferasirox. A variety of factors have to be
      considered when choosing an iron chelator, including dosing schedule, route of
      administration, tolerability, and side effect profile. Deferasirox is an orally
      administered iron chelator with proven efficacy and safety in multiple
      hematological disorders. There are two formulations of deferasirox, a tablet for
      suspension, and a new tablet form. This paper is intended to provide an overview
      of iron overload, with a focus on deferasirox, and its recently approved
      formulation Jadenu((R)) for the reduction of transfusional iron overload in
      hematological disorders.
FAU - Chalmers, Anna W
AU  - Chalmers AW
```

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FAU - Chalmers, Anna W
AU  - Chalmers AW
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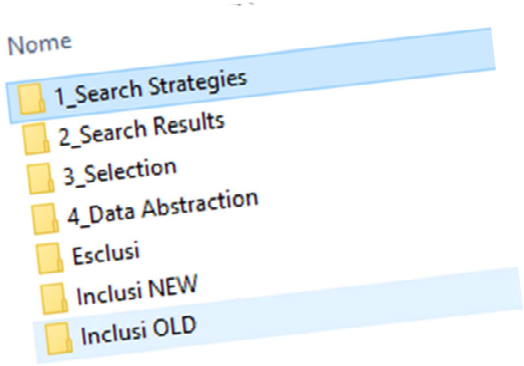
Conducting

Document

the selection process in sufficient detail to complete a PRISMA flow chart



THOMSON REUTERS
ENDNOTE

zotero

MENDELEY

Included or excluded?

Was a list of studies (included and excluded) provided?

- A list of included and excluded studies should be provided.

- Provide justification for each exclusion.

Duplicate selection

Was there duplicate study selection?

There should be at least two independent data extractors and a consensus procedure for disagreements should be in place

In pratica..

1. Ottenere una unica lista di referenze

- I risultati della ricerca di ogni database vanno importati su un programma di gestione delle referenze (endnote, excel)
- Eliminare i doppioni (stesso articolo indicizzato su più di una banca dati e quindi trovato più volte)

In pratica..

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- I risultati della ricerca di ogni database vanno importati su un programma di gestione delle referenze (endnote, excel)
- Eliminare i doppioni (stesso articolo indicizzato su più di una banca dati e quindi trovato più volte)

2. Selezionare gli articoli potenzialmente rilevanti da acquisire in full text

- Scriversi su un foglio i criteri di inclusione sotto forma di PICOS
- Valutare ogni titolo e abstract rispetto al PICOS

3. Obiettivo è non perdere nulla

- Fare il lavoro in due in modo indipendente
- In caso di dubbio, disaccordo o mancanza di abstract il titolo si seleziona lo stesso

3. Obiettivo è non perdere nulla

- Fare il lavoro in due in modo indipendente
- In caso di dubbio, disaccordo o mancanza di abstract il titolo si seleziona lo stesso

4. Procurarsi i full text

3. Obiettivo è non perdere nulla

- Fare il lavoro in due in modo indipendente
- In caso di dubbio, disaccordo o mancanza di abstract il titolo si seleziona lo stesso

4. Procurarsi i full text

5. Rivalutare ogni articolo leggendo il full text rispetto al PICOS

- Fare il lavoro in due in modo indipendente
- Confrontarsi sui risultati
- In questa fase vanno presi solo gli articoli realmente pertinenti
  In caso di differenze:
  - Risolvere il disaccordo tramite discussione
  - Rivolgersi a terzo revisore

6. Fare lista di studi esclusi

- Indicare ragione dell'esclusione sempre in base al PICOS
- Es: studi esclusi perché partecipanti non nei criteri di inclusione, intervento non nei criteri di inclusione, disegno di studio non nei criteri di inclusione
- Questo lavoro va fatto solo sui full text, non per gli studi esclusi sulla base dell' abstract

6. Fare lista di studi esclusi

- Indicare ragione dell'esclusione sempre in base al PICOS
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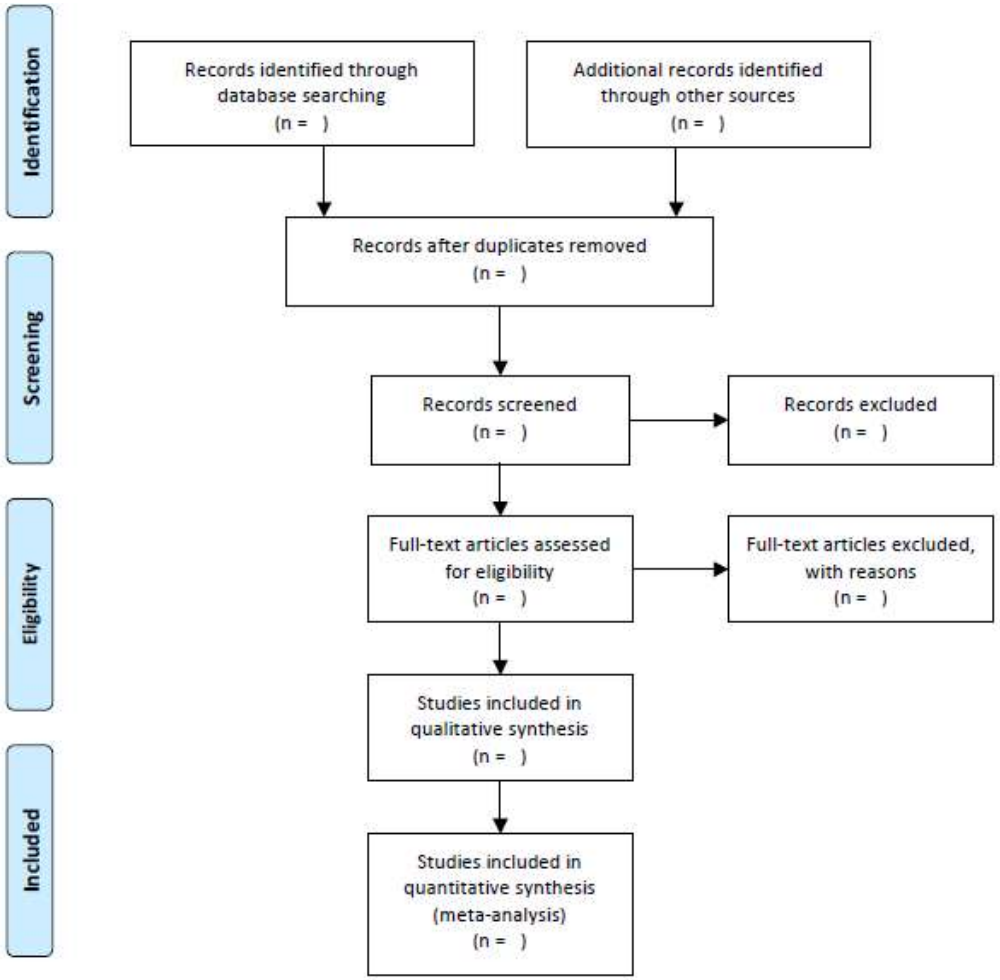
- Questo lavoro va fatto solo sui full text, non per gli studi esclusi sulla base dell' abstract

7. Fare lista finali di studi inclusi

- Se presenti più record di un articolo tenerli per eventuali dati

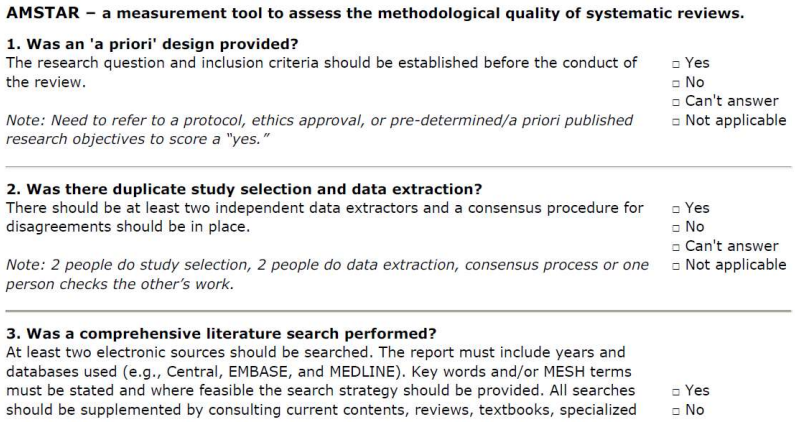
  Es: diversi periodi di follow up, analisi di sottogruppi; doppie pubblicazioni (stesso studio pubblicato più volte su riviste diverse con titolo diverso e/o diverso ordine degli autori)

8. Fare flow chart (es: PRISMA)



AMSTAR CHECKLIST

- Valuta il ***QUALITY OF CONDUCT***: la misura in cui la revisione è esente da errori sistematici
- Per aiutare chi legge a capire se la SR è affidabile e valida
- Composta di 11 items
- Shea BJ et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007 Feb 15;7:10.



AMSTAR – a measurement tool to assess the methodological quality of systematic reviews.

1. Was an 'a priori' design provided?
The research question and inclusion criteria should be established before the conduct of the review.

Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."

□ Yes
□ No
□ Can't answer
□ Not applicable

2. Was there duplicate study selection and data extraction?
There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.

□ Yes
□ No
□ Can't answer
□ Not applicable

3. Was a comprehensive literature search performed?
At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized

□ Yes
□ No

AMSTAR CHECKLIST II

- *"… The original AMSTAR instrument did not include an assessment of the risk of bias in non-randomised studies included in a review, which is a key issue given the diversity of designs that such studies may use and the biases that may affect them".*
- Shea BJ et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008
- 16 items

AMSTAR CHECKLIST II

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ☐ Population
- ☐ Intervention
- ☐ Comparator group
- ☐ Outcome

Optional (recommended)
- ☐ Timeframe for follow-up

☐ Yes
☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- ☐ review question(s)
- ☐ a search strategy
- ☐ inclusion/exclusion criteria
- ☐ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- ☐ a meta-analysis/synthesis plan, if appropriate, *and*
- ☐ a plan for investigating causes of heterogeneity
- ☐ justification for any deviations from the protocol

☐ Yes
☐ Partial Yes
☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- ☐ *Explanation for* including only RCTs
- ☐ OR *Explanation for* including only NRSI
- ☐ OR *Explanation for* including both RCTs and NRSI

☐ Yes
☐ No

AMSTAR CHECKLIST II

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):

- ☐ searched at least 2 databases (relevant to research question)
- ☐ provided key word and/or search strategy
- ☐ justified publication restrictions (eg, language)

For Yes, should also have (all the following):

- ☐ searched the reference lists/bibliographies of included studies
- ☐ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☐ conducted search within 24 months of completion of the review

- ☐ Yes
- ☐ Partial Yes
- ☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:

- ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 per cent), with the remainder selected by one reviewer

- ☐ Yes
- ☐ No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:

- ☐ at least two reviewers achieved consensus on which data to extract from included studies
- ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 per cent), with the remainder extracted by one reviewer

- ☐ Yes
- ☐ No

AMSTAR CHECKLIST II

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:	For Yes, must also have:	
☐ provided a list of all potentially relevant studies that were read in full text form but excluded from the review	☐ Justified the exclusion from the review of each potentially relevant study	☐ Yes ☐ Partial Yes ☐ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):	For Yes, should also have ALL the following:	
☐ described populations ☐ described interventions ☐ described comparators ☐ described outcomes ☐ described research designs	☐ described population in detail ☐ described intervention and comparator in detail (including doses where relevant) ☐ described study's setting ☐ timeframe for follow-up	☐ Yes ☐ Partial Yes ☐ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from	For Yes, must also have assessed RoB from:	
☐ unconcealed allocation, *and* ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all cause mortality)	☐ allocation sequence that was not truly random, *and* ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☐ No ☐ Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:	For Yes, must also have assessed RoB:	
☐ from confounding, *and* ☐ from selection bias	☐ methods used to ascertain exposures and outcomes, *and* ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☐ No ☐ Includes only RCTs

AMSTAR CHECKLIST II

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes

- ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

☐ Yes
☐ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:

- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present

☐ Yes
☐ No
☐ No meta-analysis

For NRSI

For Yes:

- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
  - ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
  - ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

☐ Yes
☐ No
☐ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:

- ☐ included only low risk of bias RCTs
- ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect

☐ Yes
☐ No
☐ No meta-analysi conducted

AMSTAR CHECKLIST II

13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?

For Yes:

- ☐ included only low risk of bias RCTs
- ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

☐ Yes
☐ No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:

- ☐ There was no significant heterogeneity in the results
- ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

☐ Yes
☐ No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:

- ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

☐ Yes
☐ No
☐ No meta-analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:

- ☐ The authors reported no competing interests OR
- ☐ The authors described their funding sources and how they managed potential conflicts of interest

☐ Yes
☐ No

ELSEVIER

CrossMark

Journal of Clinical Epidemiology 69 (2016) 225–234

Journal of Clinical Epidemiology

ROBIS: A new tool to assess risk of bias in systematic reviews was developed

Penny Whiting[a,b,c,*], Jelena Savović[a,b], Julian P.T. Higgins[a,d], Deborah M. Caldwell[a], Barnaby C. Reeves[e], Beverley Shea[f], Philippa Davies[a,b], Jos Kleijnen[c,g], Rachel Churchill[a], the ROBIS group

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[d]*Centre for Reviews and Dissemination,*
[e]*School of Clinical Sciences, University of Bristol, Bristol Royal Infirma*
[f]*Community Information and Epidemiological Technologies Institute of Popula*
[g]*School for Public Health and Primary Care (CAPHRI), Maastrich*

Accepted 5 June 2015; Pub

Abstract

Objective: To develop ROBIS, a new tool for assessing the risk
Study Design and Setting: We used four-stage approach to develc face meeting, and refine the tool through piloting.

ROBIS
QUALITY OF CONDUCT
Checklist

Phase 2: Identifying concerns with the review process

DOMAIN 1: STUDY ELIGIBILITY CRITERIA	
Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Y/PY/PN/N/NI
1.2 Were the eligibility criteria appropriate for the review question?	Y/PY/PN/N/NI
1.3 Were eligibility criteria unambiguous?	Y/PY/PN/N/NI
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Y/PY/PN/N/NI
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Y/PY/PN/N/NI
Concerns regarding specification of study eligibility criteria	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES	
Describe methods of study identification and selection (e.g. number of reviewers involved):	
2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y/PY/PN/N/NI
2.2 Were methods additional to database searching used to identify	Y/PY/PN/N/NI

QUALITY OF REPORTING

PRISMA Statement

OPEN ACCESS Freely available online

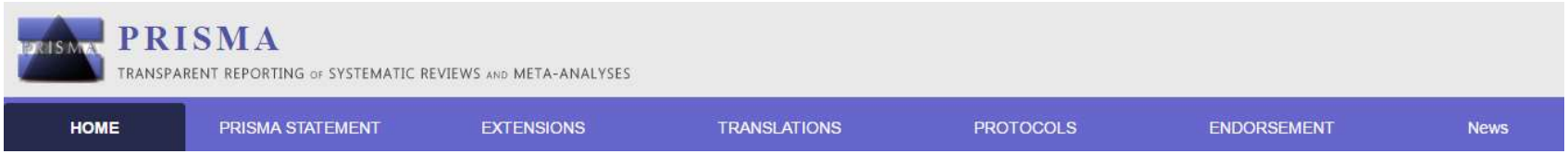
PLoS MEDICINE

Guidelines and Guidance

Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

David Moher[1,2]*, Alessandro Liberati[3,4], Jennifer Tetzlaff[1], Douglas G. Altman[5], The PRISMA Group[¶]

1 Ottawa Methods Centre, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada, **2** Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada, **3** Università di Modena e Reggio Emilia, Modena, Italy, **4** Centro Cochrane Italiano, Istituto Ricerche Farmacologiche Mario Negri, Milan, Italy, **5** Centre for Statistics in Medicine, University of Oxford, Oxford, United Kingdom



PRISMA

- PRISMA is an evidence-based **minimum set of items** for reporting in systematic reviews and meta-analyses. PRISMA focuses on the reporting of reviews evaluating randomized trials, but can also be used as a basis for reporting systematic reviews of other types of research, particularly evaluations of interventions.

http://www.prisma-statement.org/

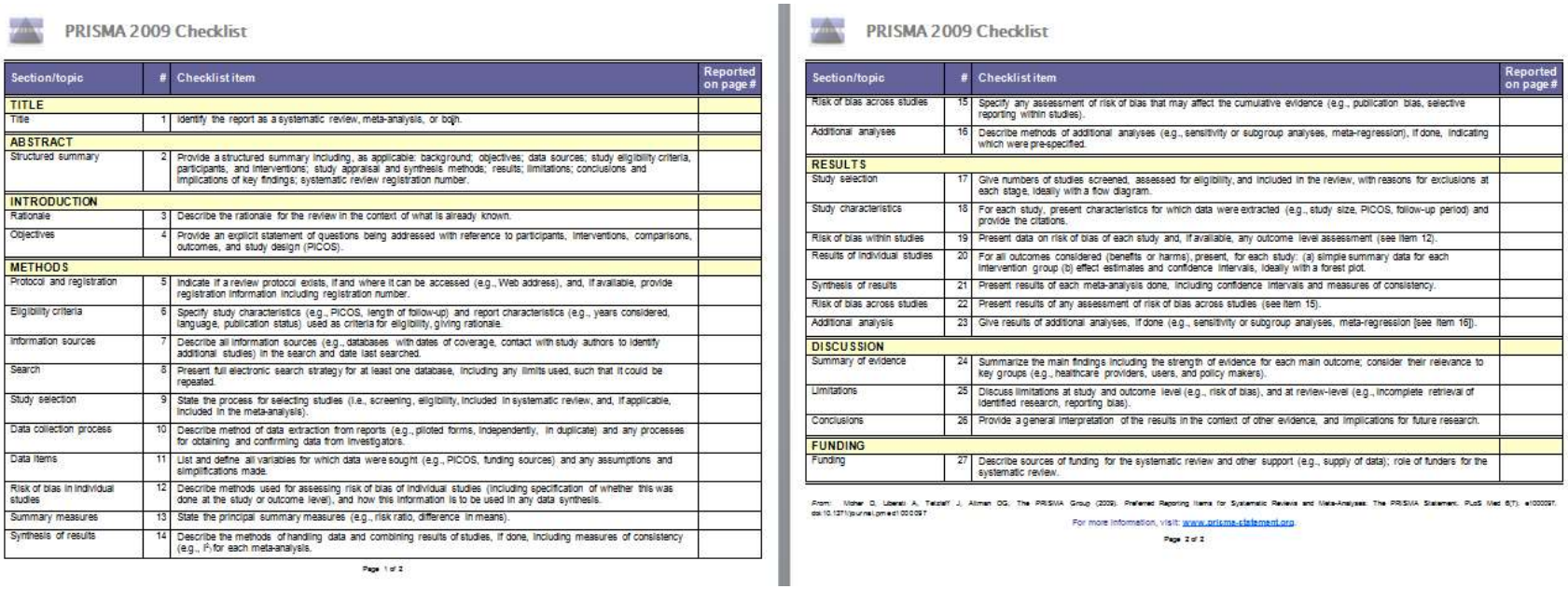
PRISMA

- Pubblicato nel 2009, evoluzione del QUOROM statement (guida, pubblicata nel 1999, per migliorare il reporting di meta-analisi di RCT).
- Valuta il ***QUALITY OF REPORTING***
- Pubblicato in Annals of Internal Medicine, PLoS Medicine, Open Medicine, the British Medical Journal and the Journal of Clinical Epidemiology.

KEY DOCUMENTS

- PRISMA Statement
- PRISMA Checklist
- PRISMA flow diagram
- PRISMA E&E

PRISMA Checklist



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

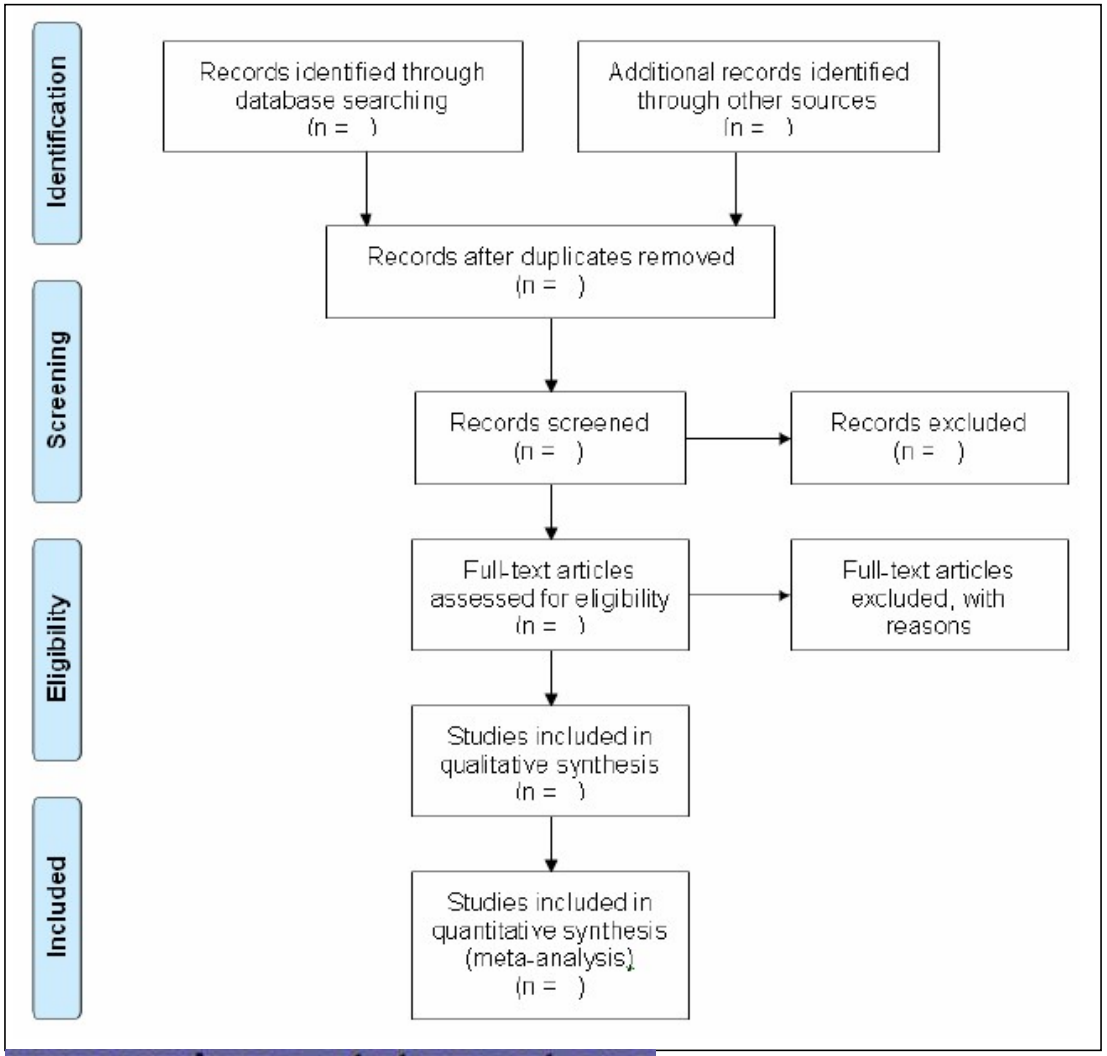
PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

PRISMA Flow diagram



www.prisma-statement.org

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Submission Guidelines

PLOS Medicine publishes original research articles of outstanding medical importance. We will consider manuscripts of any length; we encourage the submission of both substantial full-length bodies of work and shorter manuscripts that report novel findings that might be based on a more limited range of experiments.

The writing style should be concise and accessible, avoiding jargon so that the paper is understandable for readers outside a specialty or those whose first language is not English. Editors will make suggestions for how to achieve this, as well as suggestions for deletions or additions that could be made to the article to strengthen the argument. Our aim is to make the editorial process rigorous and consistent, but not intrusive or overbearing. Authors are encouraged to use their own voice and to decide how best to present their ideas, results, and conclusions.

Systematic reviews and meta-analyses

Reports of systematic reviews and meta-analyses must adhere to the PRISMA Statement or alternative guidelines appropriate to the study design, and include the completed checklist and flow diagram to accompany the main text. Authors must complete the appropriate reporting checklist not only with page references, but also with sufficient text excerpted from the manuscript to explain how they accomplished all applicable items.

Download blank templates of the checklist and flow diagram from the EQUATOR web site.

Abstracts should follow PRISMA for Abstracts using the PLOS abstract format. Authors must also state within the Methods section of their paper whether a protocol exists for their systematic review, and if so, provide a copy of the protocol as supporting information.

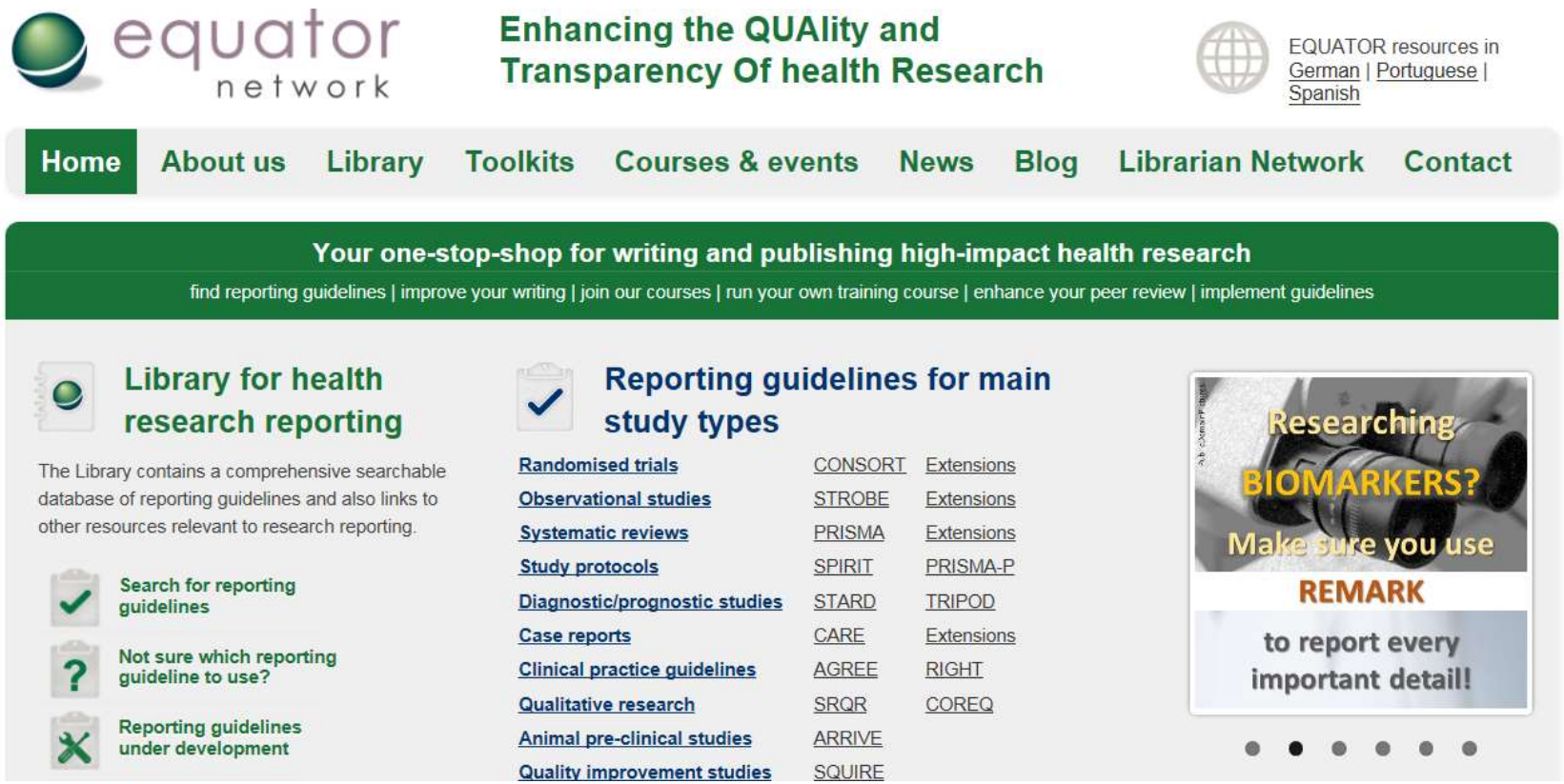
Esempio

PLOS ONE

Efficacy of muscle exercise in patients with muscular dystrophy: a systematic review showing a missed opportunity to improve outcomes

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	done
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Structured abstract done
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page #2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page #2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	None
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page #2-3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page #3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page #3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page #3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	Page #4

http://www.equator-network.org/



Example of bad reporting

Hip Int. 2012 Jul-Aug;22 Suppl 8:S19-24. doi: 10.5301/HIP.2012.9566.

Value of debridement and irrigation for the treatment of peri-prosthetic infections. A systematic review.

Abstract

Debridement and irrigation has been proposed as a salvage procedure for early post-operative and late acute haematogenous periprosthetic hip and knee infections, however the effective ability of this procedure to avoid recurrent infection is still debated. In this systematic review of the literature we reviewed full-text papers published from 1970 through 2011, that reported the success rate of infection eradication after debridement and irrigation with prosthesis retention for the treatment of early septic complications (within six weeks from surgery) or late acute haematogenous infections after hip or knee prosthesis. In all, 14 original articles, reporting the results of 710 patients were retrieved. The average success rate has been, respectively, 45.9% and 52% after a single or repeated debridement and irrigation procedures, at a mean follow-up of 53.3 months. The methodological limitations of this study and the heterogeneous material in the reviewed papers notwithstanding, this systematic review shows that debridement and irrigation procedure is associated with a rather poor outcome, even in a population of patients selected on the basis of symptoms' duration and patients should be adequately informed prior to undergo this salvage procedure.

- ✓ **ABSTRACT NON STRUTTURATO IN INTRODUZIONE, OBIETTIVI, RISORSE RICERCA, CRITERI DI ELIGIBILITA', INTERVENTI, CRITICAL APPRISAL, SINTESI DEI METODI, RISULTATI, LIMITAZIONI CONCLUSIONI, IMPLICAZIONI**
- ✓ **SYSTEMATIC REVIEW REGISTRATION NUMBER**
- ✓ **MANCANO BANCHE DATI**

Example of good reporting

Virtual Reality Therapy for Adults Post-Stroke: A Systematic Review and Meta-Analysis Exploring Virtual Environments and Commercial Games in Therapy

Abstract

Background: The objective of this analysis was to systematically review the evidence for virtual reality (VR) therapy in an adult post-stroke population in both custom built virtual environments (VE) and commercially available gaming systems (CG).

Methods: MEDLINE, CINAHL, EMBASE, ERIC, PSYCInfo, DARE, PEDro, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews were systematically searched from the earliest available date until April 4, 2013. Controlled trials that compared VR to conventional therapy were included. Population criteria included adults (>18) post-stroke, excluding children, cerebral palsy, and other neurological disorders. Included studies were reported in English. Quality of studies was assessed with the Physiotherapy Evidence Database Scale (PEDro).

Resu VR thera VE and C 32, 0.85], rall effec

ABSTRACT STRUTTURATO IN INTRODUZIONE, OBIETTIVI, RISORSE RICERCA, CRITERI DI ELIGIBILITA', INTERVENTI, CRITICAL APPRISAL, SINTESI DEI METODI, RISULTATI, LIMITAZIONI CONCLUSIONI, IMPLICAZIONI, SYSTEMATIC REVIEW REGISTRATION NUMBER

Discussion: VR rehabilitation moderately improves outcomes compared to conventional therapy in adults post-stroke. Current CG interventions have been too few and too small to assess potential benefits of CG. Future research in this area should aim to clearly define conventional therapy, report on participation measures, consider motivational components of therapy, and investigate commercially available systems in larger RCTs.

Trial Registration: Prospero CRD42013004338

Eterogeneità. Confronti indiretti tradizionali e NMA

Principi di una meta-analisi

Una **meta-analisi** può:

•Combinare i risultati dei singoli studi per ottenere una stima complessiva dell'effetto del trattamento;

•Esplorare l'eterogeneità tra gli studi (e le relative fonti di eterogeneità).

When can/should you do a meta-analysis?

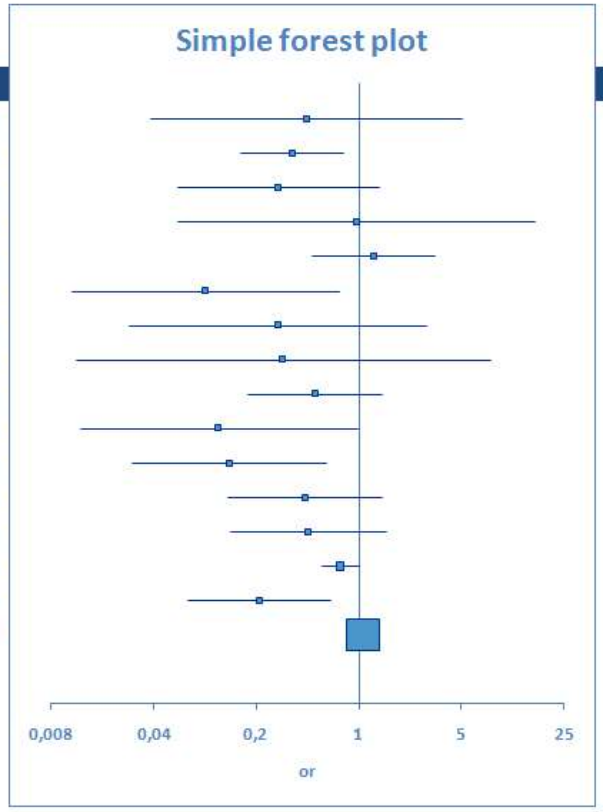
- When more than one study has estimated an effect
- When there are no differences in the study characteristics that are likely to substantially affect outcome
- When the outcome has been measured in similar ways
- When the data are available (take care with interpretation when only some data are available)

E' efficace?

Author(s)		Reference					
Teo et al.		Effects of intravenous magnesium in suspected acute myocardial infarction. BMJ 1991;303:1499–50					
Outcome object	Unit	Intervention (e)		Control (c)			
Mortality	Event	Intravenous magnesium		Control			
Study ID	Ref #	n[e]	n[e](E=1)	n[c]	n[c](E=1)	Study date	-
Morton	1	40	1	36	2	1984	
Rasmussen	2	135	9	135	23	1986	
Smith	3	200	2	200	7	1986	
Abraham	4	48	1	46	1	1987	
Feldstedt	5	150	10	148	8	1988	
Schechter	6	59	1	56	9	1989	
Ceremuzynski	7	25	1	23	3	1989	
Bertschat	8	22	0	21	1	1989	
Singh	9	76	6	75	11	1990	
Pereira	10	27	1	27	7	1990	
Schechter 1	11	89	2	80	12	1991	
Golf	12	23	5	33	13	1991	
Thogersen	13	130	4	122	8	1991	
LIMIT-2	14	1159	90	1157	118	1992	
Schechter 2	15	107	4	108	17	1995	
ISIS-4	16	29011	2216	29039	2103	1995	

Forest plot (meta-graph) analitico

author	year	n[I]	N[I]	n[C]	N[C]	Weight	or	ci-	ci+	p
Morton	1984	1	40	2	36	0,06%	0,44	0,04	5,02	0,51
Rasmussen	1986	9	135	23	135	0,54%	0,35	0,15	0,78	0,01
Smith	1986	2	200	7	200	0,14%	0,28	0,06	1,36	0,11
Abraham	1987	1	48	1	46	0,05%	0,96	0,06	15,77	0,98
Feldstedt	1988	10	150	8	148	0,39%	1,25	0,48	3,26	0,65
Schechter	1989	1	59	9	56	0,08%	0,09	0,01	0,74	0,02
Ceremuzynsk	1989	1	25	3	23	0,07%	0,28	0,03	2,88	0,28
Bertschat	1989	0	22	1	21	0,03%	0,30	0,01	7,88	0,47
Singh	1990	6	76	11	75	0,32%	0,50	0,17	1,43	0,19
Pereira	1990	1	27	7	27	0,08%	0,11	0,01	0,97	0,05
Schechter 1	1991	2	89	12	80	0,15%	0,13	0,03	0,60	0,01
Golf	1991	5	23	13	33	0,24%	0,43	0,13	1,44	0,17
Thogersen	1991	4	130	8	122	0,24%	0,45	0,13	1,54	0,21
LIMIT-2	1992	90	1159	118	1157	4,33%	0,74	0,56	0,99	0,04
Schechter 2	1995	4	107	17	108	0,28%	0,21	0,07	0,64	0,01
ISIS-4	1995	2216	29011	2103	29039	92,99%	1,06	1,00	1,13	0,07



META-ANALYSIS

General

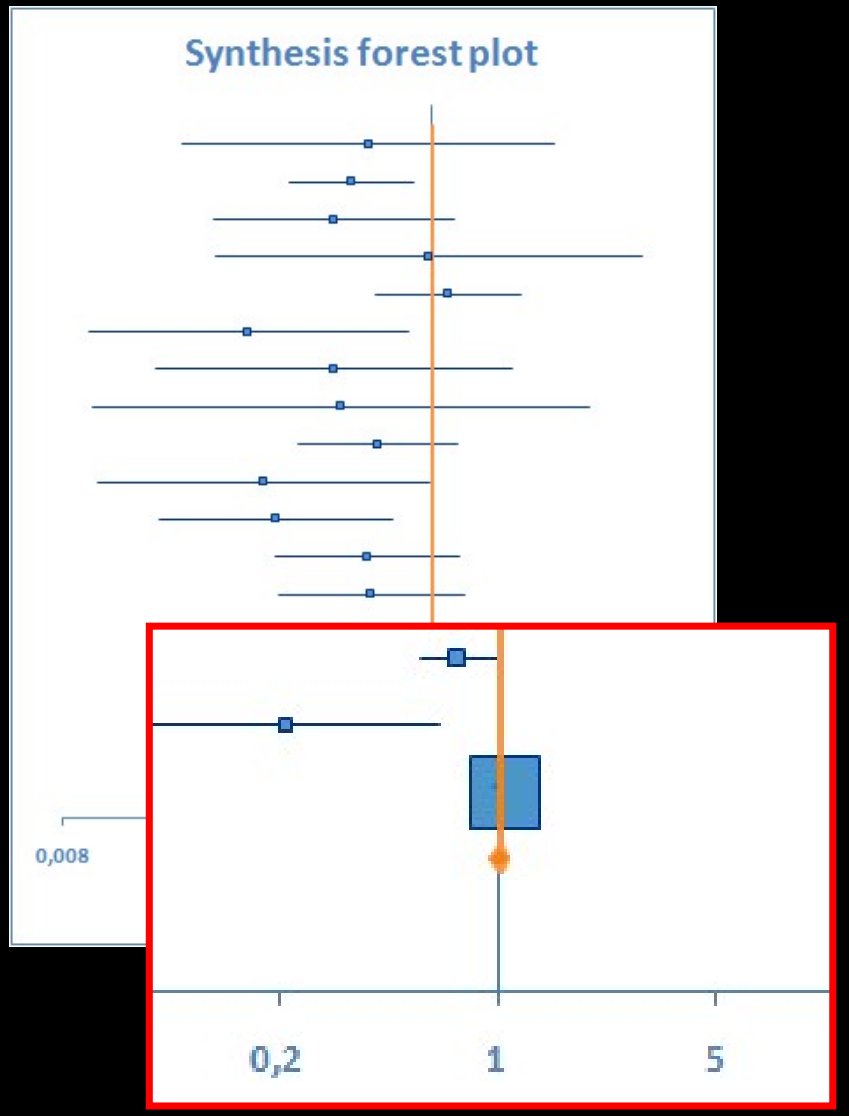
Number of studies	16
Number of participants	62607 (62607)

OR (MH) - Fixed effect model

Meta-analysis outcome	1,0063
95% CI lower limit	0,9482
95% CI upper limit	1,068
z	0,2073
p-value (two-tailed)	0,8358

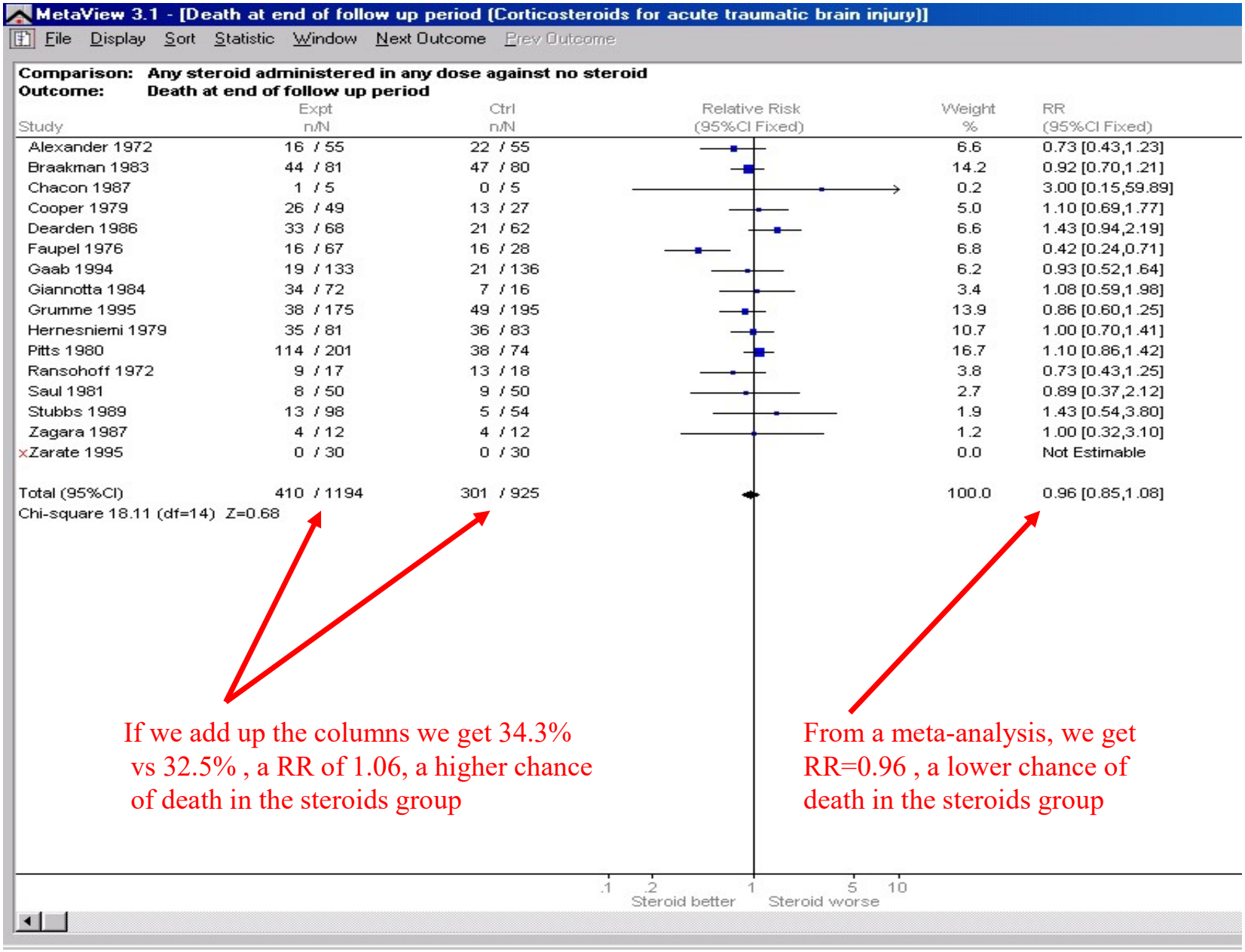
Heterogeneity

Q	47,1363
p-value (two-tailed)	< 0,0001
I^2	68,18%
95% CI lower limit	46,53%
95% CI upper limit	81,06%



Could we just add the data from all the trials together?

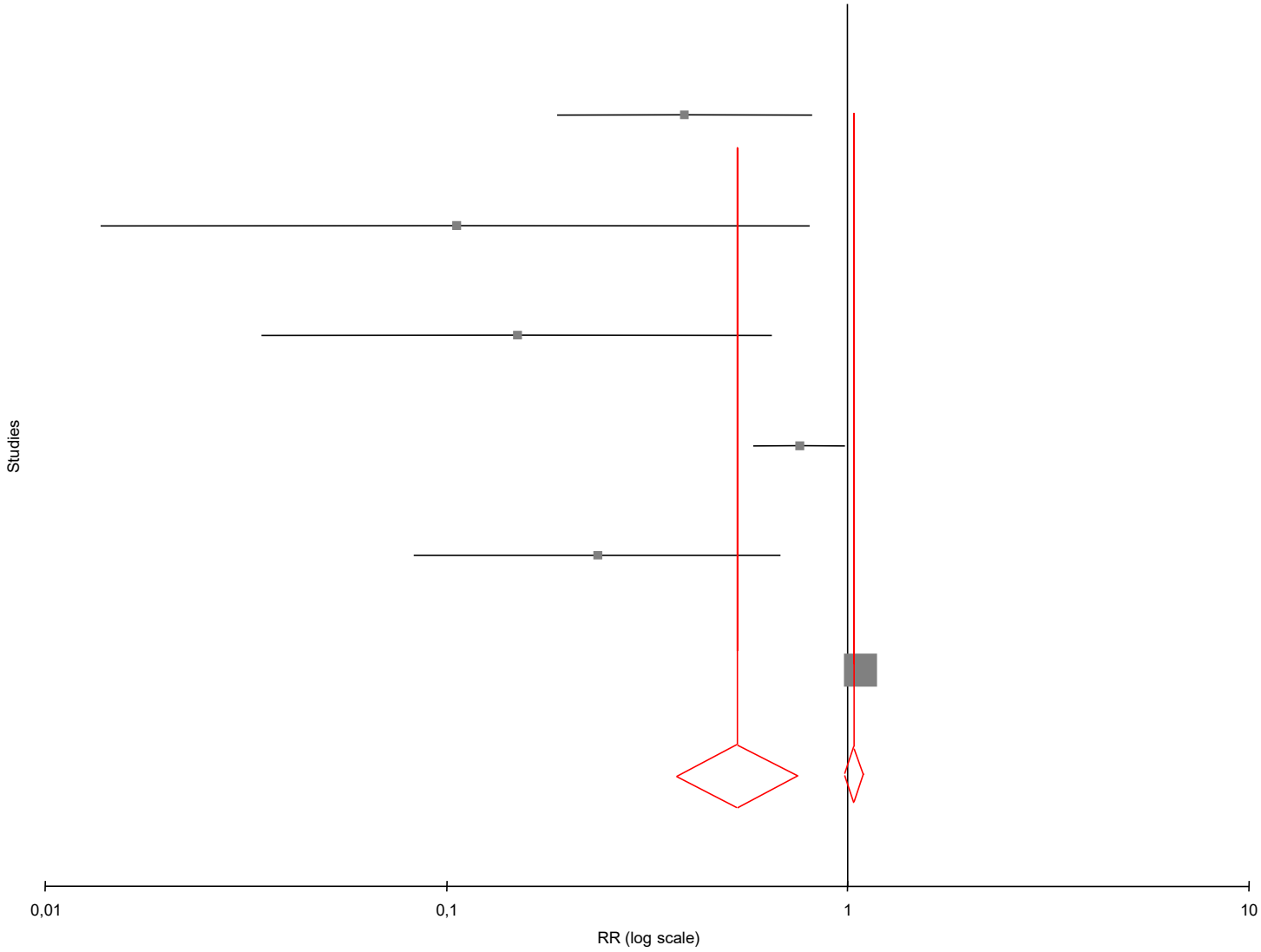
- One approach to combining trials would be to add all the treatment groups together, add all the control groups together, and compare the totals
- This is wrong for several reasons, and it can give the wrong answer


MetaView 3.1 - [Death at end of follow up period (Corticosteroids for acute traumatic brain injury)]
File Display Sort Statistic Window Next Outcome Prev Outcome
Comparison: Any steroid administered in any dose against no steroid
Outcome: Death at end of follow up period
Study
Expt n/N
Ctrl n/N
Relative Risk (95%CI Fixed)
Weight %
RR (95%CI Fixed)
Alexander 1972 16 / 55 22 / 55 6.6 0.73 [0.43,1.23]
Braakman 1983 44 / 81 47 / 80 14.2 0.92 [0.70,1.21]
Chacon 1987 1 / 5 0 / 5 0.2 3.00 [0.15,59.89]
Cooper 1979 26 / 49 13 / 27 5.0 1.10 [0.69,1.77]
Dearden 1986 33 / 68 21 / 62 6.6 1.43 [0.94,2.19]
Faupel 1976 16 / 67 16 / 28 6.8 0.42 [0.24,0.71]
Gaab 1994 19 / 133 21 / 136 6.2 0.93 [0.52,1.64]
Giannotta 1984 34 / 72 7 / 16 3.4 1.08 [0.59,1.98]
Grumme 1995 38 / 175 49 / 195 13.9 0.86 [0.60,1.25]
Hernesniemi 1979 35 / 81 36 / 83 10.7 1.00 [0.70,1.41]
Pitts 1980 114 / 201 38 / 74 16.7 1.10 [0.86,1.42]
Ransohoff 1972 9 / 17 13 / 18 3.8 0.73 [0.43,1.25]
Saul 1981 8 / 50 9 / 50 2.7 0.89 [0.37,2.12]
Stubbs 1989 13 / 98 5 / 54 1.9 1.43 [0.54,3.80]
Zagara 1987 4 / 12 4 / 12 1.2 1.00 [0.32,3.10]
xZarate 1995 0 / 30 0 / 30 0.0 Not Estimable
Total (95%CI) 410 / 1194 301 / 925 100.0 0.96 [0.85,1.08]
Chi-square 18.11 (df=14) Z=0.68
.1 .2 1 5 10
Steroid better
Steroid worse
If we add up the columns we get 34.3% vs 32.5% , a RR of 1.06, a higher chance of death in the steroids group
From a meta-analysis, we get RR=0.96 , a lower chance of death in the steroids group

L'intervento funziona?

Valore neutro ("nullo")	Esito sfavorevole (es. morte)	Esito favorevole (es. smettere di fumare)	Effetto avverso (es. vomito)
L'intervento non ha effetto	L'intervento funziona	L'intervento funziona	L'intervento funziona
RD = 0	RD < 0	RD > 0	RD < 0
RR = 1	RR < 1	RR > 1	RR < 1
OR = 1	OR < 1	OR > 1	OR < 1

RD: Risk Difference **RR: Relative Risk** **OR: Odds Ratio**


Studies
0,01
0,1
1
10
RR (log scale)

Come si decide quanto pesa uno studio?

- Il peso è proporzionale al contributo informativo dello studio alla capacità di effettuare una stima
- Studi di ampie dimensione e/o con molti eventi potrebbero contribuire di più
- In gergo sono quelli più precisi

- Ma tutto è relativo … tutti gli studi stanno misurando lo stesso effetto?

Mettere insieme … studi diversi… che testano quesiti diversi… considerando popolazione diverse… usando interventi lievemente diversi… ma partendo da protocolli profondamente diversi… e dando risultati …

Eterogeneità

What is heterogeneity?

- Heterogeneity is variation between the studies' results

What is heterogeneity?

Differences between studies with respect to:

Clinical heterogeneity (clinical diversity)

- *Participants*
  - e.g. conditions under investigation, eligibility criteria for trials, geographical variation
- *Interventions*
  - e.g. intensity / dose / duration, sub-type of drug, mode of administration, experience of practitioners, nature of the control (placebo/none/standard care)
- *Outcomes*
  - e.g. definition of an event, follow-up duration, ways of measuring outcomes, cut-off points on scales

What is heterogeneity?

Differences between studies with respect to:

Methodological heterogeneity (methodological diversity)

- *Design*
  - e.g. randomised vs non-randomised, crossover vs parallel group vs cluster randomised, pre-test and long follow up
- *Conduct*
  - e.g. allocation concealment, blinding etc, approach to analysis, imputation methods for missing data

What is heterogeneity?

What do we do if there ***is*** statistical heterogeneity?

- Variation in the *true effects* underlying the studies
- ...which may manifest itself in more observed variation than expected by chance alone

- May be due to clinical diversity (different treatment effects) or methodological diversity (different biases)

Come si misura questa eterogeneità?

- Confidence interval overlapping Eyeball test

- Cochran's Q: to assess whether observed differences in results are compatible with change alone

χ^2 distribution; low power (small number of studies, small sample size)

p=<0.10 (heterogeneity)

- I^2 quantifing heterogeneity (describes the percentage of variation across studies that is due to heterogeneity rather than chance)

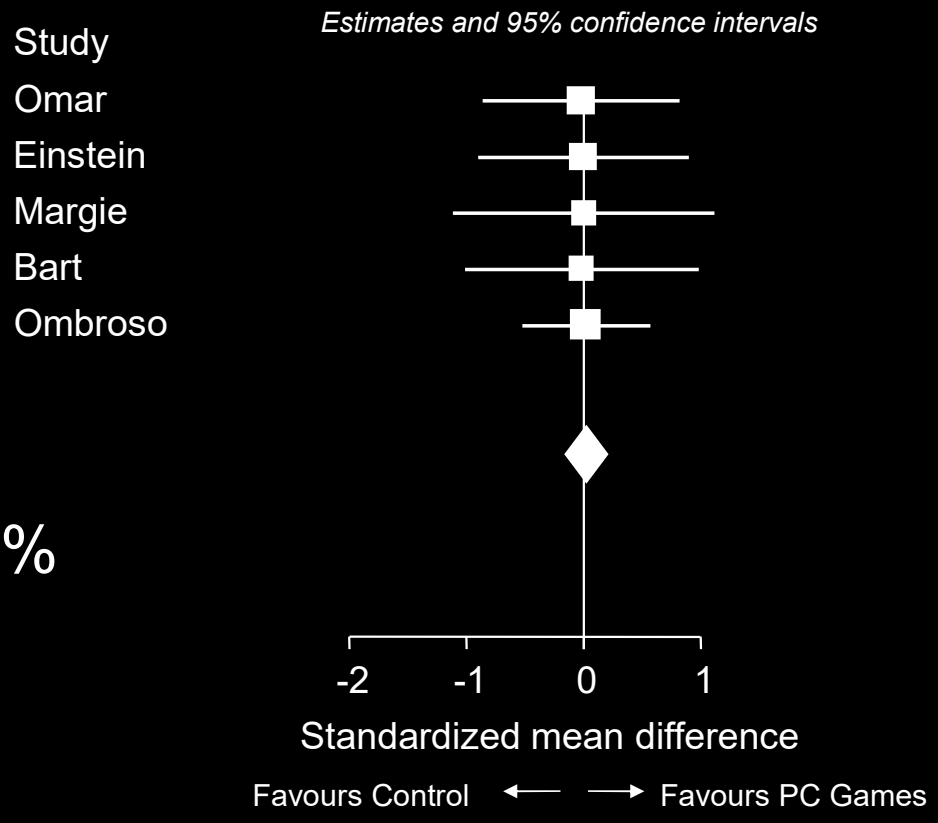
0-40% might not be important
30-60% may represent moderate heterogeneity
50-90% may represent substantial heterogeneity
75-100% considerable heterogeneity

- Tau….

How to deal with heterogeneity

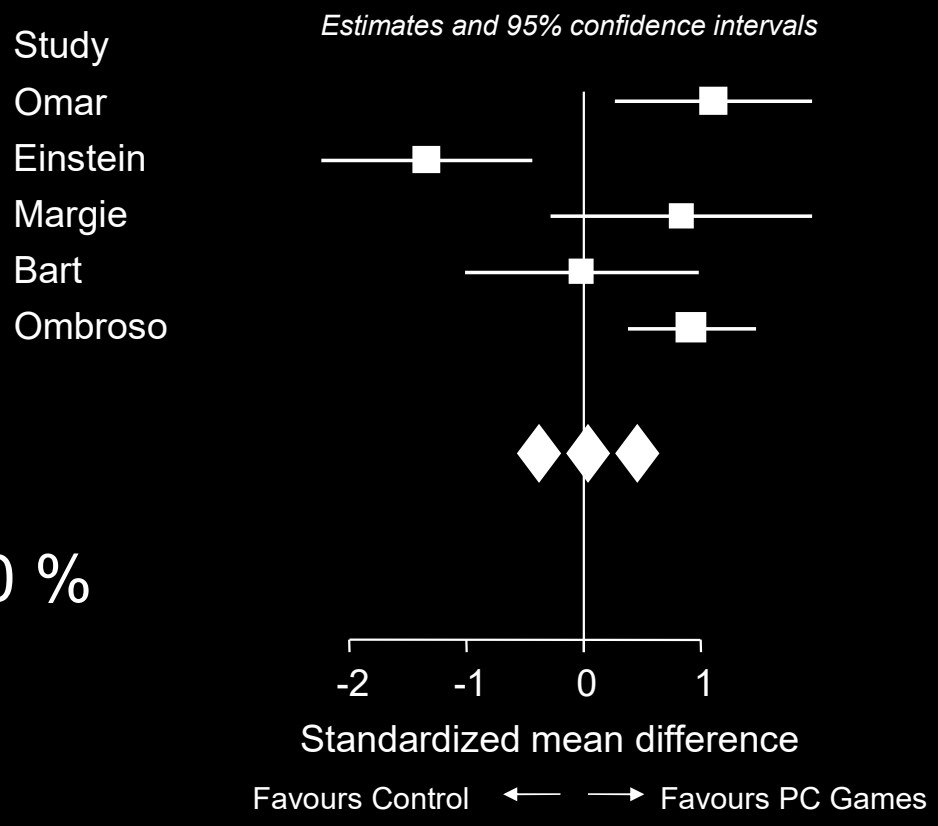
1. Do not pool at all
2. Ignore heterogeneity: use ***fixed effect model***
3. Allow for heterogeneity: use ***random effects model***
4. Explore heterogeneity: subgroups analysis or meta-regression (tricky)

Example: PC Games for intelligence



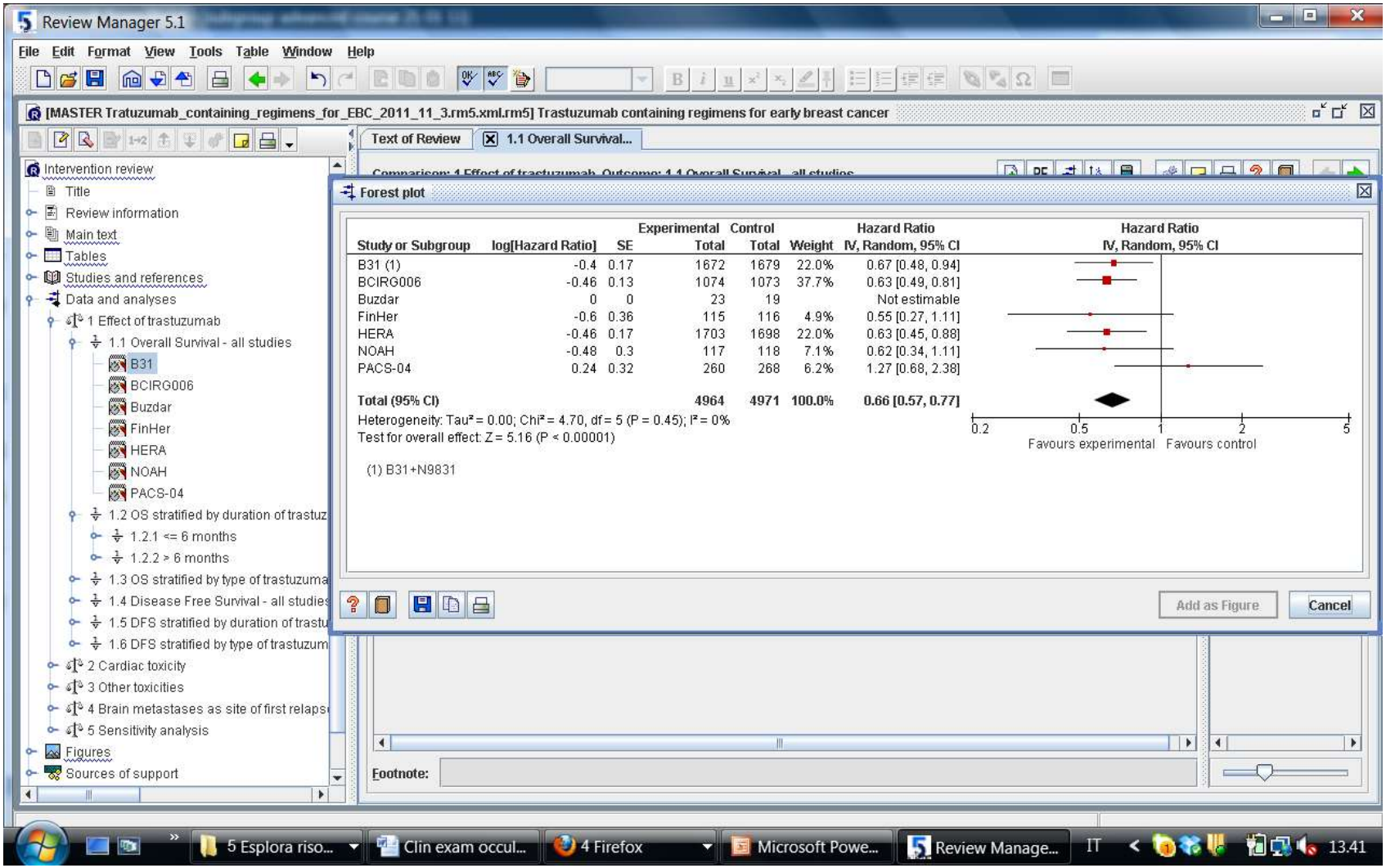
$I^2 = 0\ \%$

Example: PC Games for intelligence



I^2= 80 %

SOTTOGRUPPI


Review Manager 5.1
File Edit Format View Tools Table Window Help
[MASTER Tratuzumab_containing_regimens_for_EBC_2011_11_3.rm5.xml.rm5] Trastuzumab containing regimens for early breast cancer
Text of Review
1.1 Overall Survival...
Intervention review
Title
Review information
Main text
Tables
Studies and references
Data and analyses
1 Effect of trastuzumab
1.1 Overall Survival - all studies
B31
BCIRG006
Buzdar
FinHer
HERA
NOAH
PACS-04
1.2 OS stratified by duration of trastuz
1.2.1 <= 6 months
1.2.2 > 6 months
1.3 OS stratified by type of trastuzuma
1.4 Disease Free Survival - all studies
1.5 DFS stratified by duration of trastu
1.6 DFS stratified by type of trastuzum
2 Cardiac toxicity
3 Other toxicities
4 Brain metastases as site of first relaps
5 Sensitivity analysis
Figures
Sources of support
Forest plot
Experimental
Control
Hazard Ratio
Hazard Ratio
Study or Subgroup log[Hazard Ratio] SE Total Total Weight IV, Random, 95% CI
IV, Random, 95% CI
B31 (1) -0.4 0.17 1672 1679 22.0% 0.67 [0.48, 0.94]
BCIRG006 -0.46 0.13 1074 1073 37.7% 0.63 [0.49, 0.81]
Buzdar 0 0 23 19 Not estimable
FinHer -0.6 0.36 115 116 4.9% 0.55 [0.27, 1.11]
HERA -0.46 0.17 1703 1698 22.0% 0.63 [0.45, 0.88]
NOAH -0.48 0.3 117 118 7.1% 0.62 [0.34, 1.11]
PACS-04 0.24 0.32 260 268 6.2% 1.27 [0.68, 2.38]
Total (95% CI) 4964 4971 100.0% 0.66 [0.57, 0.77]
Heterogeneity: Tau² = 0.00; Chi² = 4.70, df = 5 (P = 0.45); I² = 0%
Test for overall effect: Z = 5.16 (P < 0.00001)
0.2 0.5 1 2 5
Favours experimental Favours control
(1) B31+N9831
Add as Figure
Cancel
Footnote:
5 Esplora riso...
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Microsoft Powe...
Review Manage...
IT
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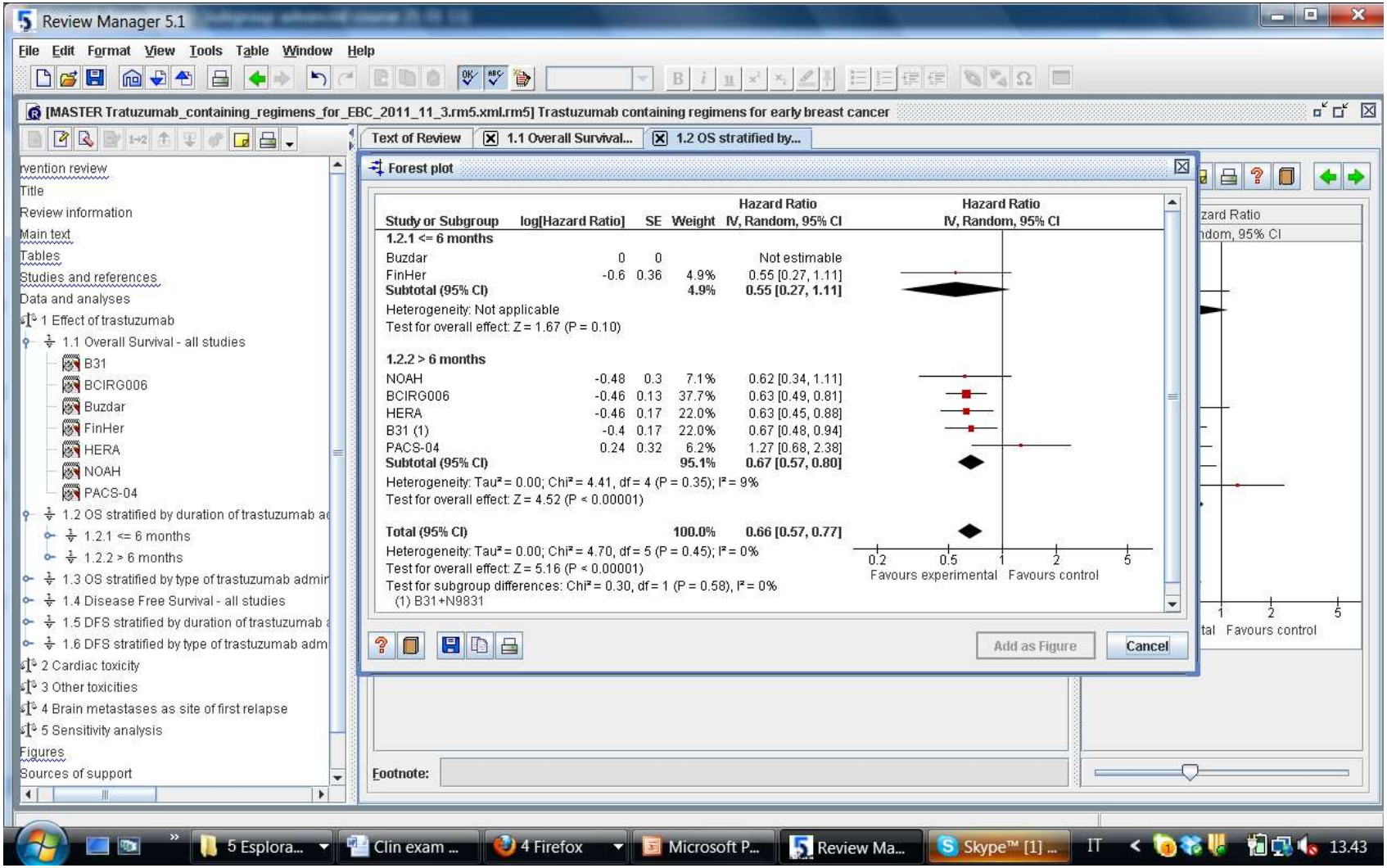
Review Manager 5.1
File Edit Format View Tools Table Window Help
[MASTER Tratuzumab_containing_regimens_for_EBC_2011_11_3.rm5.xml.rm5] Trastuzumab containing regimens for early breast cancer
Text of Review
1.1 Overall Survival...
1.2 OS stratified by...
Forest plot
Study or Subgroup log[Hazard Ratio] SE Weight Hazard Ratio IV, Random, 95% CI
1.2.1 <= 6 months
Buzdar 0 0 Not estimable
FinHer -0.6 0.36 4.9% 0.55 [0.27, 1.11]
Subtotal (95% CI) 4.9% 0.55 [0.27, 1.11]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.67 (P = 0.10)
1.2.2 > 6 months
NOAH -0.48 0.3 7.1% 0.62 [0.34, 1.11]
BCIRG006 -0.46 0.13 37.7% 0.63 [0.49, 0.81]
HERA -0.46 0.17 22.0% 0.63 [0.45, 0.88]
B31 (1) -0.4 0.17 22.0% 0.67 [0.48, 0.94]
PACS-04 0.24 0.32 6.2% 1.27 [0.68, 2.38]
Subtotal (95% CI) 95.1% 0.67 [0.57, 0.80]
Heterogeneity: Tau² = 0.00; Chi² = 4.41, df = 4 (P = 0.35); I² = 9%
Test for overall effect: Z = 4.52 (P < 0.00001)
Total (95% CI) 100.0% 0.66 [0.57, 0.77]
Heterogeneity: Tau² = 0.00; Chi² = 4.70, df = 5 (P = 0.45); I² = 0%
Test for overall effect: Z = 5.16 (P < 0.00001)
Test for subgroup differences: Chi² = 0.30, df = 1 (P = 0.58), I² = 0%
(1) B31+N9831
0.2 0.5 1 2 5
Favours experimental Favours control
Add as Figure
Cancel
Footnote:
ivention review
Title
Review information
Main text
Tables
Studies and references
Data and analyses
1 Effect of trastuzumab
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B31
BCIRG006
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1.4 Disease Free Survival - all studies
1.5 DFS stratified by duration of trastuzumab a
1.6 DFS stratified by type of trastuzumab adm
2 Cardiac toxicity
3 Other toxicities
4 Brain metastases as site of first relapse
5 Sensitivity analysis
Figures
Sources of support
5 Esplora...
Clin exam ...
4 Firefox
Microsoft P...
Review Ma...
Skype™ [1] ...
IT
13.43

What are subgroup / sensitivity analyses?

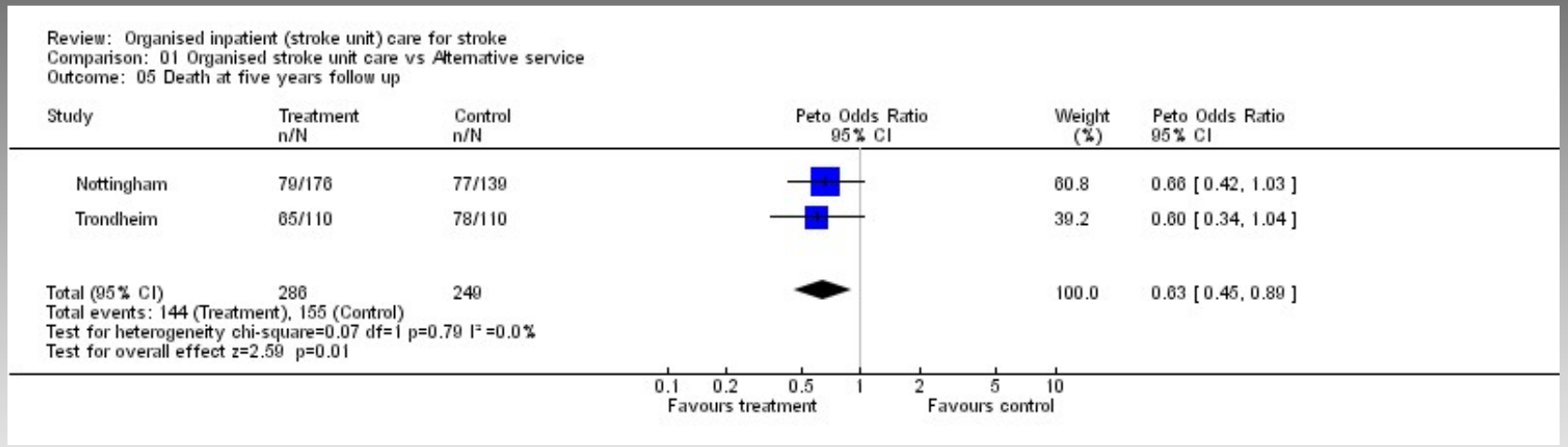
- An analysis of treatment effects within subgroups of patients enrolled on a clinical trial who might be expected to respond to treatment differently
- "Should all patients be given XYZ? Can/should treatment be limited to a selected group?"
- Methods for investigating possible causes of heterogeneity in a meta-analysis

•*Only one thing is worse than doing subgroup analyses---believing the results* R. Peto

General Assumptions in Subgroup Analysis

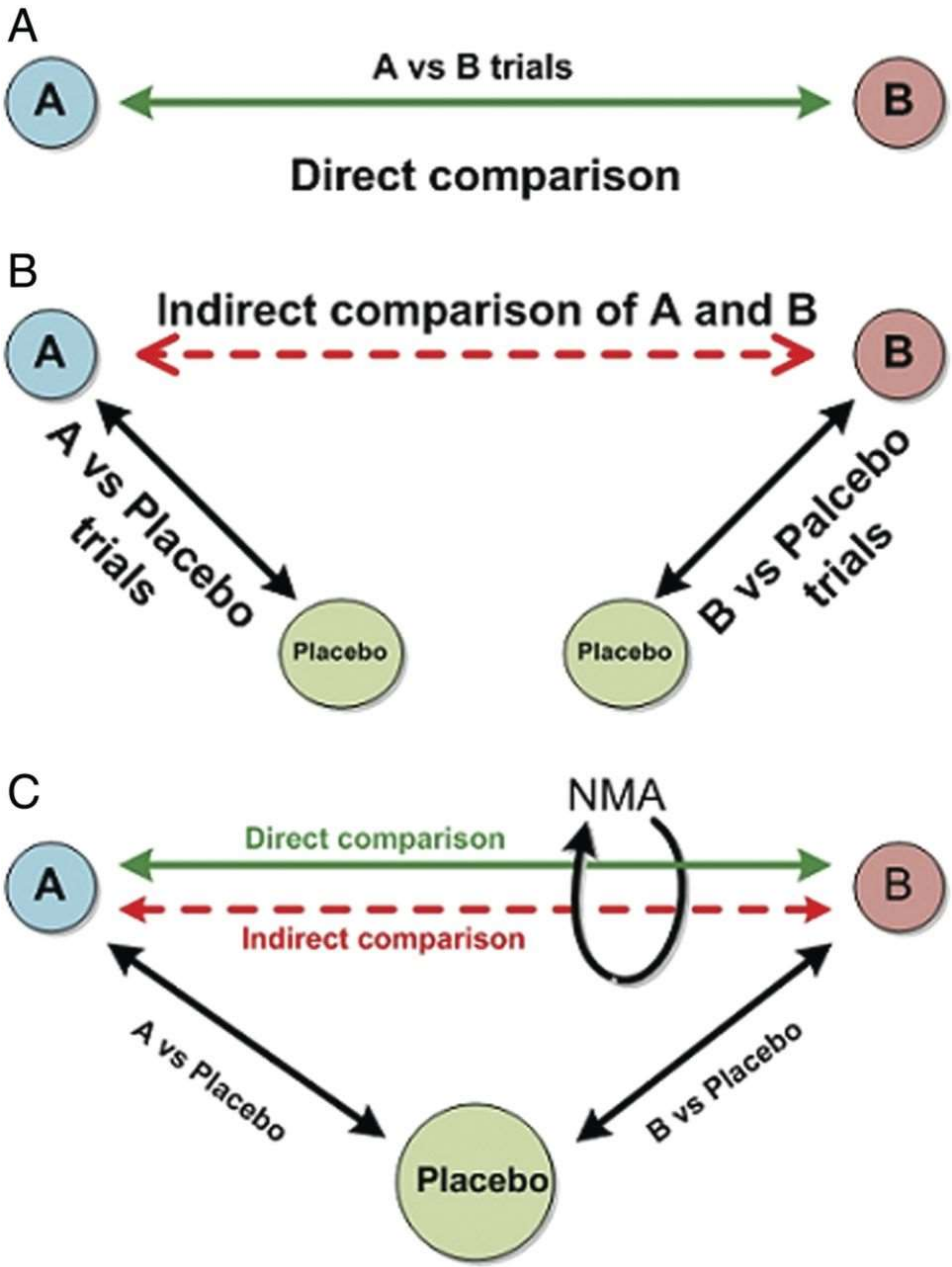
- Hypotheses tested usually address an overall or ‘average’ treatment effect in the study population
- No assumption of homogeneity of effect across subgroups - interaction
- Direction, not magnitude, of the treatment effect is expected be the same in subgroups

Esempio di Metaview



Motivation for Network Meta-Analysis

- There are often many treatments for health conditions
- Published systematic reviews and meta-analyses typically focus on pair-wise comparisons
- An alternative approach would involve extending the standard meta-analysis techniques to accommodate multiple treatment
- This emerging field has been described as both network meta-analysis and mixed treatment comparisons


A
A vs B trials
A
B
Direct comparison
B
Indirect comparison of A and B
A
B
A vs Placebo trials
B vs Palcebo trials
Placebo
Placebo
C
NMA
Direct comparison
A
B
Indirect comparison
A vs Placebo
B vs Placebo
Placebo

Indirect Comparisons of Multiple Treatments – Network Meta-Analysis

Trial			
1	A	B	
2	A	B	
3		B	C
4		B	C
5	A		C
6	A		C
7	A	B	C

- Want to compare A vs. B
  Direct evidence from trials 1, 2 and 7
  Indirect evidence from trials 3, 4, 5, 6 and 7

- Combining all “A” arms and comparing with all “B” arms destroys randomization

- Use indirect evidence of A vs. C and B vs. C comparisons as additional evidence to preserve randomization and within-study comparison

Indirect Comparisons

Basic assumptions underlying indirect comparisons include:

- ✓ **homogeneity** assumption for standard meta-analysis,
- ✓ **similarity** assumption for adjusted indirect comparison and
- ✓ **consistency** assumption for the combination of direct and indirect evidence. It is essential to fully understand and appreciate these basic assumptions in order to use adjusted indirect and mixed treatment comparisons appropriately.

What is indirect comparison? Fujian Song BMed MMed PhD Reader in Research Synthesis, Faculty of Health, University of East Anglia
www.whatisseries.co.uk http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/What_is_ind_comp.pdf

HOMOGENEITY ASSUMPTION

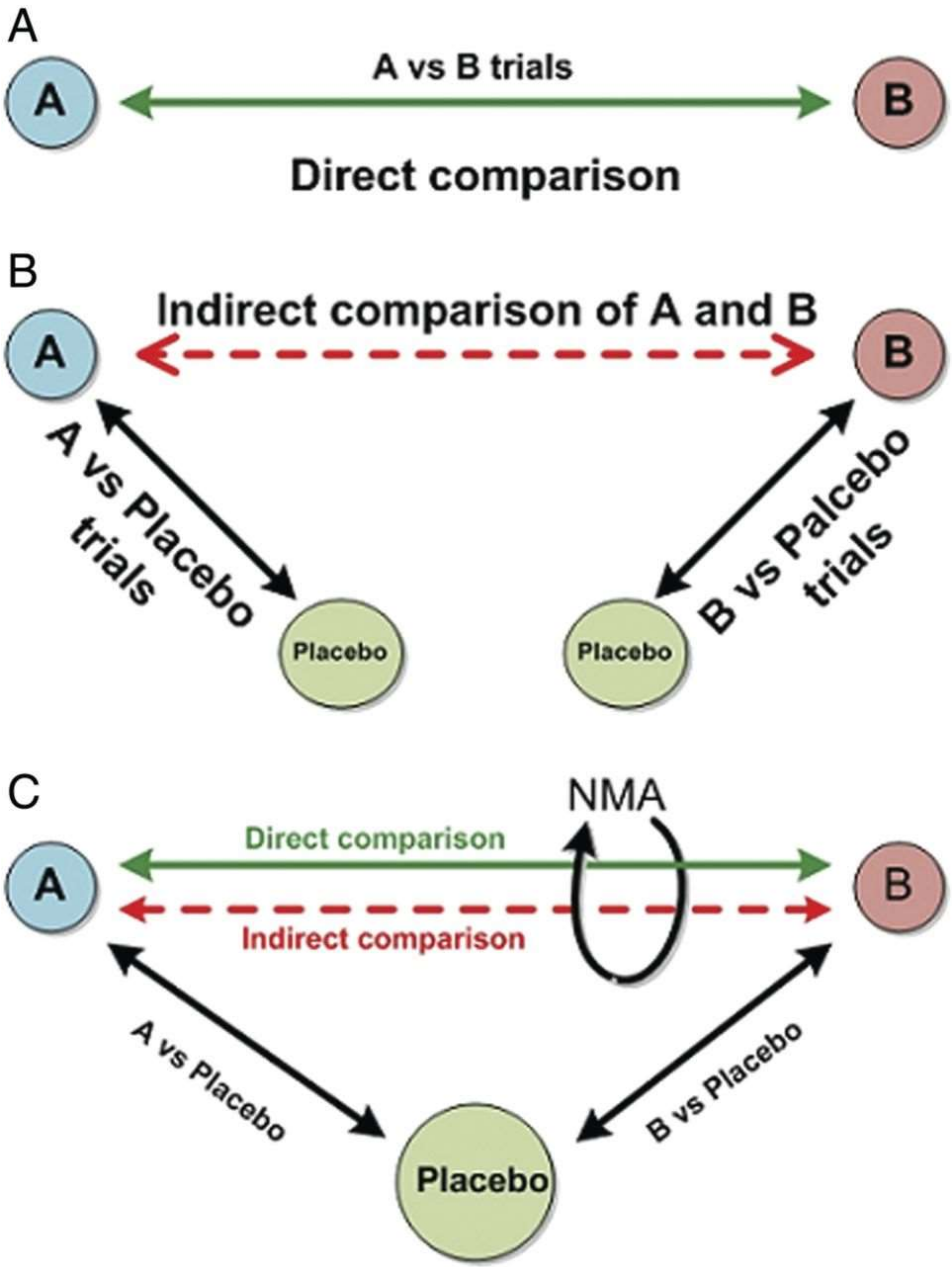
- When multiple trials are available for a given comparison, the results from multiple trials can be pooled in meta-analyses before an adjusted indirect comparison is conducted.
- For a meta-analysis to be valid, it is commonly established that results from different trials should be sufficiently homogeneous from a clinical and statistical perspective.
- This is usually demonstrated by a 2-tailed p value for homogeneity at Pearson chi-squared test or Cochran Q test > 0.10 and a I^2 (inconsistency) < 50%.
- When homogeneity is unlikely (e.g. I^2>50%) than heterogeneity and inconsistency are likely.

Song, What is …? 2009; Higgins et al, BMJ 2003

SIMILARITY (TRANSITIVITY) ASSUMPTION

- For an adjusted indirect comparison (A vs B) to be valid, a similarity assumption is required in terms of moderators of relative treatment effect.
- That is, patients included should be sufficiently similar in the two sets of control arms (C_1 from the trial comparing A vs C_1, and C_2, from the trial comparing B vs C_2).
- This is crucial as only a large theoretical overlap between patients enrolled in C_1 and C_2 enables the relative effect estimated by trials of A versus C_1 to be generalizable to patients in trials of B versus C_1, and the relative effect estimated by trials of B versus C_2 to be generalizable to patients in trials of A versus C_2.

Song, What is …? 2009


A
A vs B trials
A
B
Direct comparison
B
Indirect comparison of A and B
A
B
A vs Placebo trials
B vs Palcebo trials
Placebo
Placebo
C
NMA
Direct comparison
A
B
Indirect comparison
A vs Placebo
B vs Placebo
Placebo

CONSISTENCY ASSUMPTION

- When both direct and indirect evidence is available, an assumption of evidence consistency is required to quantitatively combine the direct and indirect estimates.
- It is important to investigate possible causes of discrepancy between the direct and indirect evidence, such as the play of chance, invalid indirect comparison, bias in head-to-head comparative trials, and clinically meaningful heterogeneity
- When the direct comparison differs from the adjusted indirect comparison, we should usually give more credibility to evidence from head-to-head comparative trials. However, evidence from direct comparative trials may not always be valid.

Song, What is …? 2009; Song et al, J Clin Epidemiol 2008

Presenting the data

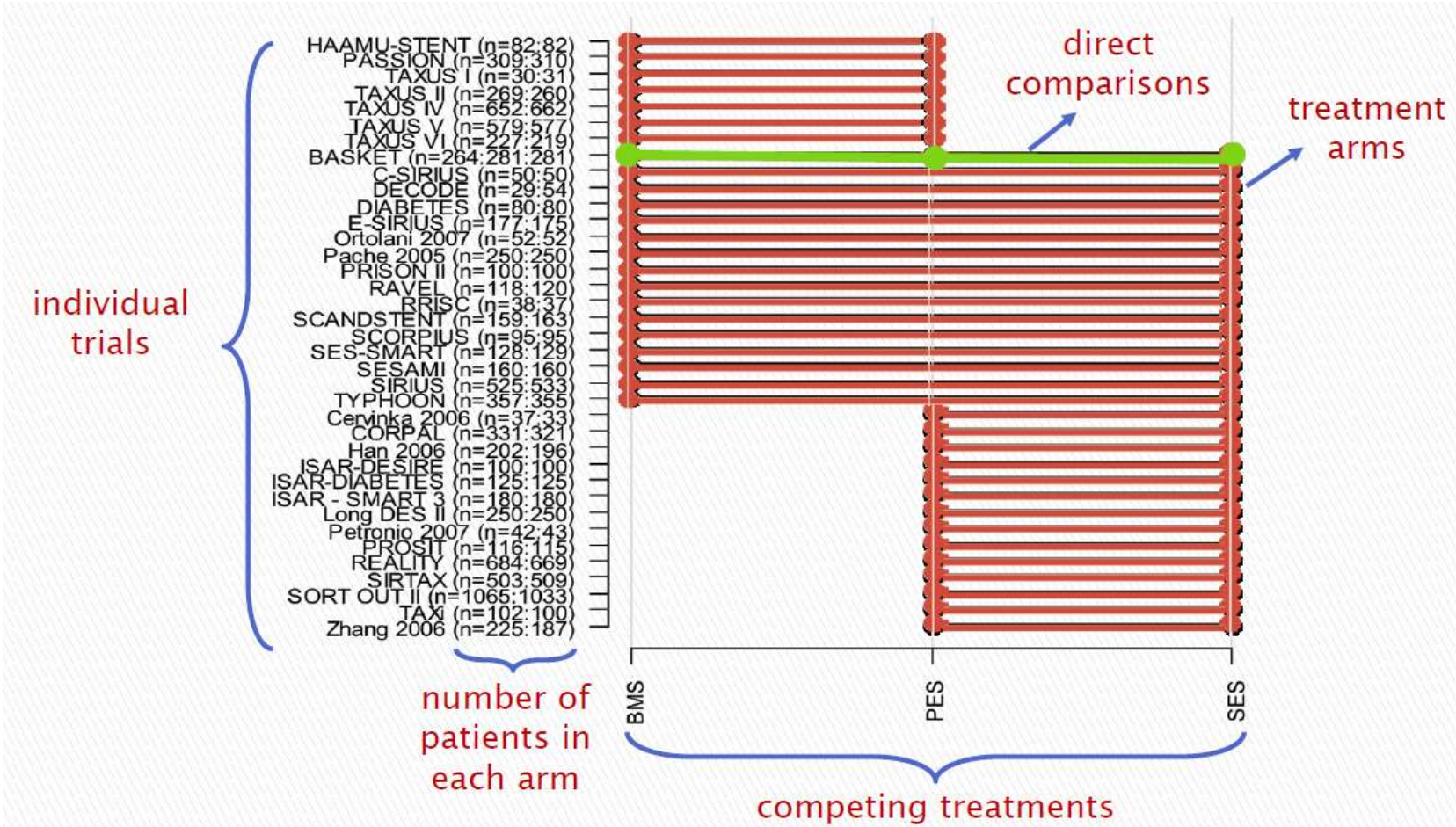
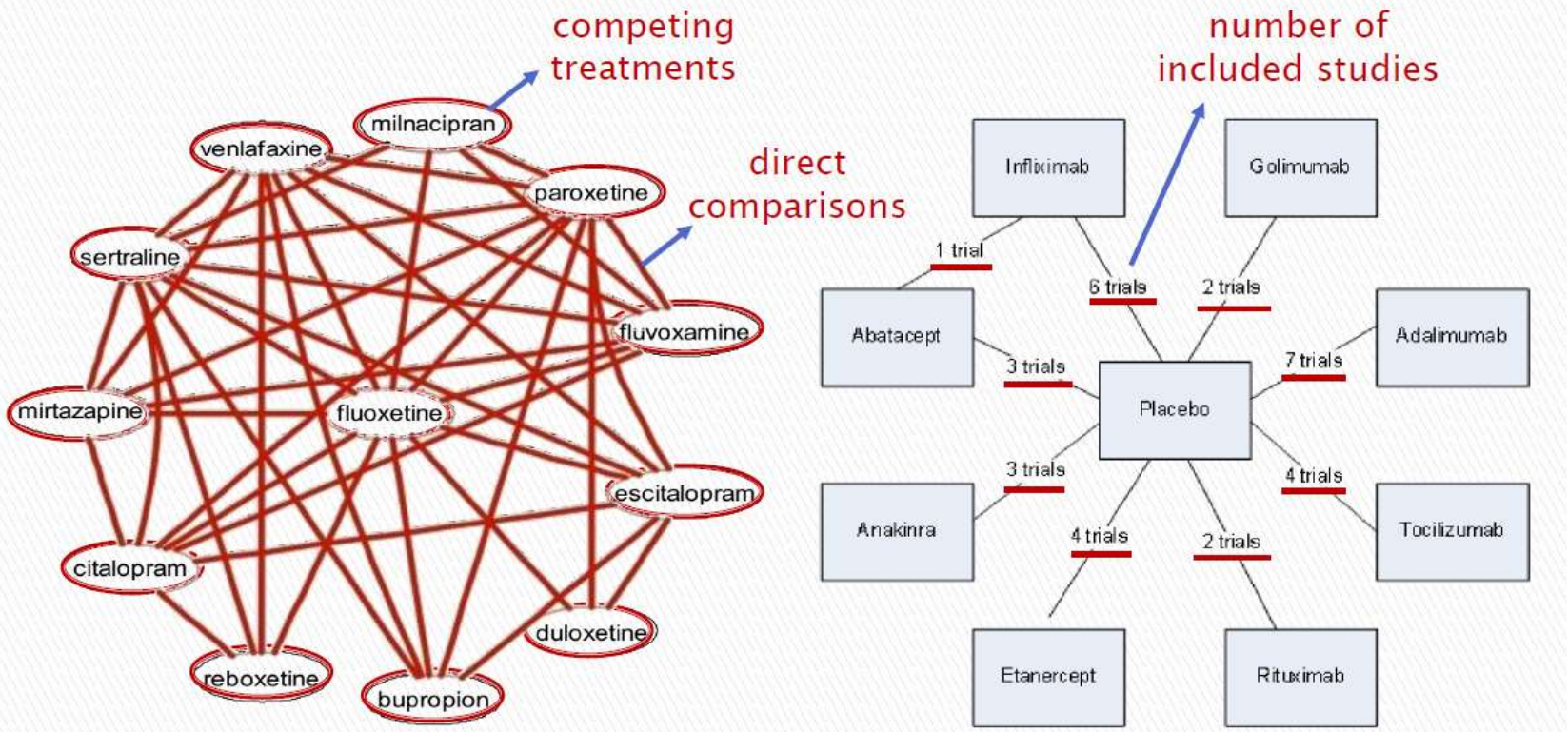


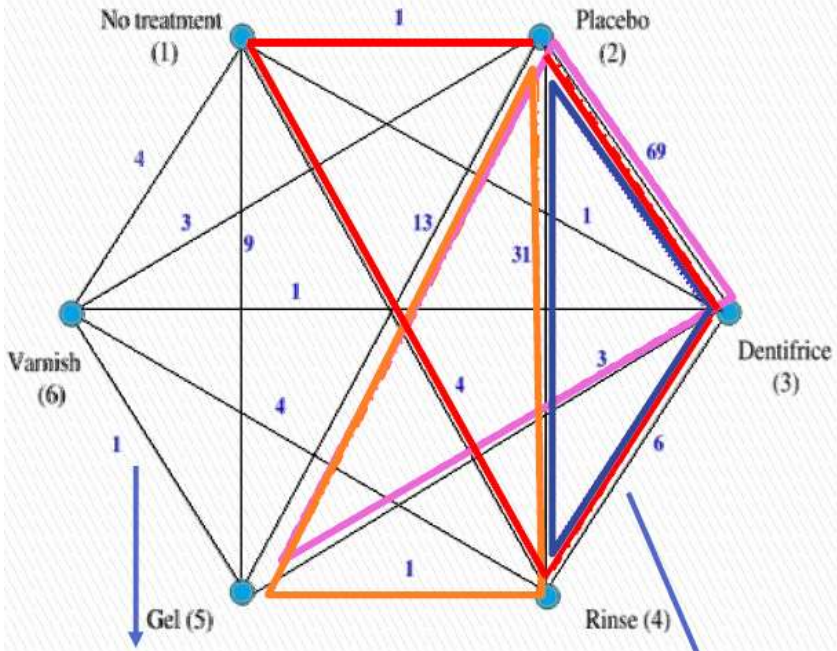
Diagram showing the comparisons involved in the individual studies of the network

[Example in Hoaglin et al. 2011]



Network graph showing the available direct comparisons in the network

[Examples in Hoaglin et al. 2011 & Jonas et al. 2013]



Type (g)	No. of studies	No. trt (1)	Placebo (2)	Dentifrice (3)	Rinse (4)	Gel (5)	Varnish (6)
1	9	X				X	
2	3	X			X		
3	4	X					X
4	61		X	X			
5	9		X			X	
6	25		X		X		
7	3		X				X
8	1			X	X		
9	1			X		X	
10	1					X	X
11	4				X		X
12	4		X	X	X		
13	3		X	X		X	
14	1		X		X	X	
15	1	X	X	X	X		

direct comparisons from two-arm trials

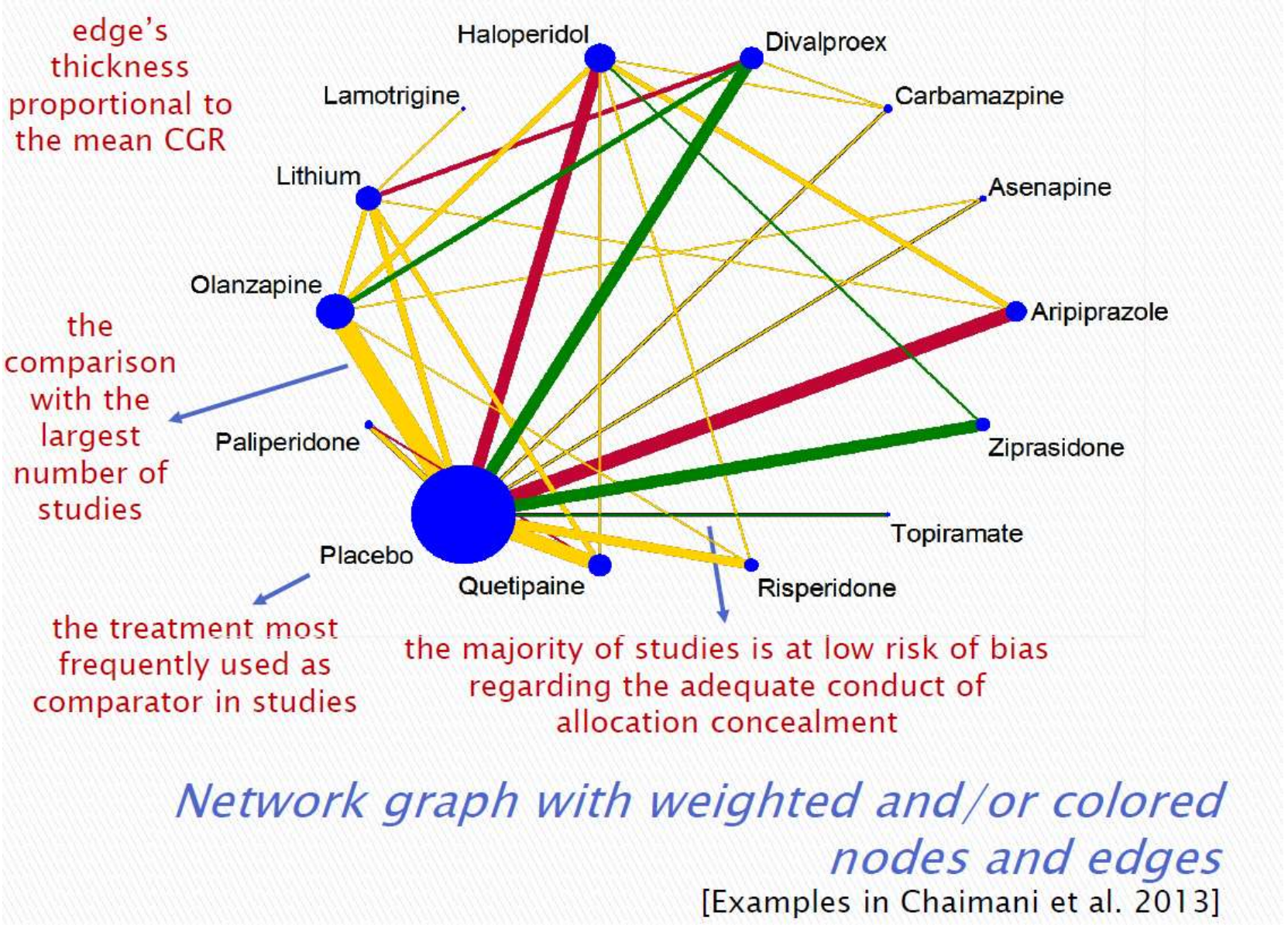
direct comparisons from multi-arm trials

15 different study designs

treatment arms in each design

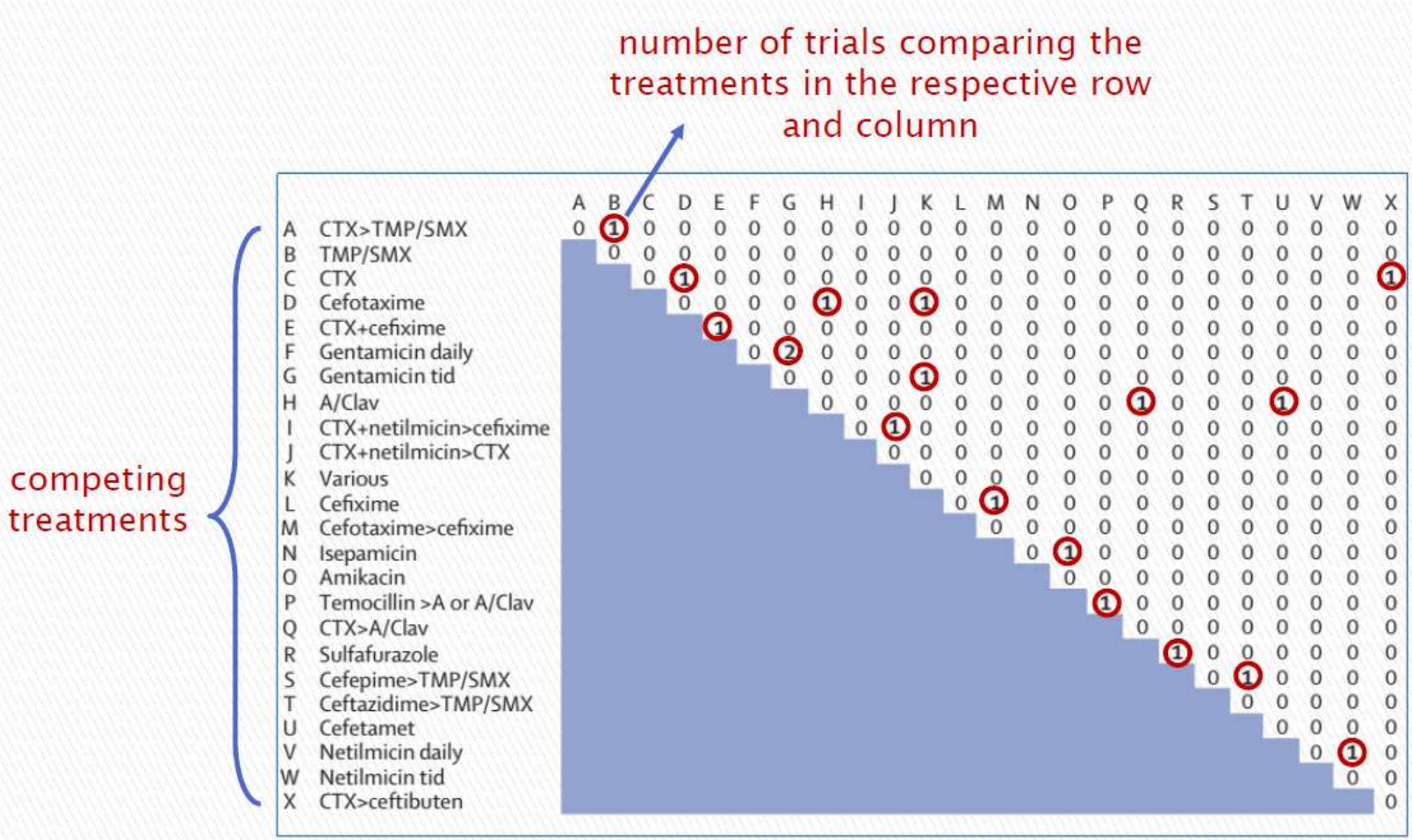
Network graph showing the presence of multi-arm trials & table showing the network structure; the available study designs in the network

[Examples in Lu et al. 2011]



Network graph with weighted and/or colored nodes and edges

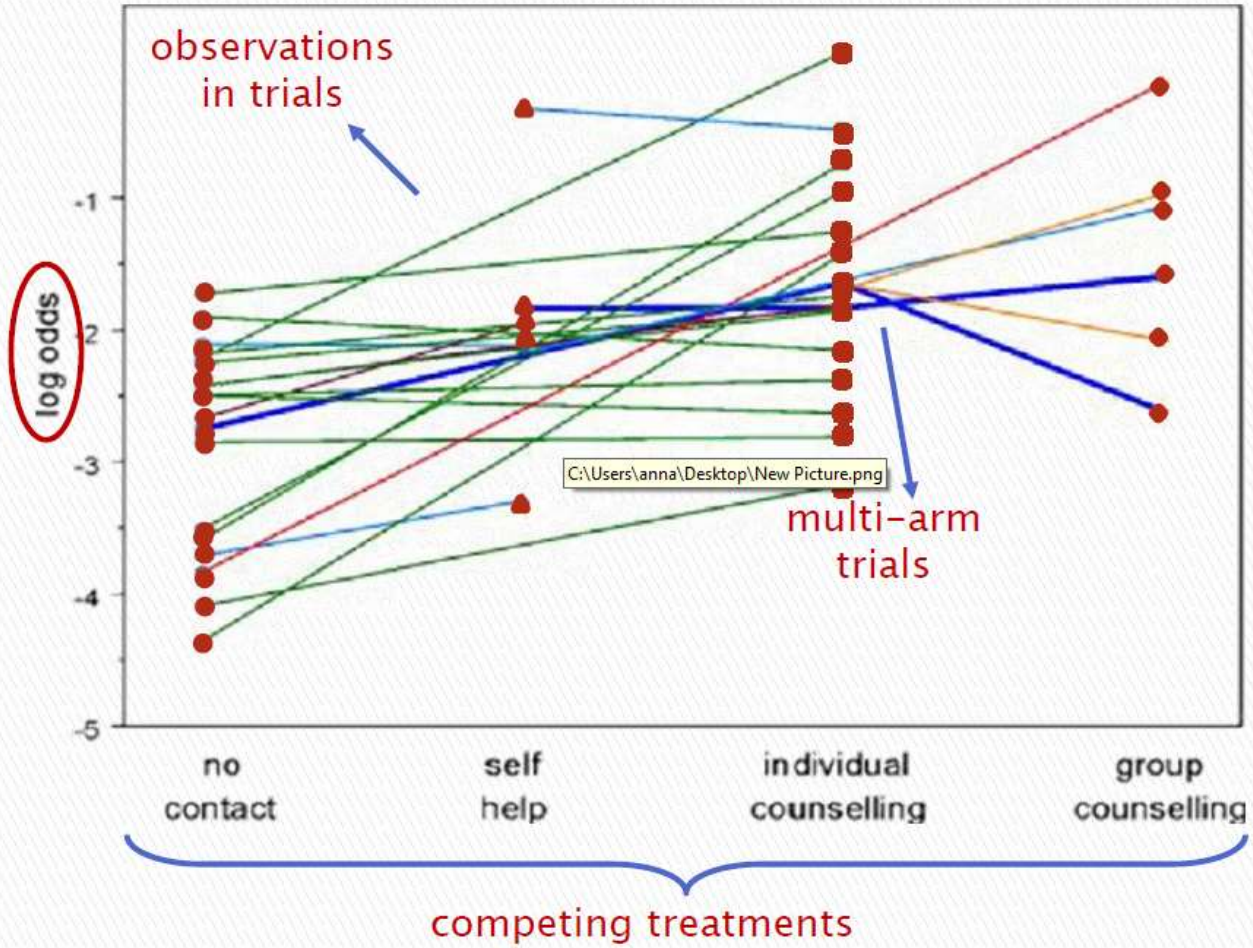
[Examples in Chaimani et al. 2013]



Matrix showing the available direct comparisons in the network

[Example in Ioannidis 2006]

the slope of the lines shows which treatments are favored in studies

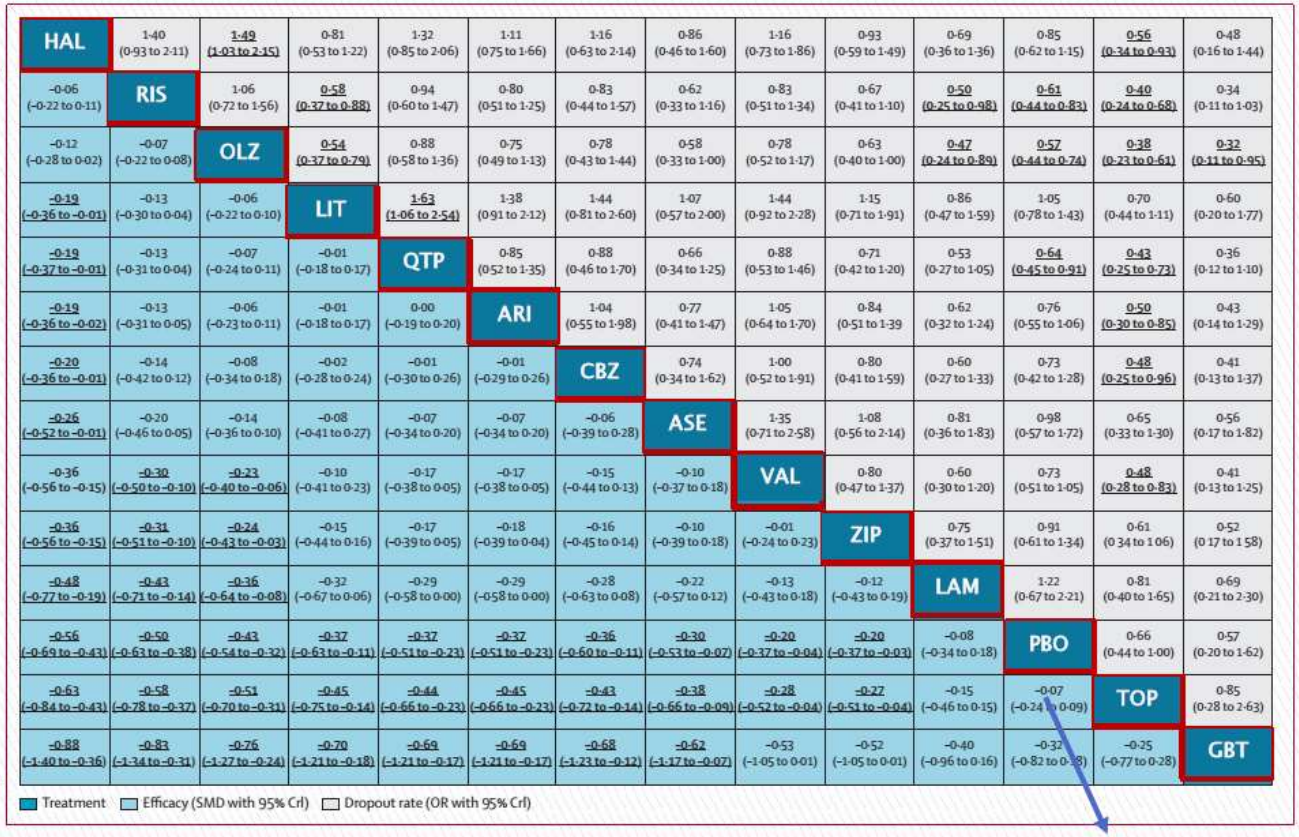


Graph showing the data provided by the individual studies of the network

[Example in Lu & Ades 2006]

Presenting the results
measures of effect

relative treatment effects for efficacy
SMD<0 favor the treatment in column



HAL	1·40 (0·93 to 2·11)	**1·49 (1·03 to 2·15)**	0·81 (0·53 to 1·22)	1·32 (0·85 to 2·06)	1·11 (0·75 to 1·66)	1·16 (0·63 to 2·14)	0·86 (0·46 to 1·60)	1·16 (0·73 to 1·86)	0·93 (0·59 to 1·49)	0·69 (0·36 to 1·36)	0·85 (0·62 to 1·15)	**0·56 (0·34 to 0·93)**	0·48 (0·16 to 1·44)
−0·06 (−0·22 to 0·11)	**RIS**	1·06 (0·72 to 1·56)	**0·58 (0·37 to 0·88)**	0·94 (0·60 to 1·47)	0·80 (0·51 to 1·25)	0·83 (0·44 to 1·57)	0·62 (0·33 to 1·16)	0·83 (0·51 to 1·34)	0·67 (0·41 to 1·10)	**0·50 (0·25 to 0·98)**	**0·61 (0·44 to 0·83)**	**0·40 (0·24 to 0·68)**	0·34 (0·11 to 1·03)
−0·12 (−0·28 to 0·02)	−0·07 (−0·22 to 0·08)	**OLZ**	**0·54 (0·37 to 0·79)**	0·88 (0·58 to 1·36)	0·75 (0·49 to 1·13)	0·78 (0·43 to 1·44)	0·58 (0·33 to 1·00)	0·78 (0·52 to 1·17)	0·63 (0·40 to 1·00)	**0·47 (0·24 to 0·89)**	**0·57 (0·44 to 0·74)**	**0·38 (0·23 to 0·61)**	**0·32 (0·11 to 0·95)**
−0·19 (−0·36 to −0·01)	−0·13 (−0·30 to 0·04)	−0·06 (−0·22 to 0·10)	**LIT**	**1·63 (1·06 to 2·54)**	1·38 (0·91 to 2·12)	1·44 (0·81 to 2·60)	1·07 (0·57 to 2·00)	1·44 (0·92 to 2·28)	1·15 (0·71 to 1·91)	0·86 (0·47 to 1·59)	1·05 (0·78 to 1·43)	0·70 (0·44 to 1·11)	0·60 (0·20 to 1·77)
−0·19 (−0·37 to −0·01)	−0·13 (−0·31 to 0·04)	−0·07 (−0·24 to 0·11)	−0·01 (−0·18 to 0·17)	**QTP**	0·85 (0·52 to 1·35)	0·88 (0·46 to 1·70)	0·66 (0·34 to 1·25)	0·88 (0·53 to 1·46)	0·71 (0·42 to 1·20)	0·53 (0·27 to 1·05)	**0·64 (0·45 to 0·91)**	**0·43 (0·25 to 0·73)**	0·36 (0·12 to 1·10)
−0·19 (−0·36 to −0·02)	−0·13 (−0·31 to 0·05)	−0·06 (−0·23 to 0·11)	−0·01 (−0·18 to 0·17)	0·00 (−0·19 to 0·20)	**ARI**	1·04 (0·55 to 1·98)	0·77 (0·41 to 1·47)	1·05 (0·64 to 1·70)	0·84 (0·51 to 1·39	0·62 (0·32 to 1·24)	0·76 (0·55 to 1·06)	**0·50 (0·30 to 0·85)**	0·43 (0·14 to 1·29)
−0·20 (−0·36 to −0·01)	−0·14 (−0·42 to 0·12)	−0·08 (−0·34 to 0·18)	−0·02 (−0·28 to 0·24)	−0·01 (−0·30 to 0·26)	−0·01 (−0·29 to 0·26)	**CBZ**	0·74 (0·34 to 1·62)	1·00 (0·52 to 1·91)	0·80 (0·41 to 1·59)	0·60 (0·27 to 1·33)	0·73 (0·42 to 1·28)	**0·48 (0·25 to 0·96)**	0·41 (0·13 to 1·37)
−0·26 (−0·52 to −0·01)	−0·20 (−0·46 to 0·05)	−0·14 (−0·36 to 0·10)	−0·08 (−0·41 to 0·27)	−0·07 (−0·34 to 0·20)	−0·07 (−0·34 to 0·20)	−0·06 (−0·39 to 0·28)	**ASE**	1·35 (0·71 to 2·58)	1·08 (0·56 to 2·14)	0·81 (0·36 to 1·83)	0·98 (0·57 to 1·72)	0·65 (0·33 to 1·30)	0·56 (0·17 to 1·82)
−0·36 (−0·56 to −0·15)	**−0·30 (−0·50 to −0·10)**	**−0·23 (−0·40 to −0·06)**	−0·10 (−0·41 to 0·23)	−0·17 (−0·38 to 0·05)	−0·17 (−0·38 to 0·05)	−0·15 (−0·44 to 0·13)	−0·10 (−0·37 to 0·18)	**VAL**	0·80 (0·47 to 1·37)	0·60 (0·30 to 1·20)	0·73 (0·51 to 1·05)	**0·48 (0·28 to 0·83)**	0·41 (0·13 to 1·25)
−0·36 (−0·56 to −0·15)	**−0·31 (−0·51 to −0·10)**	**−0·24 (−0·43 to −0·03)**	−0·15 (−0·44 to 0·16)	−0·17 (−0·39 to 0·05)	−0·18 (−0·39 to 0·04)	−0·16 (−0·45 to 0·14)	−0·10 (−0·39 to 0·18)	−0·01 (−0·24 to 0·23)	**ZIP**	0·75 (0·37 to 1·51)	0·91 (0·61 to 1·34)	0·61 (0·34 to 1·06)	0·52 (0·17 to 1·58)
−0·48 (−0·77 to −0·19)	**−0·43 (−0·71 to −0·14)**	**−0·36 (−0·64 to −0·08)**	−0·32 (−0·67 to 0·06)	−0·29 (−0·58 to 0·00)	−0·29 (−0·58 to 0·00)	−0·28 (−0·63 to 0·08)	−0·22 (−0·57 to 0·12)	−0·13 (−0·43 to 0·18)	−0·12 (−0·43 to 0·19)	**LAM**	1·22 (0·67 to 2·21)	0·81 (0·40 to 1·65)	0·69 (0·21 to 2·30)
−0·56 (−0·69 to −0·43)	**−0·50 (−0·63 to −0·38)**	**−0·43 (−0·54 to −0·32)**	**−0·37 (−0·63 to −0·11)**	**−0·37 (−0·51 to −0·23)**	**−0·37 (−0·51 to −0·23)**	**−0·36 (−0·60 to −0·11)**	**−0·30 (−0·53 to −0·07)**	**−0·20 (−0·37 to −0·04)**	**−0·20 (−0·37 to −0·03)**	−0·08 (−0·34 to 0·18)	**PBO**	0·66 (0·44 to 1·00)	0·57 (0·20 to 1·62)
−0·63 (−0·84 to −0·43)	**−0·58 (−0·78 to −0·37)**	**−0·51 (−0·70 to −0·31)**	**−0·45 (−0·75 to −0·14)**	**−0·44 (−0·66 to −0·23)**	**−0·45 (−0·66 to −0·23)**	**−0·43 (−0·72 to −0·14)**	**−0·38 (−0·66 to −0·09)**	**−0·28 (−0·52 to −0·04)**	**−0·27 (−0·51 to −0·04)**	−0·15 (−0·46 to 0·15)	−0·07 (−0·24 to 0·09)	**TOP**	0·85 (0·28 to 2·63)
−0·88 (−1·40 to −0·36)	**−0·83 (−1·34 to −0·31)**	**−0·76 (−1·27 to −0·24)**	**−0·70 (−1·21 to −0·18)**	**−0·69 (−1·21 to −0·17)**	**−0·69 (−1·21 to −0·17)**	**−0·68 (−1·23 to −0·12)**	**−0·62 (−1·17 to −0·07)**	−0·53 (−1·05 to 0·01)	−0·52 (−1·05 to 0·01)	−0·40 (−0·96 to 0·16)	−0·32 (−0·82 to 0·18)	−0·25 (−0·77 to 0·28)	**GBT**

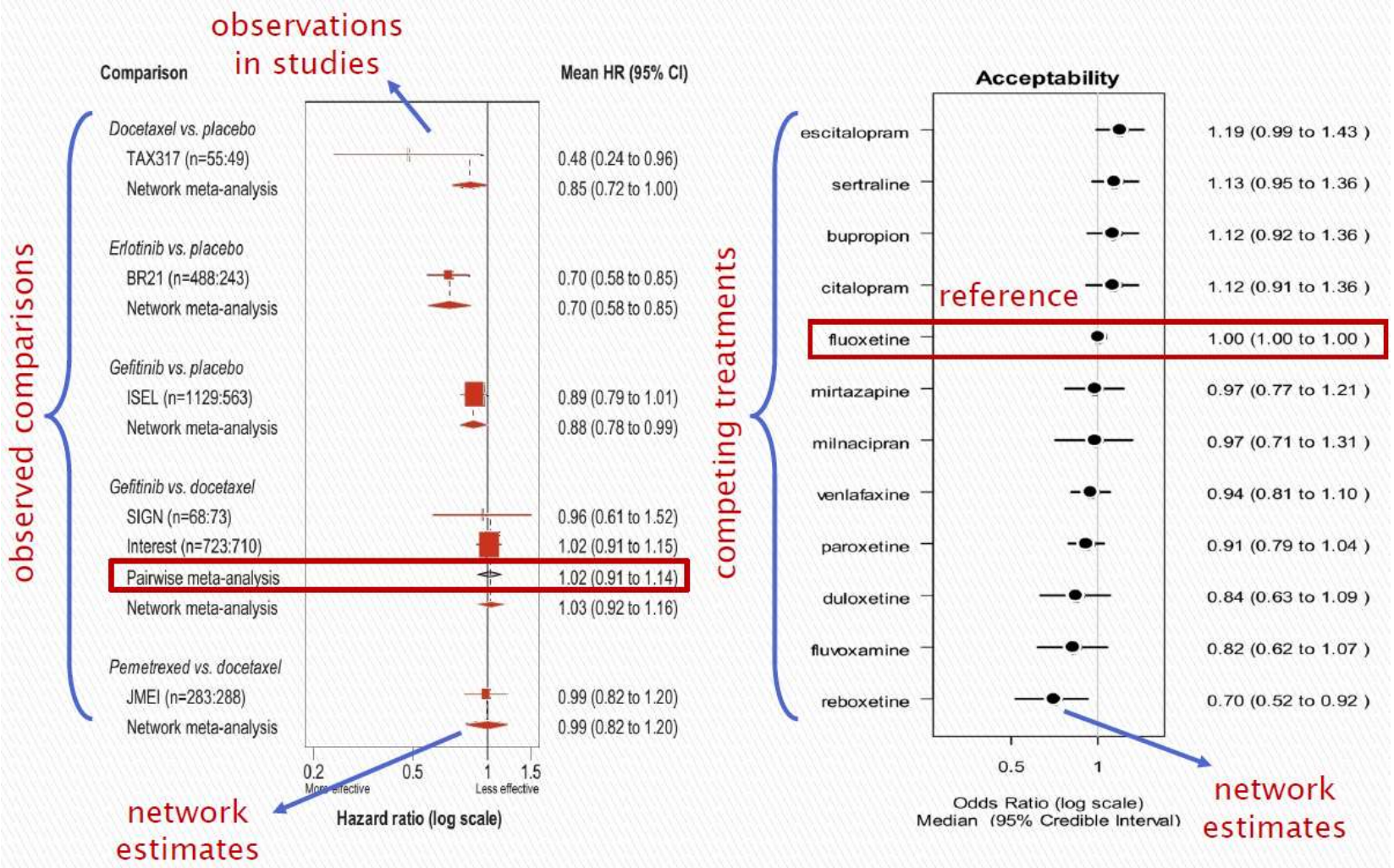
Treatment Efficacy (SMD with 95% CrI) Dropout rate (OR with 95% CrI)

relative treatment effects for dropout rate
OR>1 favor the treatment in column

significant effects are in bold and competing treatments *underscored font*

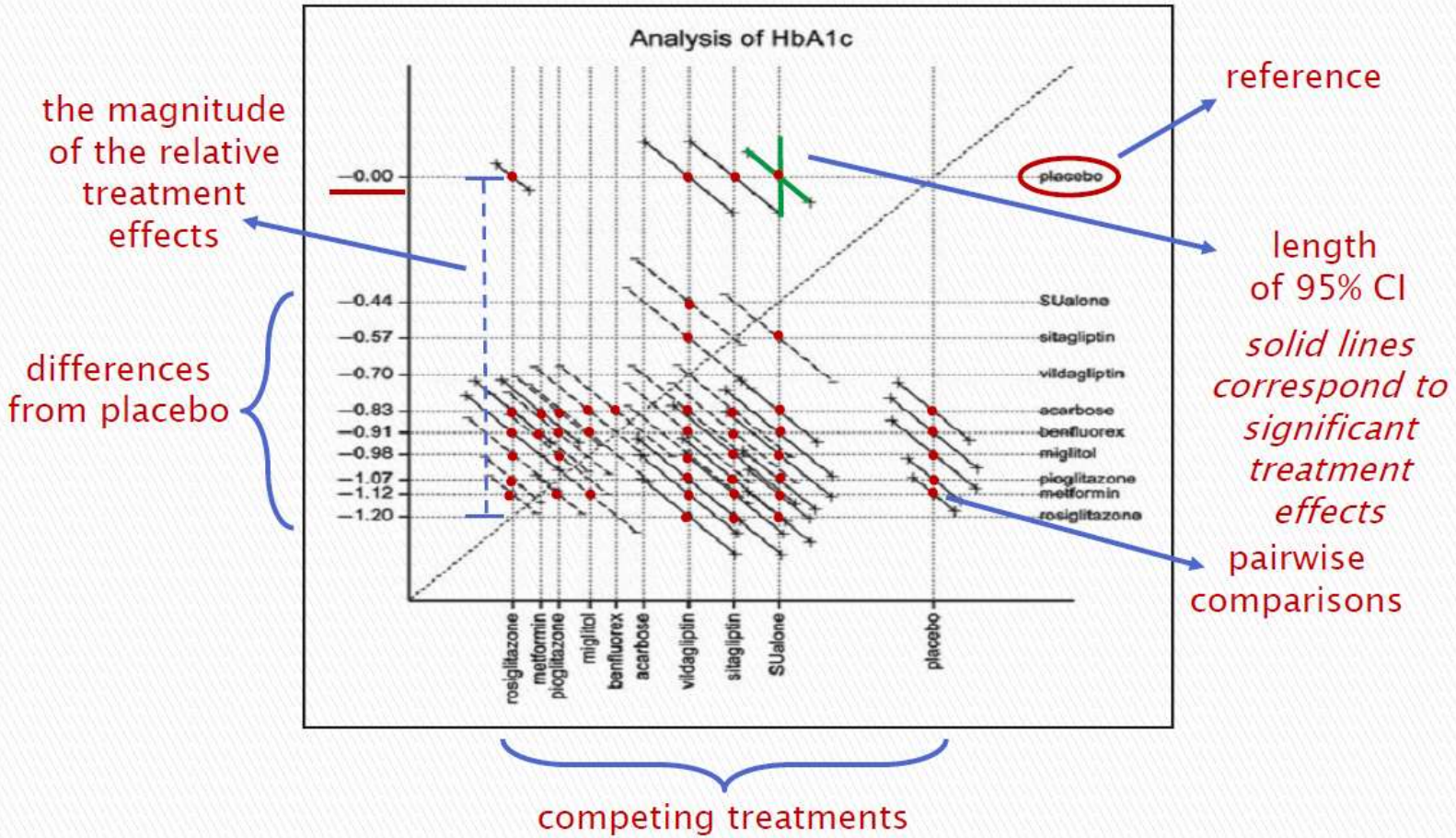
Table showing all the pairwise relative treatment effects with their 95% CI for one or two outcomes

[Example in Cipriani et al. 2011]



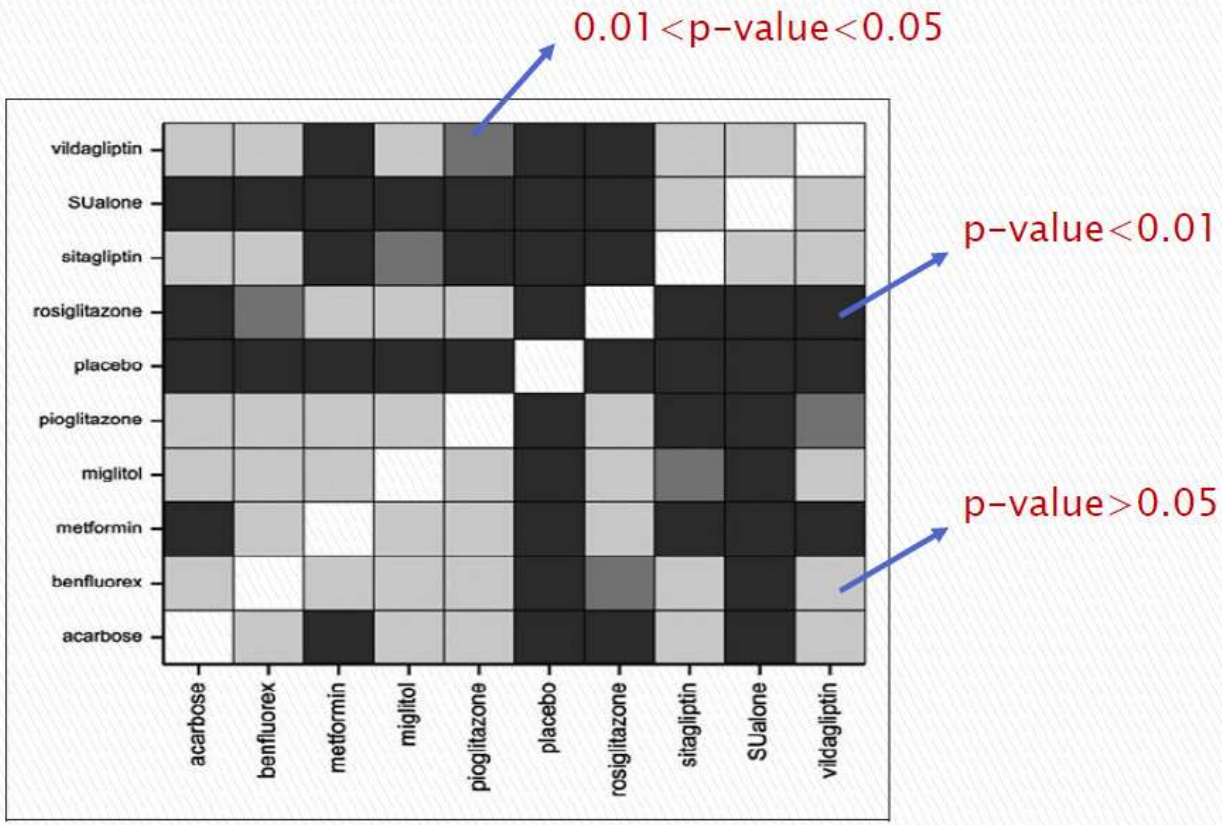
Forest plot with the treatment effects estimates for the pairwise comparisons

[Examples in Hawkins et al. 2009 & Hoaglin et al. 2011]



'Hsu mean-mean plot' showing the network estimates with the 95% CI for all pairwise comparisons

[Example in Senn et al. 2013]

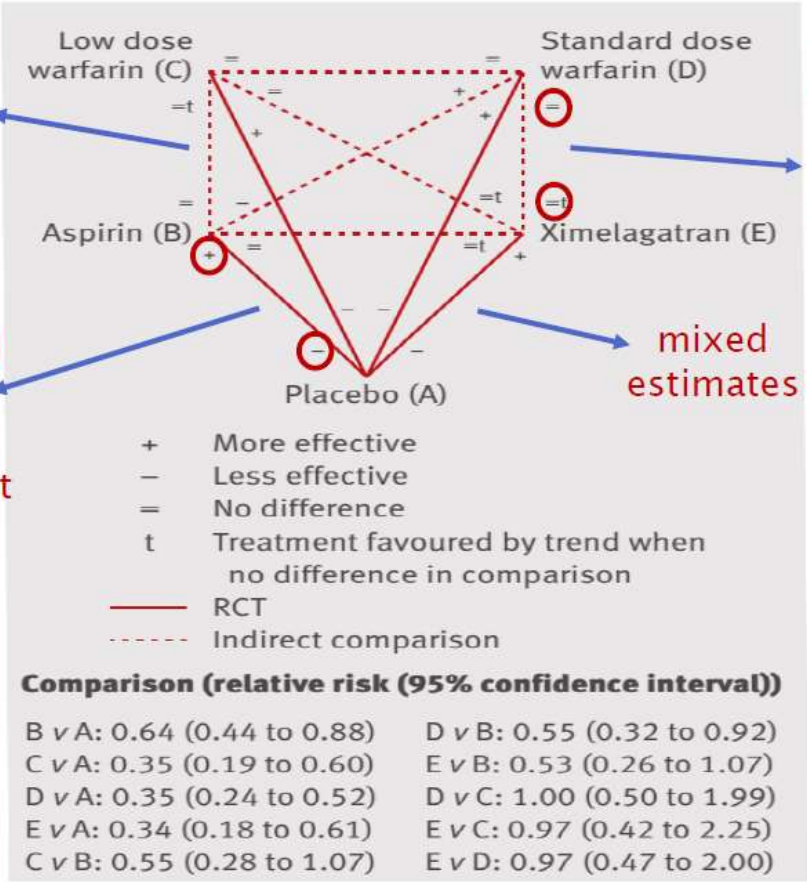


Shade plot showing the p-values of the treatment effects for all pairwise comparisons in the network

[Example in Senn et al. 2013]

indirect estimates

in comparisons with significant relative treatment effects (based on the network estimates):
'+' the favored treatment
'–' the non-favored treatment



mixed estimates

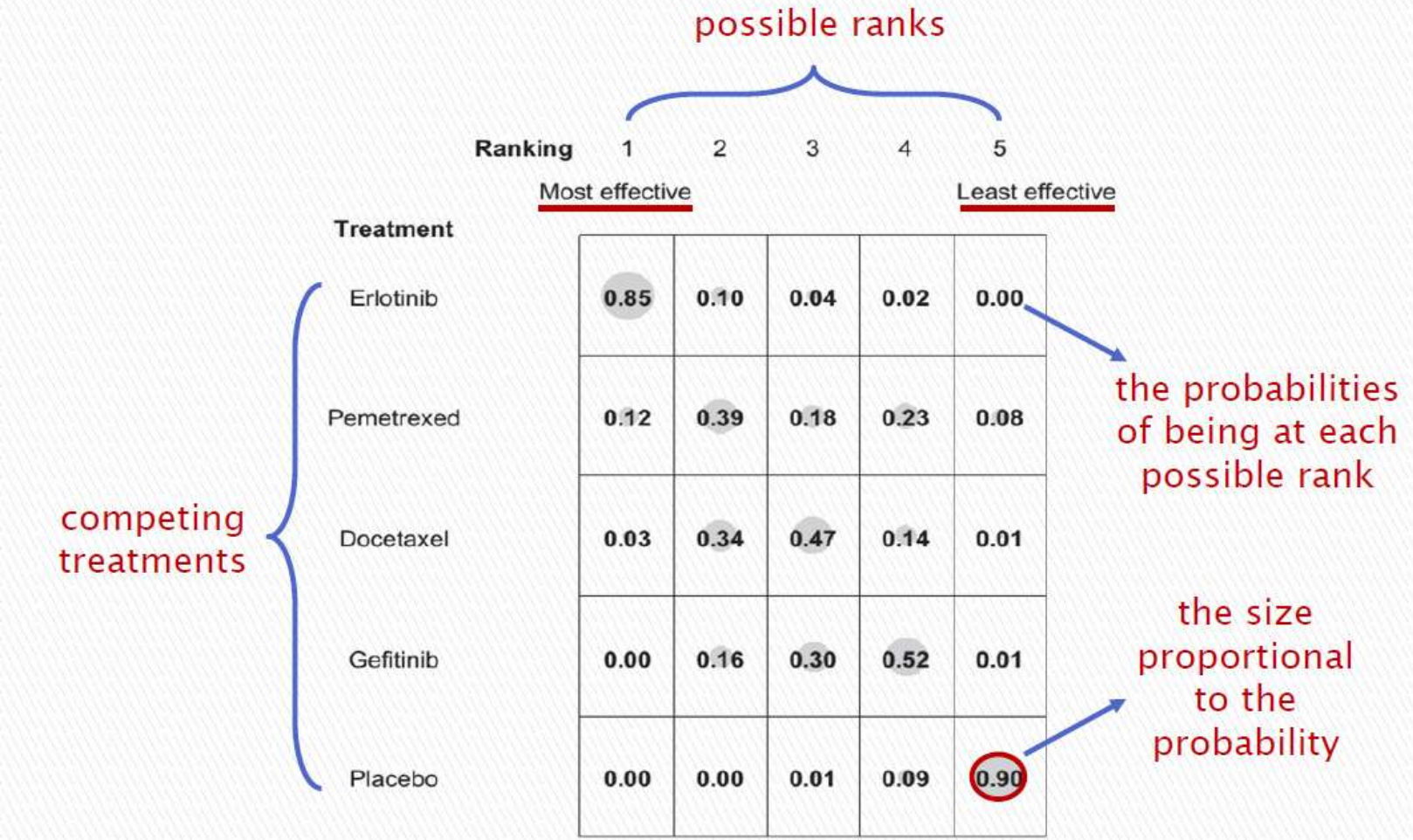
in comparisons with non-significant relative treatment effects (based on the network estimates):
'=t' the favored treatment
'=' the non-favored treatment

Network graph presenting the relative treatment effects for each pairwise comparison

[Example in Fadda et al. 2011]

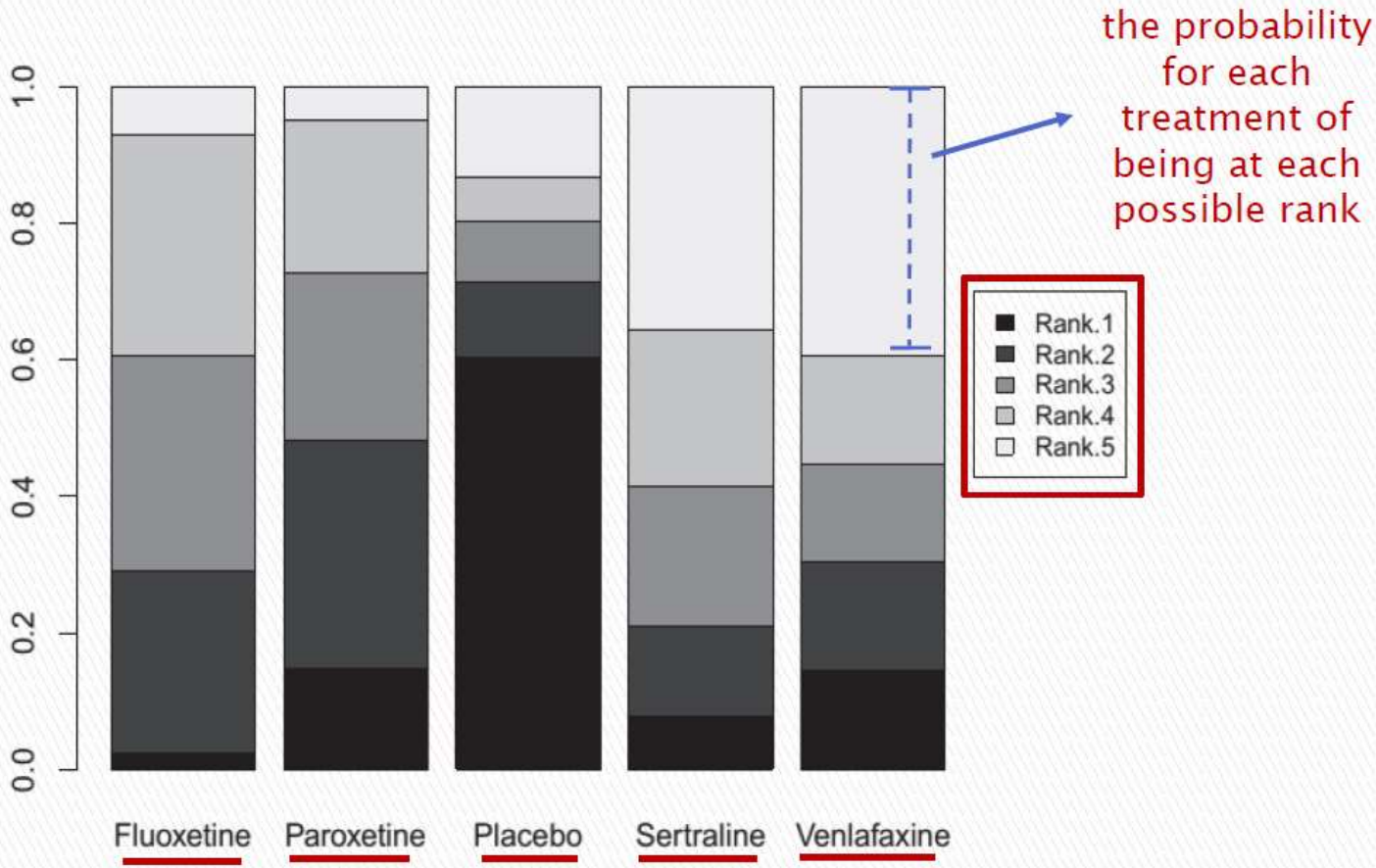
Presenting the results ranking

- Using probability of being the best
- Using probabilities of being at each possible rank
- Using SUCRAS



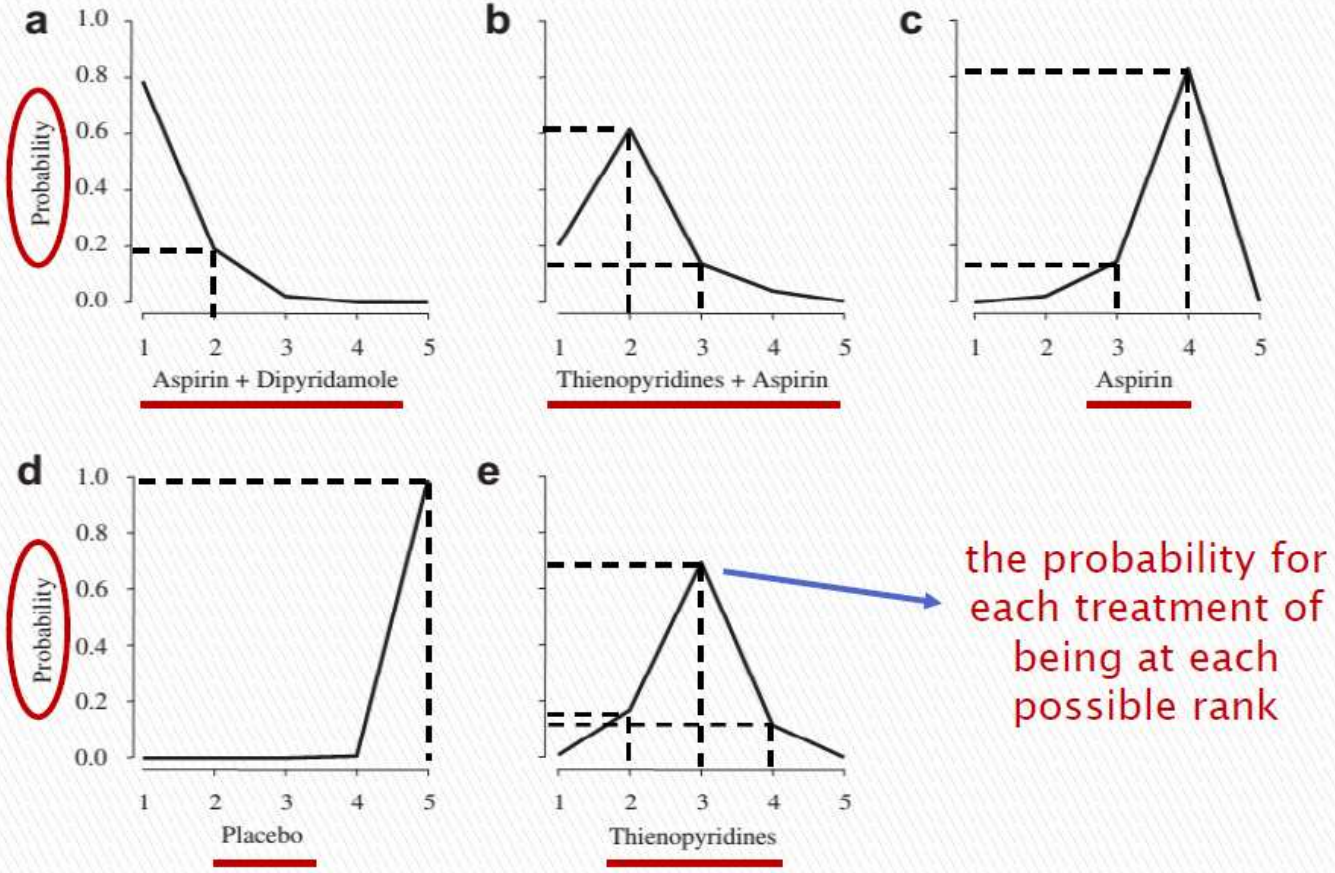
'Bubble-plot' including the ranking probabilities for all treatments

[Example in Hawkins et al. 2009]



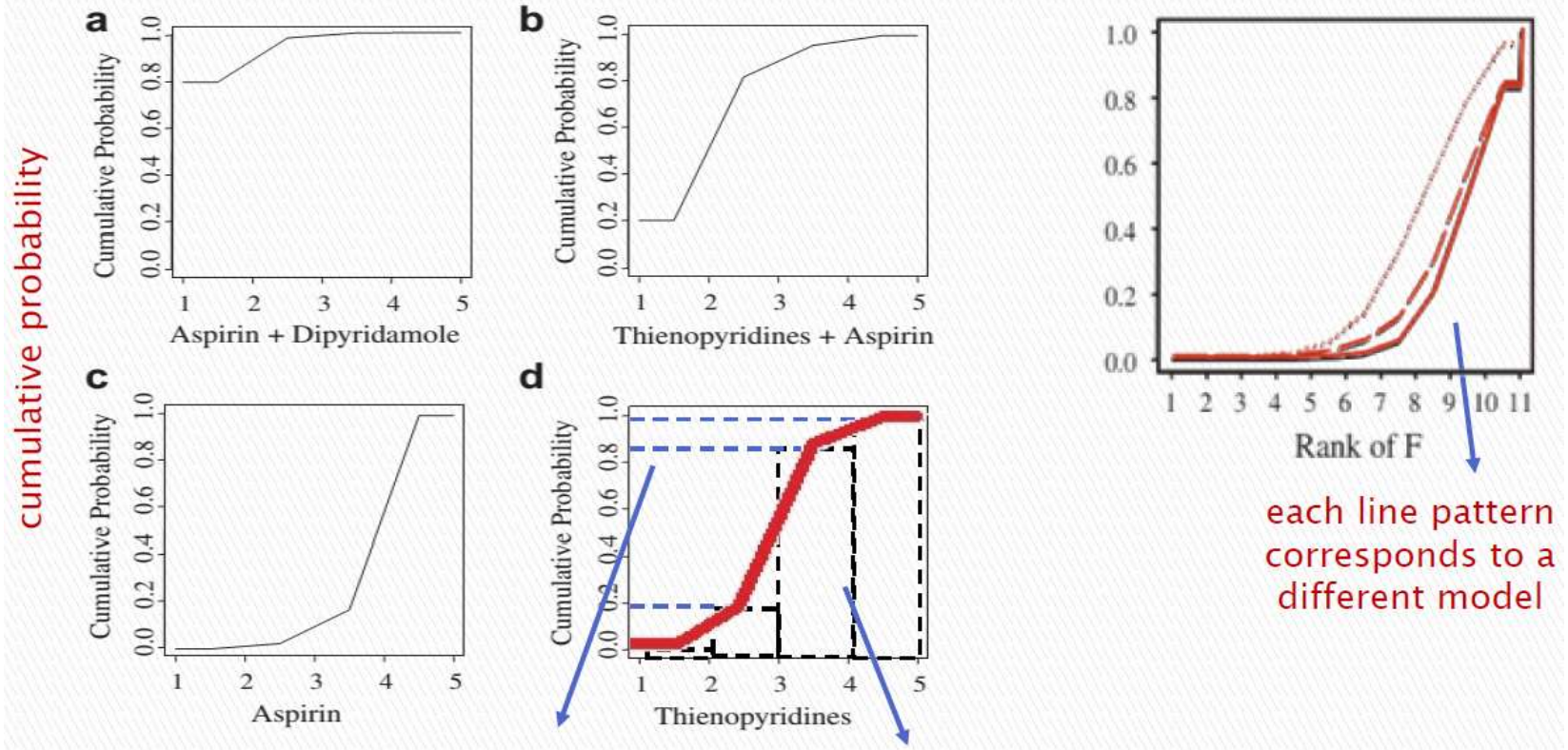
Bar plots showing the probability for each treatment of being at a specific rank

[Example in van Valkenhoef et al. 2012]



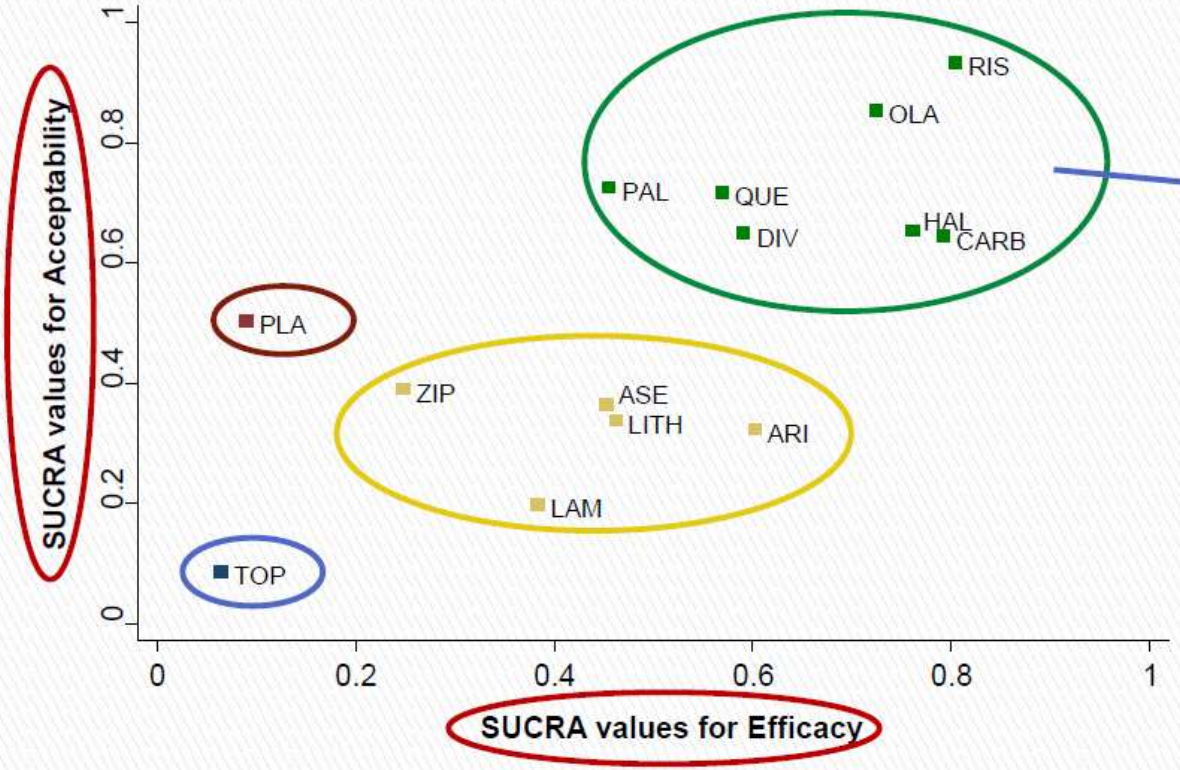
'Rankograms' showing the probability for each treatment of being at a specific rank

[Example in Salanti et al. 2011]



'SUCRA plots' showing the cumulative probability for each treatment of being up to a specific rank

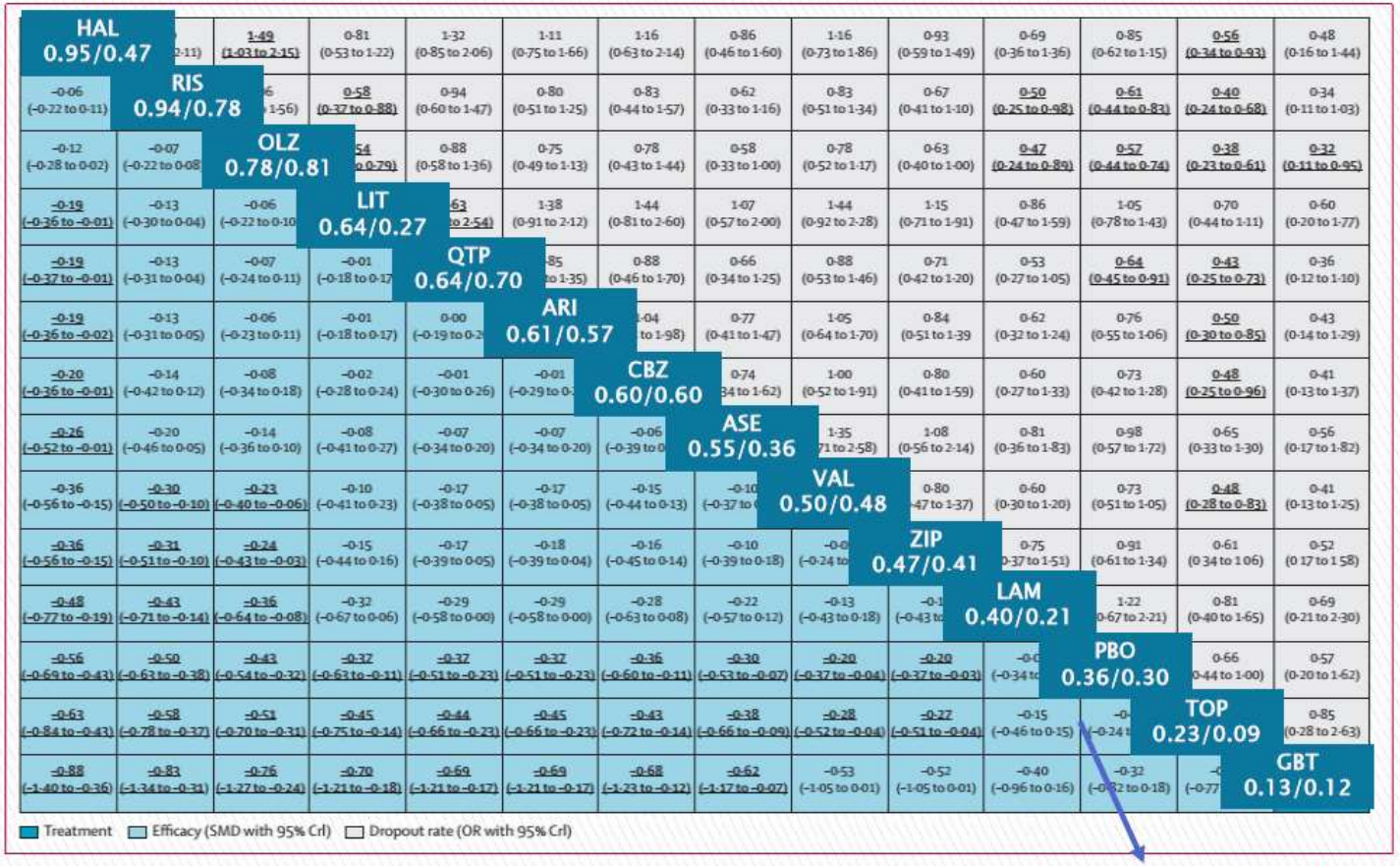
[Examples in Salanti et al. 2011 & Salanti et al. 2010]



the treatment group that performs well considering both outcomes

Scatterplot showing jointly the ranking results for two different outcomes

[Example in Chaimani et al. 2013]



competing treatments ordered according to their relative ranking for efficacy

Table showing all the pairwise relative treatment effects with their 95% CI for one or two outcomes along with the SUCRA values

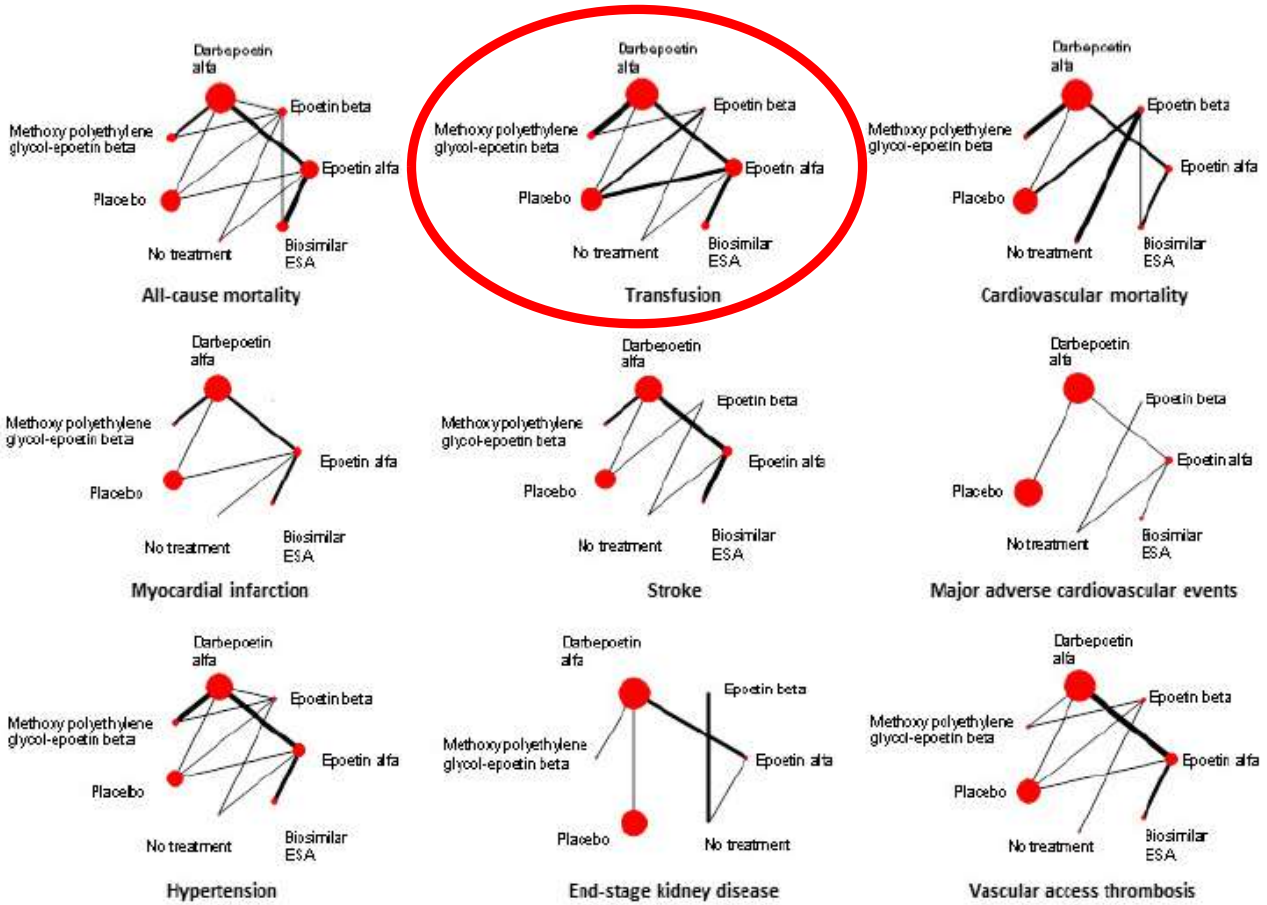
Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis (Review)

Palmer SC, Saglimbene V, Mavridis D, Salanti G, Craig JC, Tonelli M, Wiebe N, Strippoli GFM

OBJECTIVES

To compare the efficacy and safety of ESAs (epoetin alfa, epoetin beta, darbepoetin alfa, or methoxy polyethylene glycol-epoetin beta, and biosimilar ESAs, against each other, placebo, or no treatment) to treat anaemia in adults with CKD.

Figure 5. Networks of the treatment efficacy and safety of ESA drugs in the treatment of anaemia in chronic kidney disease. Values lower than 1 favour the active treatment in the comparison



Assessment of clinical and methodological

Analysis 1.1. Comparison 1 ESA versus ESA or placebo/no treatment, Outcom

Review: Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis

Comparison: 1 ESA versus ESA or placebo/no treatment

Outcome: 1 Blood transfusion

Study or subgroup	Intervention n/N	Comparator n/N	Odds Ratio M-H,Random,95% CI	Weig
1 Epoetin alfa versus placebo				
Kleinman 1989	0/7	3/7		24.9
Canadian EPO Study 1990	2/67	23/32		36.4
Roth 1994	4/43	9/40		38.7
Subtotal (95% CI)	**117**	**79**		**100.0**
Total events: 6 (Intervention), 35 (Comparator)				
Heterogeneity: $Tau^2 = 3.61$; $Chi^2 = 10.53$, df = 2 (P = 0.01); $I^2 = 81\%$				
Test for overall effect: Z = 2.10 (P = 0.036)				
2 Epoetin beta versus placebo				
Bennett 1991	0/90	1/41		10.4
Bahlmann 1991	5/53	28/46		89.6
Subtotal (95% CI)	**143**	**87**		**100.0**
Total events: 5 (Intervention), 29 (Comparator)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.21$, df = 1 (P = 0.64); $I^2 = 0.0\%$				
Test for overall effect: Z = 4.95 (P < 0.00001)				
3 Darbepoetin alfa versus placebo				
TREAT Study 2005	297/2012	496/2026		100.0

0.001 0.01 0.1 1 10 100 1000

Favours intervention Favours comparator

(. . . Continued)

Study or subgroup	Intervention n/N	Comparator n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Subtotal (95% CI)	**2012**	**2026**		**100.0 %**	**0.53 [0.46, 0.63]**
Total events: 297 (Intervention), 496 (Comparator)					
Heterogeneity: not applicable					
Test for overall effect: Z = 7.71 (P < 0.00001)					
4 Epoetin alfa versus control					
Patel 2012	4/118	0/39		100.0 %	3.10 [0.16, 58.97]
Subtotal (95% CI)	**118**	**39**		**100.0 %**	**3.10 [0.16, 58.97]**
Total events: 4 (Intervention), 0 (Comparator)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.75 (P = 0.45)					
5 Epoetin beta versus no control					
Van Biesen 2005	2/22	4/18		100.0 %	0.35 [0.06, 2.18]
Subtotal (95% CI)	**22**	**18**		**100.0 %**	**0.35 [0.06, 2.18]**
Total events: 2 (Intervention), 4 (Comparator)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.12 (P = 0.26)					
6 Epoetin alfa versus darbepoetin alfa					
Akizawa 2011	0/160	1/161		2.8 %	0.33 [0.01, 8.24]
Locatelli 2001	3/37	6/129		14.2 %	1.81 [0.43, 7.61]
Nissenson 2002	37/335	17/369		82.9 %	2.57 [1.42, 4.66]
Subtotal (95% CI)	**532**	**659**		**100.0 %**	**2.31 [1.34, 3.97]**
Total events: 40 (Intervention), 24 (Comparator)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.64$, df = 2 (P = 0.44); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.03 (P = 0.0025)					
7 Epoetin alfa versus biosimilar ESA					
Krivoshiev 2010	1/230	3/232		5.5 %	0.33 [0.03, 3.23]
Krivoshiev 2008	9/304	10/305		33.6 %	0.90 [0.36, 2.25]
Martin 2007	11/192	46/560		60.9 %	0.68 [0.34, 1.34]
Subtotal (95% CI)	**726**	**1097**		**100.0 %**	**0.72 [0.42, 1.22]**
Total events: 21 (Intervention), 59 (Comparator)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.70$, df = 2 (P = 0.70); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.22 (P = 0.22)					
8 Epoetin beta versus methoxy polyethylene glycol-epoetin beta					
AMICUS Study 2007	2/46	7/135		100.0 %	0.83 [0.17, 4.15]
	46	**135**		**100.0 %**	**0.83 [0.17, 4.15]**
rator)					
2)					
ethylene glycol-epoetin beta					
	0/25	1/46		4.7 %	0.59 [0.02, 15.14]

0.001 0.01 0.1 1 10 100 1000

Favours intervention Favours comparator

(. . . Continued)

Study or subgroup	Intervention n/N	Comparator n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
ARCTOS Study 2008	11/162	4/162		23.7 %	2.88 [0.90, 9.23]
CORDATUS Study 2011	5/154	10/153		25.4 %	0.48 [0.16, 1.44]
PATRONUS Study 2010	32/244	39/245		46.2 %	0.80 [0.48, 1.32]
Subtotal (95% CI)	**585**	**606**		**100.0 %**	**0.94 [0.45, 1.95]**
Total events: 48 (Intervention), 54 (Comparator)					
Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 5.35$, df = 3 (P = 0.15); $I^2 = 44\%$					
Test for overall effect: Z = 0.18 (P = 0.86)					

0.001 0.01 0.1 1 10 100 1000

Favours intervention Favours comparator

Assessment of similarity (transitivity) across treatment comparisons

Evaluation of the assumption is important and its plausibility determines the validity of the network meta-analysis results.

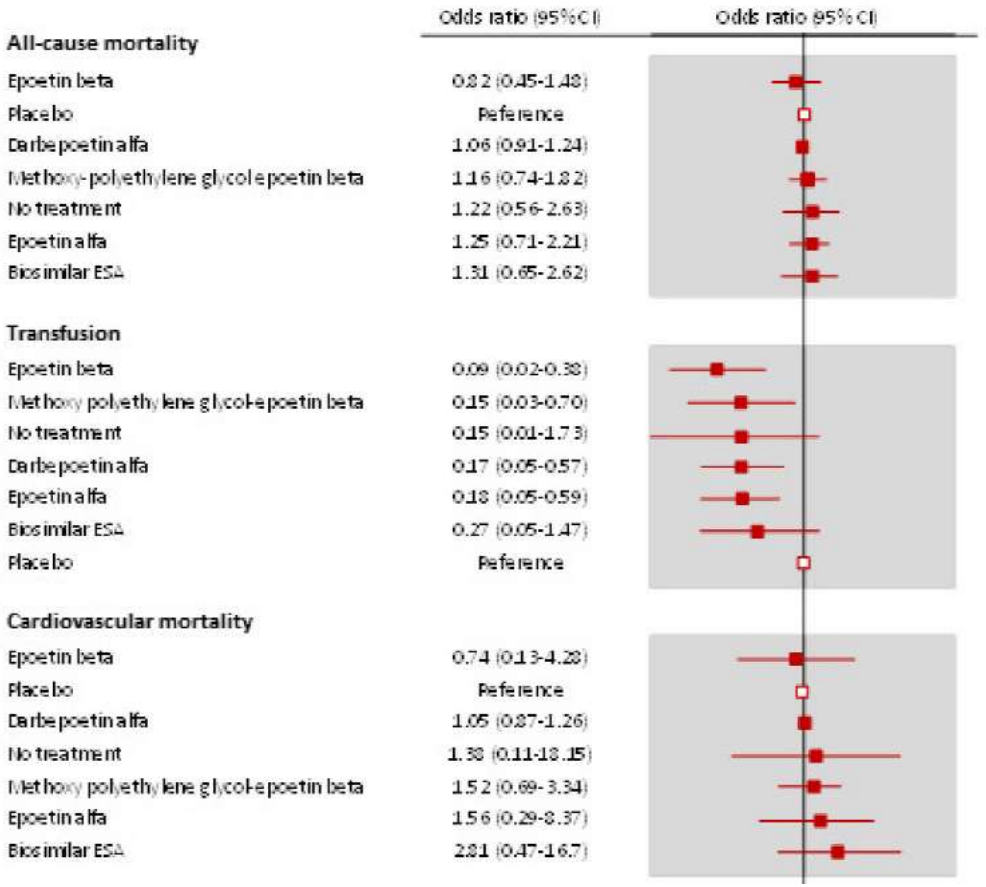
We inferred about the assumption of transitivity:

1. We assessed whether the included interventions were similar when they were evaluated in studies with different designs, for example, whether ESAs are administered the same way in studies comparing ESAs to placebo and in those comparing ESAs to other ESAs
2. We compared the distribution of the potential effect modifiers (age, stage of CKD, duration of treatment) across the different pairwise comparisons.

The inconsistency factor is the absolute difference in the log odds ratio estimated from indirect and direct treatment comparisons and is reported together with the 95% confidence interval. A 95% confidence interval that includes zero indicates that the result is compatible with zero inconsistency between effect estimates using indirect (networkmeta-analysis) and direct (conventional pairwise meta-analysis) treatment comparisons.

Transfusion		
Epoetin alfa - epoetin beta - placebo – no treatment	2.09	0.00-6.91
Epoetin alfa - darbepoetin alfa - placebo	1.97	0.00-4.20
Epoetin beta - darbepoetin alfa – methoxy polyethylene glycol-epoetin beta - placebo	1.26	0.00-3.39

Figure 6. Forest plots for results from network meta-analyses comparing ESAs versus placebo



Annals of Internal Medicine RESEARCH AND REPORTING METHODS

The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations

Brian Hutton, PhD, MSc; Georgia Salanti, PhD; Deborah M. Caldwell, PhD, MA, BA; Anna Chaimani, PhD; Christopher H. Schmid, PhD; Chris Cameron, MSc; John P.A. Ioannidis, MD, DSc; Sharon Straus, MD, MSc; Kristian Thorlund, PhD; Jeroen P. Jansen, PhD; Cynthia Mulrow, MD, MSc; Ferrán Catalá-López, PhD, MPH, PharmD; Peter C. Gøtzsche, MD, MSc; Kay Dickersin, PhD, MA; Isabelle Boutron, MD, PhD; Douglas G. Altman, DSc; and David Moher, PhD

The PRISMA statement is a reporting guideline designed to improve the completeness of reporting of systematic reviews and meta-analyses. Authors have used this guideline worldwide to prepare their reviews for publication. In the past, these reports typically compared 2 treatment alternatives. With the evolution of systematic reviews that compare multiple treatments, some of them only indirectly, authors face novel challenges for conducting and reporting their reviews. This extension of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement was developed specifically to improve the reporting of systematic reviews incorporating network meta-analyses.

A group of experts participated in a systematic review, Delphi survey, and face-to-face discussion and consensus meeting to establish new checklist items for this extension statement. Current PRISMA items were also clarified. A modified, 32-item PRISMA extension checklist was developed to address what the group considered to be immediately relevant to the reporting of network meta-analyses.

This document presents the extension and provides examples of good reporting, as well as elaborations regarding the rationale for new checklist items and the modification of previously existing items from the PRISMA statement. It also highlights educational information related to key considerations in the practice of network meta-analysis. The target audience includes authors and readers of network meta-analyses, as well as journal editors and peer reviewers.

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For author affiliations, see end of text.

RESEARCH AND REPORTING METHODS

PRISMA Extension for Network Meta-analysis

Table. Checklist of Items to Include When Reporting a Systen

Section/Topic	Item # *	Checklist Item†
TITLE		
Title	1	Identify the report as a systemati *meta-analysis).*
ABSTRACT		
Structured summary	2	Provide a structured summary in Background: main objectives Methods: data sources; study and *synthesis methods, such* Results: number of studies and confidence/credible interval *to summarize pairwise comp brevity.* Discussion/Conclusions: limita Other: primary source of fundi
INTRODUCTION		
Rationale	3	Describe the rationale for the re *why a network meta-analysis*
Objectives	4	Provide an explicit statement of interventions, comparisons,
METHODS		
Protocol and registration	5	Indicate whether a review protoc and, if available, provide reg
Eligibility criteria	6	Specify study characteristics (e.g years considered, language *Clearly describe eligible trea have been clustered or merg*
Information sources	7	Describe all information sources authors to identify additiona
Search	8	Present full electronic search str it could be repeated.
Study selection	9	State the process for selecting st and, if applicable, included
Data collection process	10	Describe method of data extract and any processes for obtai
Data items	11	List and define all variables for w assumptions and simplificati
Geometry of the network	S1	Describe methods used to explo potential biases related to it summarized for presentatio the evidence base to reader
Risk of bias within individual studies	12	Describe methods used for asse whether this was done at the in any data synthesis.
Summary measures	13	State the principal summary mea *of additional summary meas cumulative ranking curve (SU summary findings from meta*
Planned methods of analysis	14	Describe the methods of handlir meta-analysis. This should in *Handling of multigroup trials; Selection of variance structure; Selection of prior distributions Assessment of model fit.*
Assessment of inconsistency	S2	Describe the statistical methods the treatment network(s) stu
Risk of bias across studies	15	Specify any assessment of risk of bias, selective reporting with
Additional analyses	16	Describe methods of additional include, but not be limited t Sensitivity or subgroup analys Meta-regression analyses; *Alternative formulations of the Use of alternative prior distributions for Bayesian analyses (if applicable).*

Table–Continued

Section/Topic	Item # *	Checklist Item†	Reported on Page #
RESULTS‡			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g., placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, researchers, and policymakers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	

(Continued on following page)