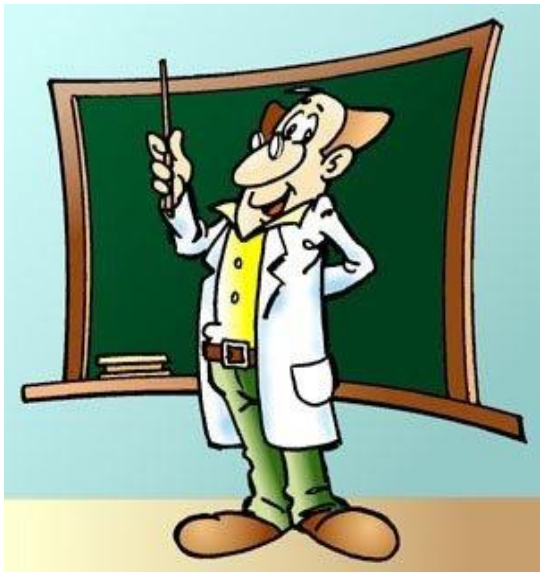
NEGRAR DI VALPOLICELLA
11-12 FEBBRAIO 2022

Centro Formazione IRCCS "Sacro Cuore-Don Calabria"

11 Febbraio 2022

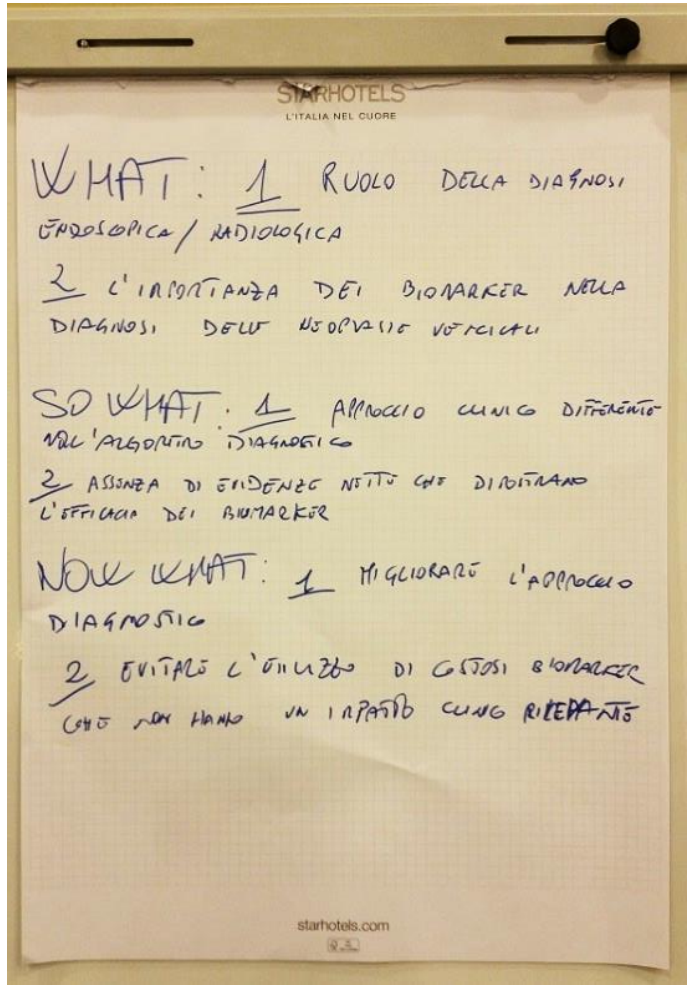
10.30-10.45	Presentazione ed obiettivi del Corso **Stefania GORI - Fabrizio NICOLIS** **Giovanni L. PAPPAGALLO**
10.45-11.30	Tipologia delle Revisioni della Letteratura Scientifica Obiettivi di una Revisione Sistematica Michela CINQUINI
11.30-12.00	Definizione del quesito clinico e degli outcome di interesse; misure di associazione Giovanni L. PAPPAGALLO
12.00-13.00	Lavoro di gruppo *Summing-Up* (metodo: *What? So What? Now What?*) (valido come prova ECM)
13.000-14.00	Colazione di lavoro
14.00-14.45	Come trovare informazioni - I database bibliografici, i siti di linee guida e studi clinici... Veronica Andrea FITTIPALDO
14.45-15.30	Definizione della strategia di ricerca e di selezione degli studi; *study flow* Michela CINQUINI
15.30-16.00	Metodi di valutazione di autori e riviste scientifiche: indici bibliometrici classici e innovativi Giulio ZUANETTI
16.00-16.30	Coffee Break
16.30-17.30	Valutazione del rischio di *bias* negli studi selezionati Ivan MOSCHETTI
17.30-18.30	Lavoro di gruppo *Summing-Up* (metodo: *What? So What? Now What?*) (valido come prova ECM)


SCUOLA DI METODOLOGIA CLINICA
IRCCS "Sacro Cuore - Don Calabria" Negrar di Valpolicella
8ª EDIZIONE
2° MODULO
REVISIONI SISTEMATICHE E METANALISI
NEGRAR DI VALPOLICELLA
11-12 FEBBRAIO 2022
Centro Formazione IRCCS "Sacro Cuore-Don Calabria"




WHAT
SO WHAT
NOW WHAT

What?, So What?, Now What?



Partendo da quanto ascoltato, cosa è emerso di particolar-mente saliente / rilevante?

WHAT?

Per quale motivo le cose emerse sono così rilevanti?

SO WHAT?

Quali ricadute nell'immediato per la mia professione?

NOW WHAT?

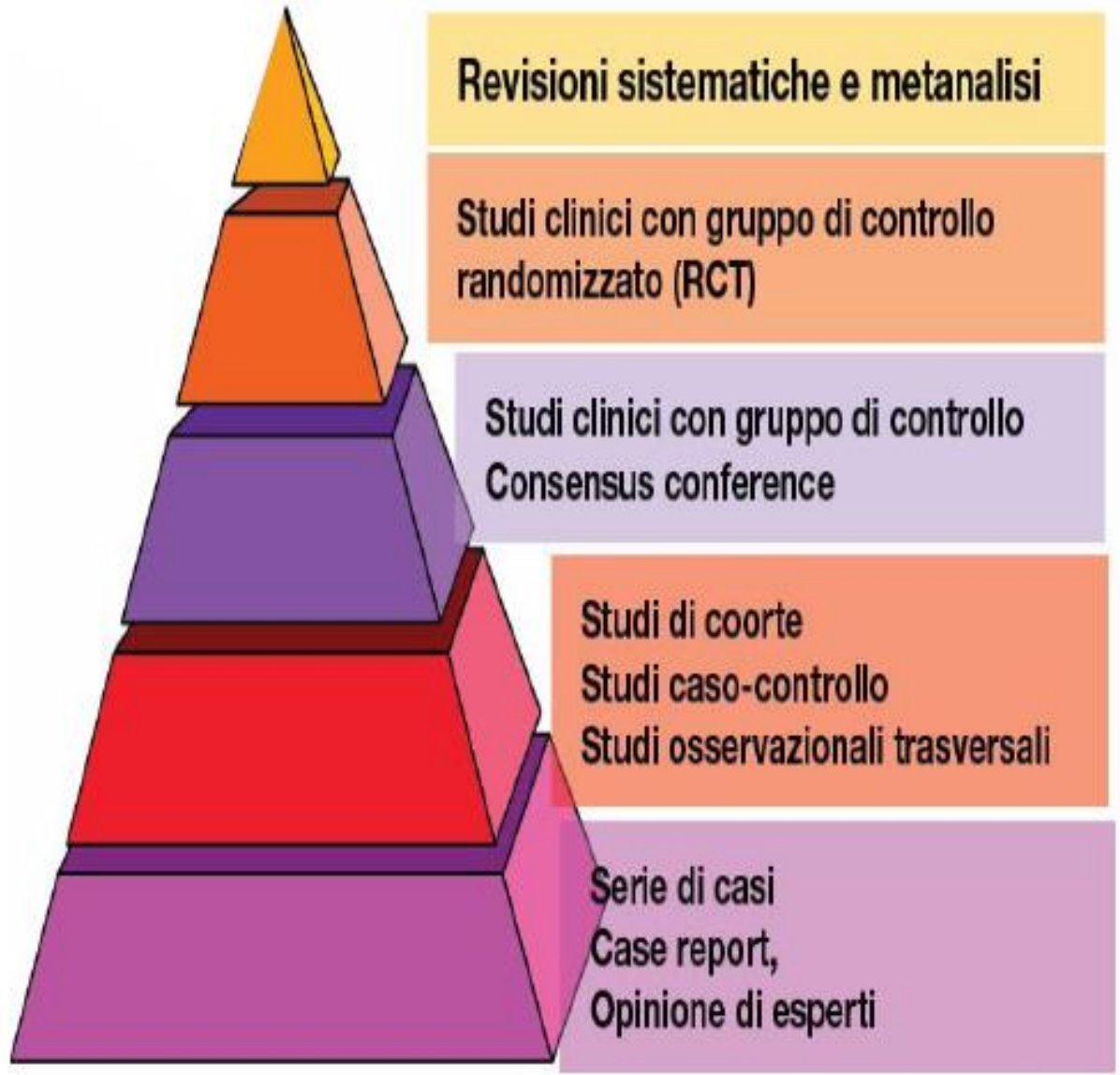
NEGRAR DI VALPOLICELLA
11-12 FEBBRAIO 2022

Centro Formazione IRCCS "Sacro Cuore-Don Calabria"

11 Febbraio 2022

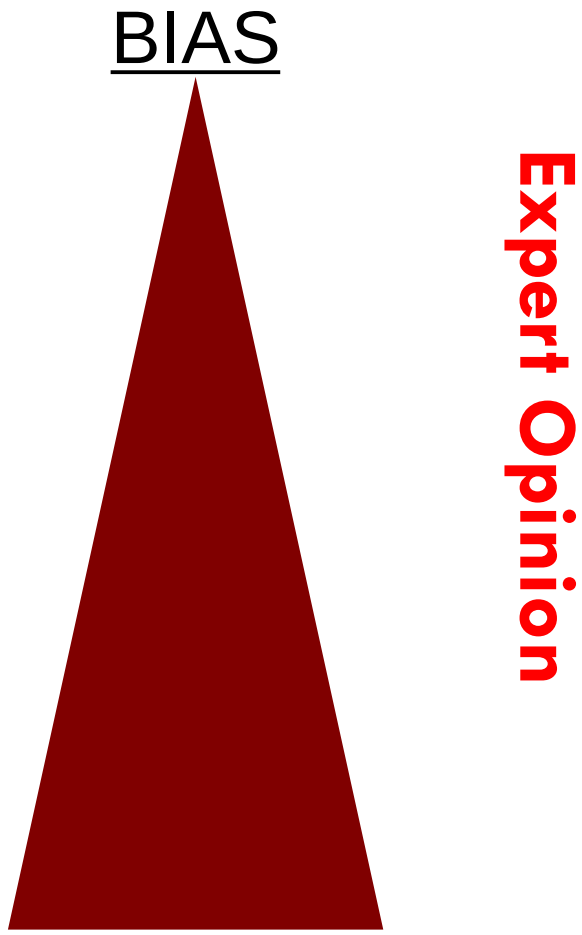
10.30-10.45	Presentazione ed obiettivi del Corso Stefania GORI - Fabrizio NICOLIS Giovanni L. PAPPAGALLO
10.45-11.30	Tipologia delle Revisioni della Letteratura Scientifica Obiettivi di una Revisione Sistematica Michela CINQUINI
11.30-12.00	Definizione del quesito clinico e degli outcome di interesse; misure di associazione Giovanni L. PAPPAGALLO
12.00-13.00	Lavoro di gruppo *Summing-Up* (metodo: *What? So What? Now What?*) (valido come prova ECM)
13.000-14.00	Colazione di lavoro
14.00-14.45	Come trovare informazioni - I database bibliografici, i siti di linee guida e studi clinici... Veronica Andrea FITTIPALDO
14.45-15.30	Definizione della strategia di ricerca e di selezione degli studi; *study flow* Michela CINQUINI
15.30-16.00	Metodi di valutazione di autori e riviste scientifiche: indici bibliometrici classici e innovativi Giulio ZUANETTI
16.00-16.30	Coffee Break
16.30-17.30	Valutazione del rischio di *bias* negli studi selezionati Ivan MOSCHETTI
17.30-18.30	Lavoro di gruppo *Summing-Up* (metodo: *What? So What? Now What?*) (valido come prova ECM)

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

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

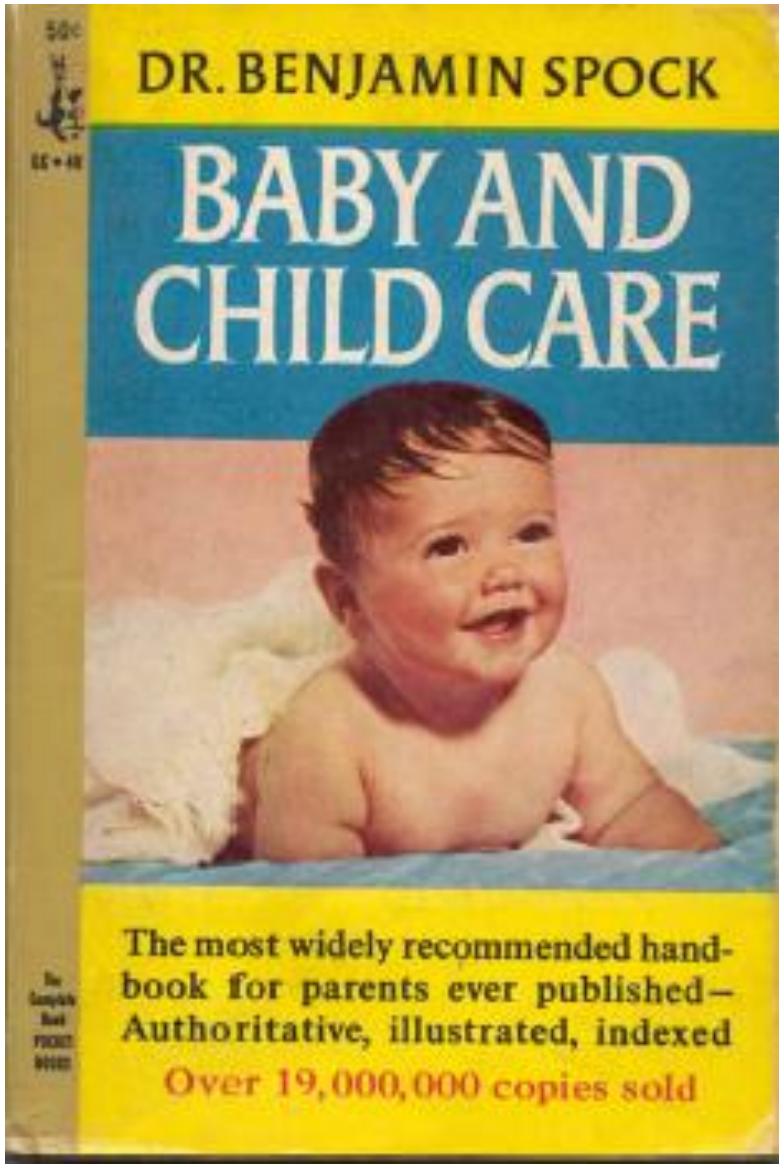
Perché sono utili le revisioni sistematiche?

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

W Edwards Deming

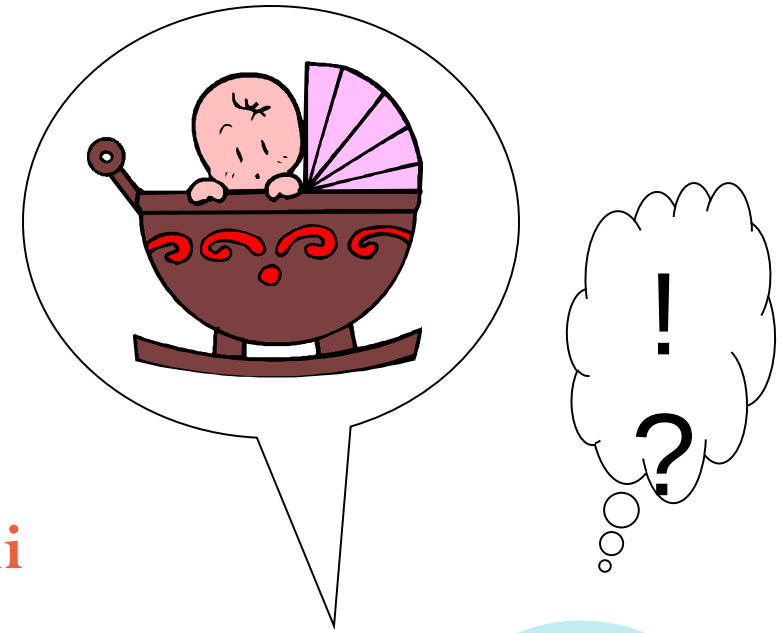
Situazioni di particolare utilità

- 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.

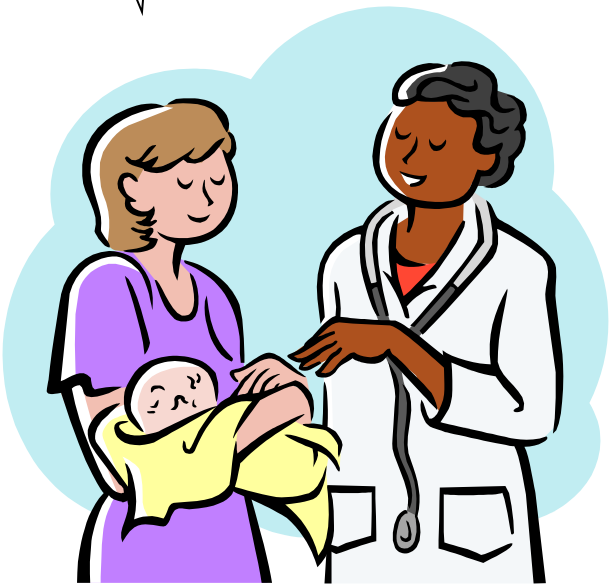
Scenario: 1970 – reparto di ostetricia



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 ?

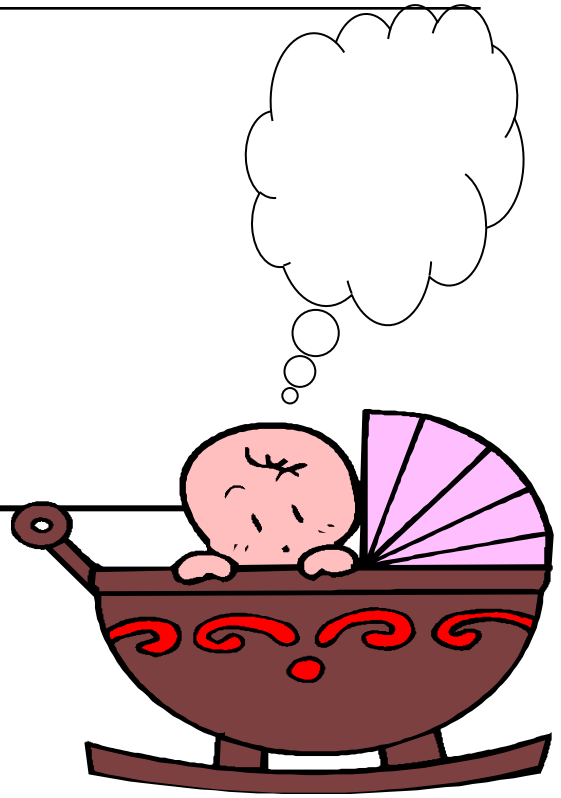
Il medico di stanza scrupoloso commissiona allo specializzando una **ricerca bibliografica …**



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

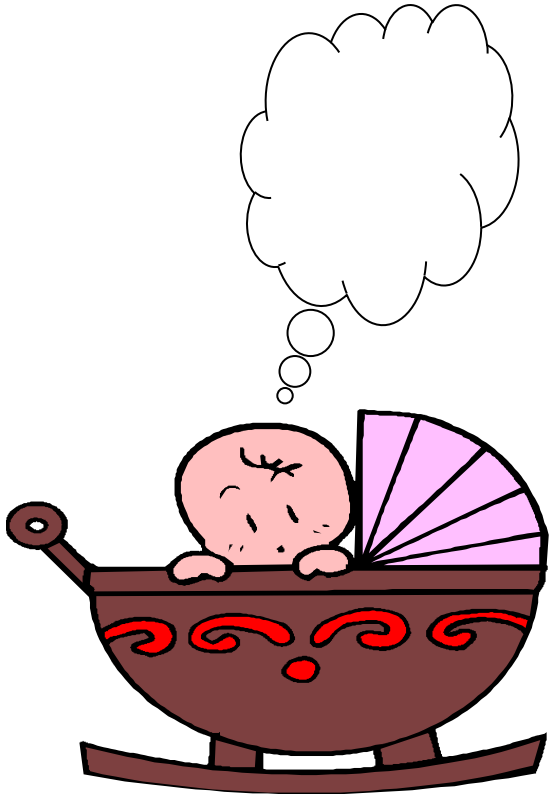


… nella lettera di dimissione, tra le raccomandazioni, viene riportato che *la posizione migliore del neonato nella culla, durante il sonno, è quella* ***prona (pancia in giù)***

...ancora sulla posizione del lattante:

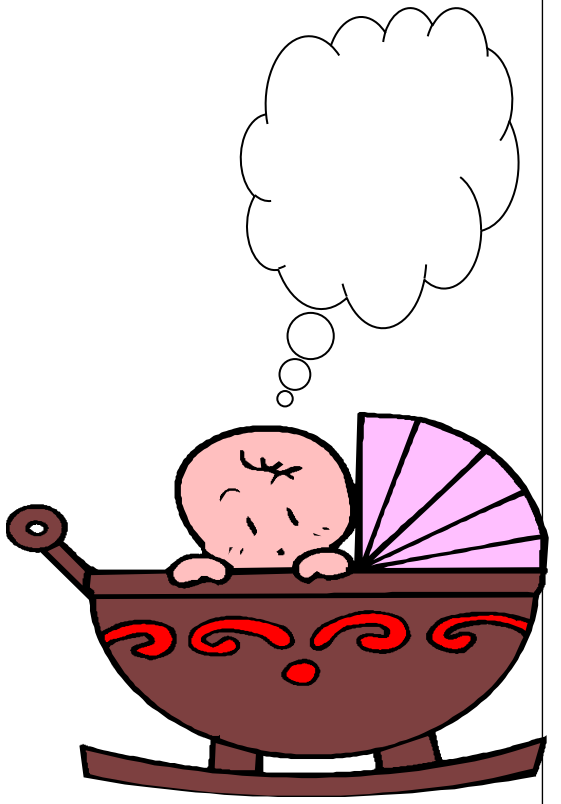
Facoltà di Medicina

Anni 90



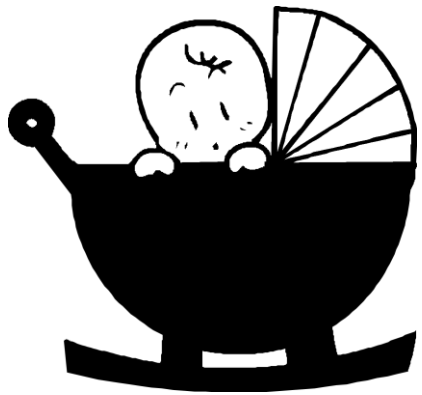
Dal testo consigliato per l'esame di pediatria

- 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
© The Author 2005; all rights reserved.

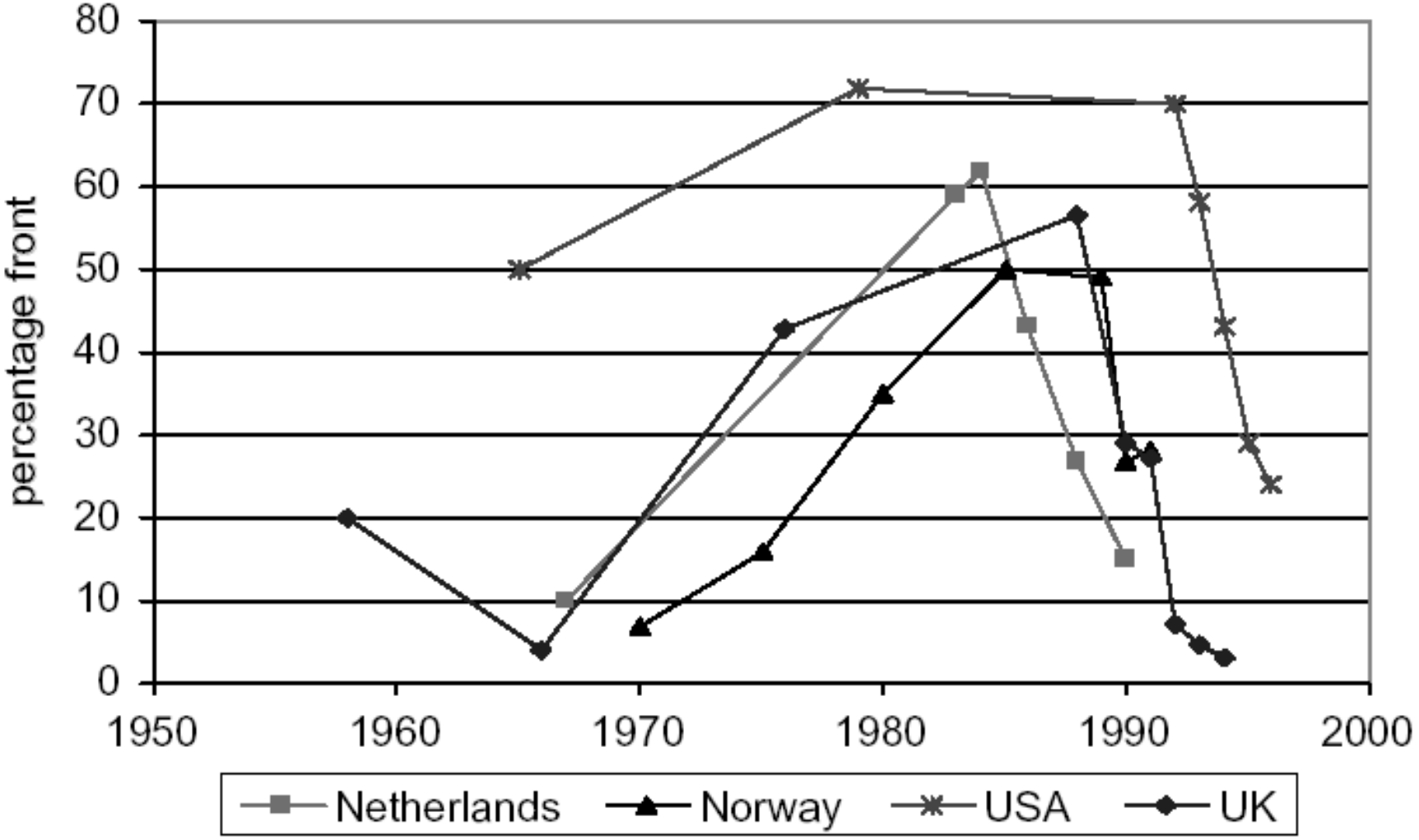
International Journal of Epidemiology
doi:10.1093/ije/dyi088

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]

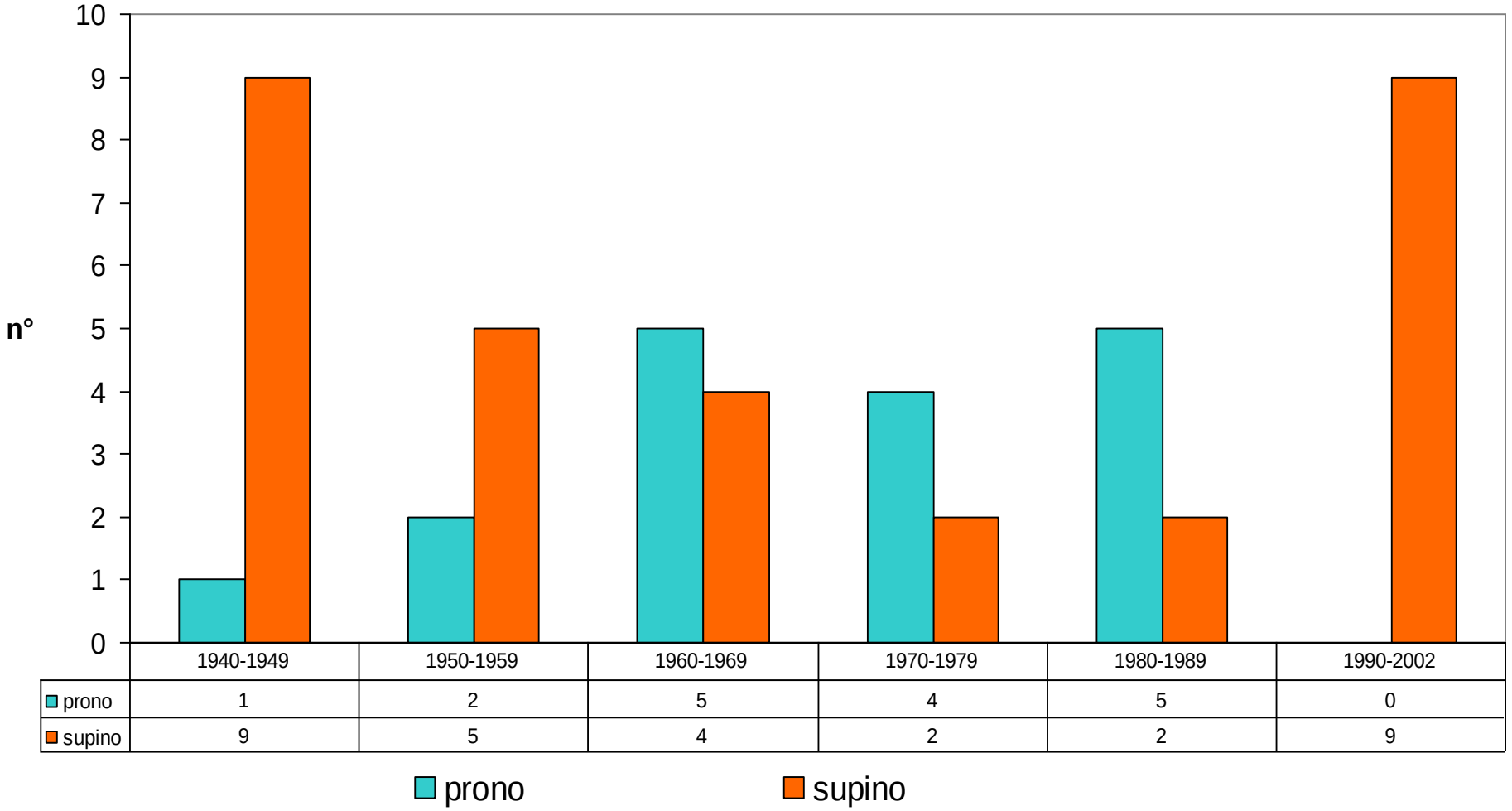
- Morte in culla

Frequenza della posizione prona del lattante nel sonno



(Gilbert 2005)

Raccomandazioni sulle posizioni del sonno nel lattante: letteratura inglese

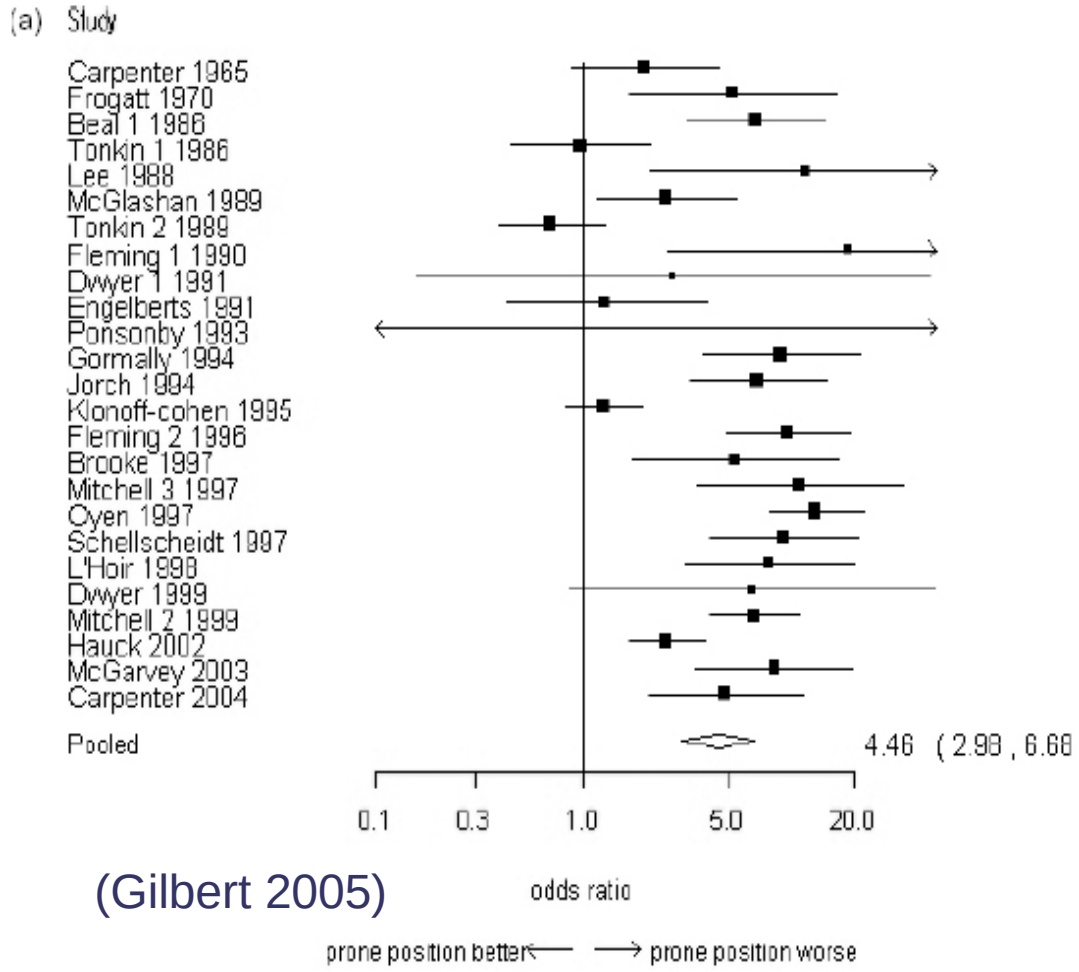


	1940-1949	1950-1959	1960-1969	1970-1979	1980-1989	1990-2002
prono	1	2	5	4	5	0
supino	9	5	4	2	2	9

(Gilbert 2005)

Morte in culla

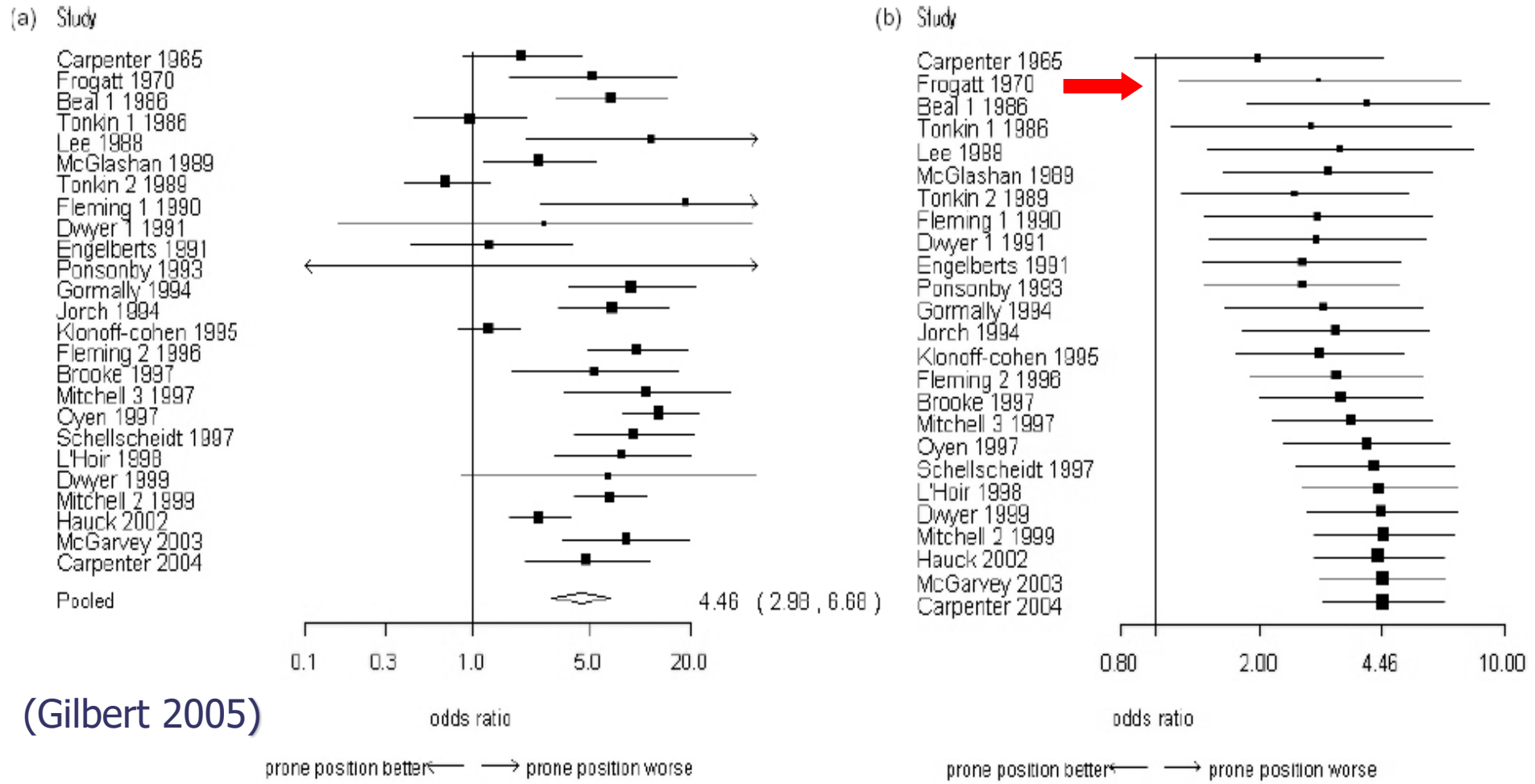
Metanalisi degli studi epidemiologici sulla posizione prona e rischio di morte del lattante nel sonno



(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)

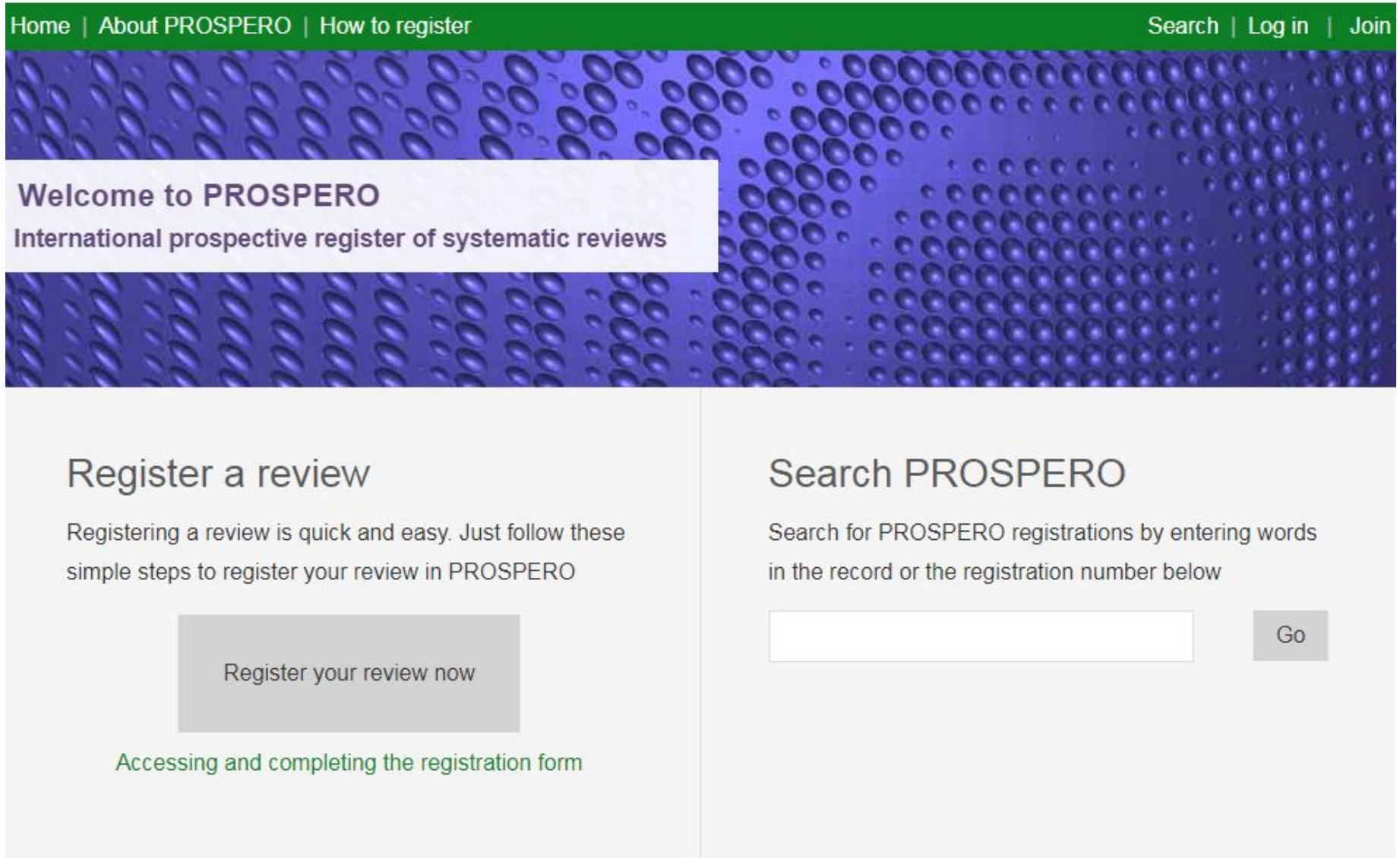
Il protocollo di una revisione sistematica

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?

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

NEGRAR DI VALPOLICELLA
11-12 FEBBRAIO 2022

Centro Formazione IRCCS "Sacro Cuore-Don Calabria"

11 Febbraio 2022

10.30-10.45	Presentazione ed obiettivi del Corso Stefania GORI - Fabrizio NICOLIS Giovanni L. PAPPAGALLO
10.45-11.30	Tipologia delle Revisioni della Letteratura Scientifica Obiettivi di una Revisione Sistematica Michela CINQUINI
11.30-12.00	Definizione del quesito clinico e degli outcome di interesse; misure di associazione **Giovanni L. PAPPAGALLO**
12.00-13.00	Lavoro di gruppo *Summing-Up* (metodo: *What? So What? Now What?*) (valido come prova ECM)
13.000-14.00	Colazione di lavoro
14.00-14.45	Come trovare informazioni - I database bibliografici, i siti di linee guida e studi clinici... Veronica Andrea FITTIPALDO
14.45-15.30	Definizione della strategia di ricerca e di selezione degli studi; *study flow* Michela CINQUINI
15.30-16.00	Metodi di valutazione di autori e riviste scientifiche: indici bibliometrici classici e innovativi Giulio ZUANETTI
16.00-16.30	Coffee Break
16.30-17.30	Valutazione del rischio di *bias* negli studi selezionati Ivan MOSCHETTI
17.30-18.30	Lavoro di gruppo *Summing-Up* (metodo: *What? So What? Now What?*) (valido come prova ECM)

Defining the review question

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

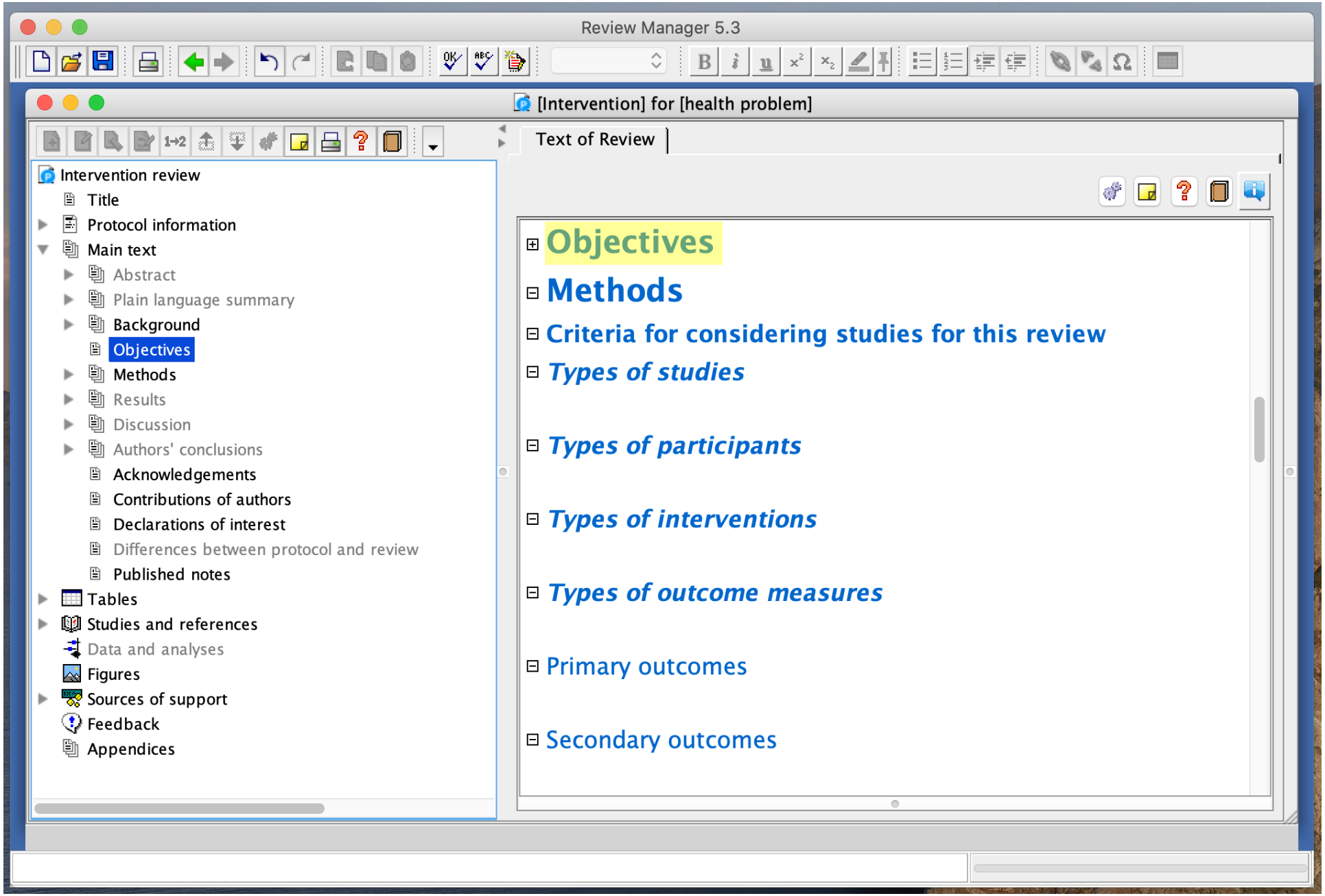
The review question should specify:

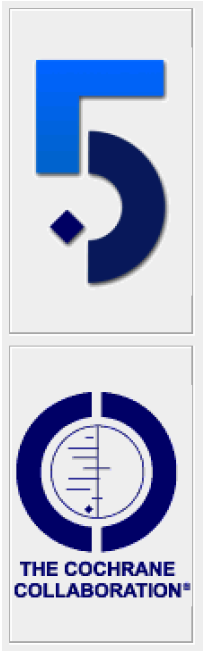
- **types of population** (participants),
- **types of interventions** (and comparisons),
- **types of outcomes** that are of interest.

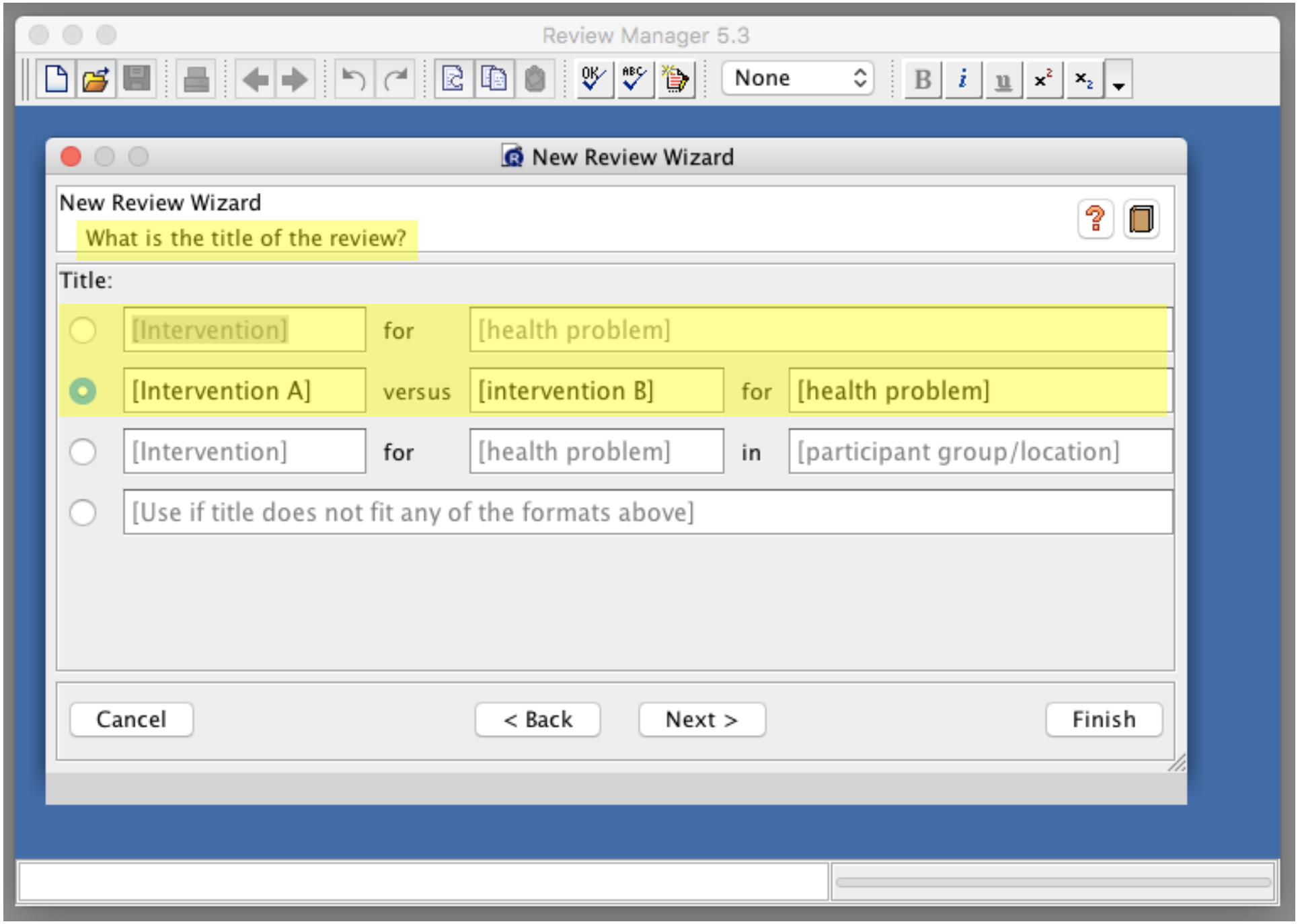
These components of the question, with the additional specification of types of study that will be included, form the basis of the pre-specified eligibility criteria for the review.

Review Manager (RevMan)

There are two versions of Cochrane RevMan: RevMan Web (online) and RevMan 5 (desktop)


Review Manager 5.3
[Intervention] for [health problem]
Text of Review
Intervention review
Title
Protocol information
Main text
Abstract
Plain language summary
Background
Objectives
Methods
Results
Discussion
Authors' conclusions
Acknowledgements
Contributions of authors
Declarations of interest
Differences between protocol and review
Published notes
Tables
Studies and references
Data and analyses
Figures
Sources of support
Feedback
Appendices
Objectives
Methods
Criteria for considering studies for this review
Types of studies
Types of participants
Types of interventions
Types of outcome measures
Primary outcomes
Secondary outcomes


THE COCHRANE
COLLABORATION®


Review Manager 5.3
None
New Review Wizard
New Review Wizard
What is the title of the review?
Title:
[Intervention] for [health problem]
[Intervention A] versus [intervention B] for [health problem]
[Intervention] for [health problem] in [participant group/location]
[Use if title does not fit any of the formats above]
Cancel
< Back
Next >
Finish

Screening for prostate cancer (Review)

Ilic D, Neuberger MM, Djulbegovic M, Dahm P

Cochrane Database of Systematic Reviews 2013, Issue 1.

OBJECTIVES

The primary objective of this review was to determine the efficacy of screening men for prostate cancer in reducing prostate cancer-specific and all-cause mortality.

The secondary objectives of this review were to:

- determine the impact of prostate cancer screening on quality of life and adverse effects; and
- document the costs of screening for prostate cancer.

Defining the review question

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

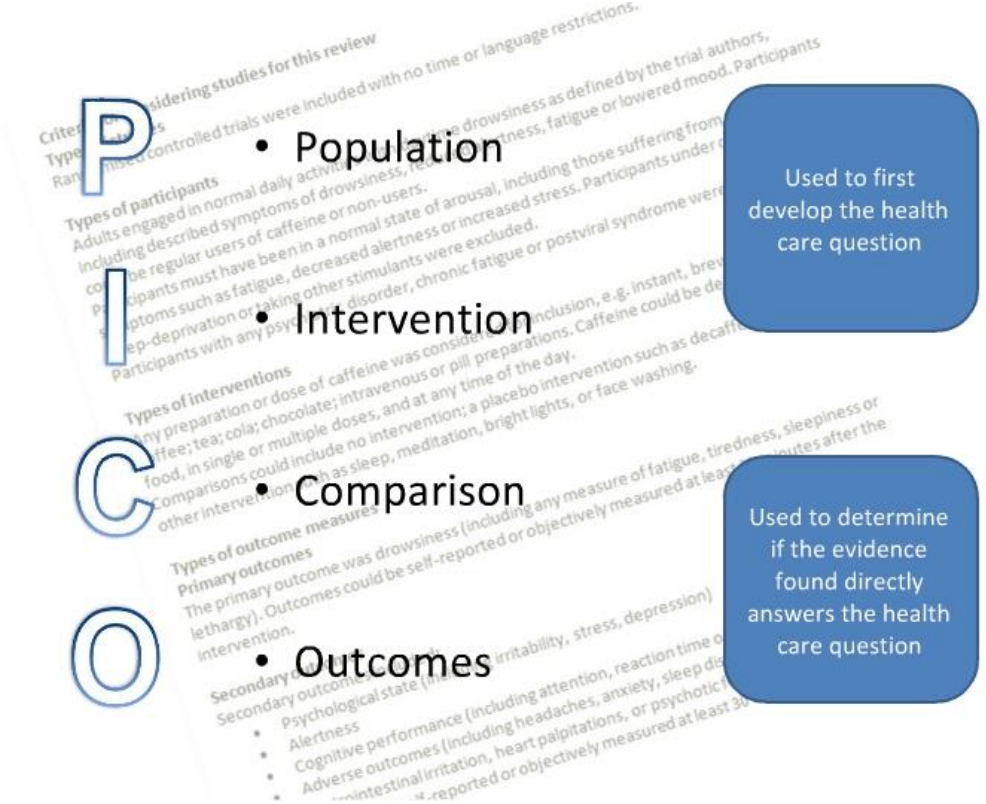
The review question should specify:

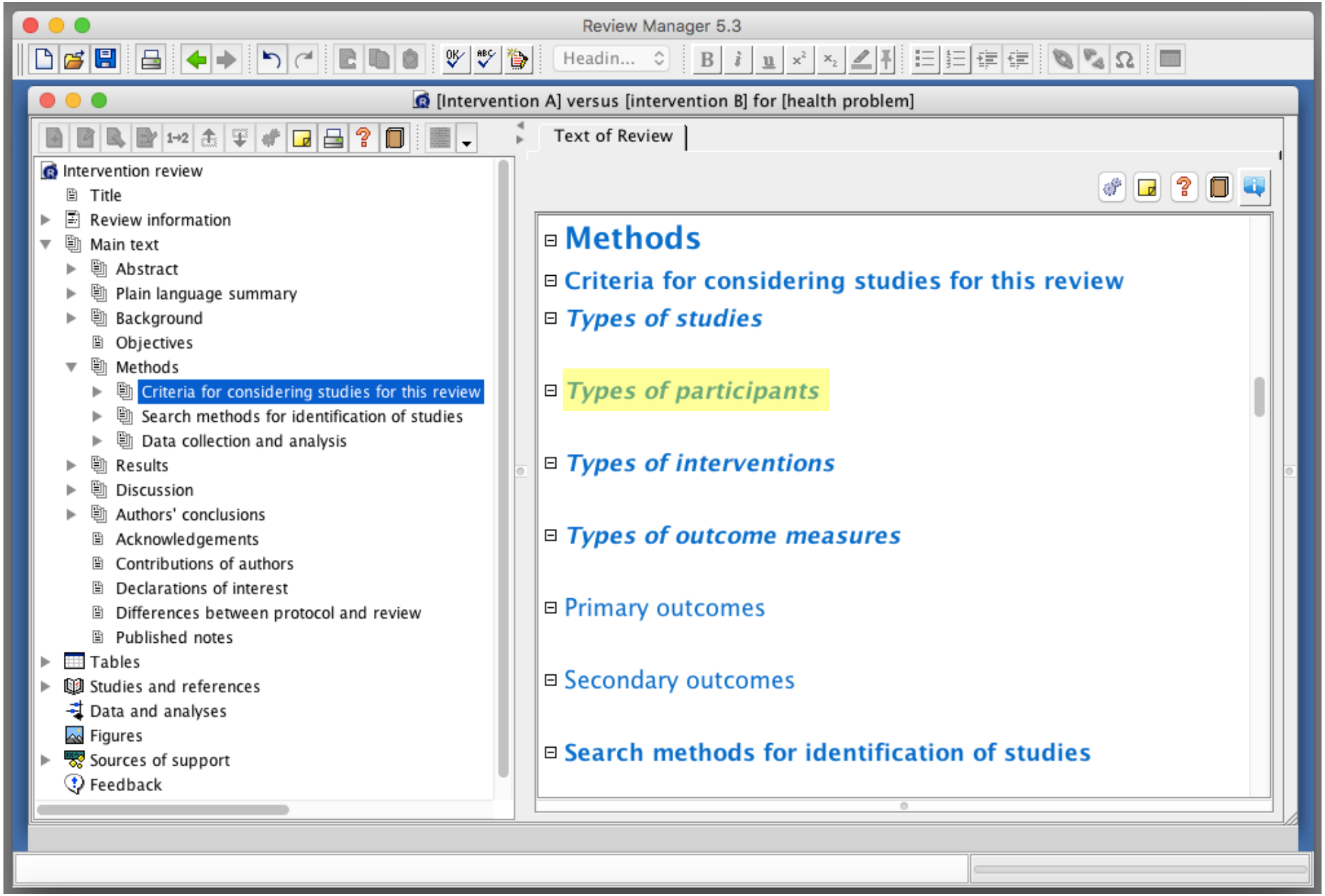
- **types of population** (participants),
- **types of interventions** (and comparisons),
- **types of outcomes** that are of interest.

These components of the question, with the additional specification of types of study that will be included, form the basis of the pre-specified eligibility criteria for the review.

The ‘clinical question’ should specify the types of population (participants), types of interventions (and comparisons), and the types of outcomes that are of interest.

The acronym PICO (**P**articipants, **I**nterventions, **C**omparisons and **O**utcomes) helps to serve as a reminder of these.

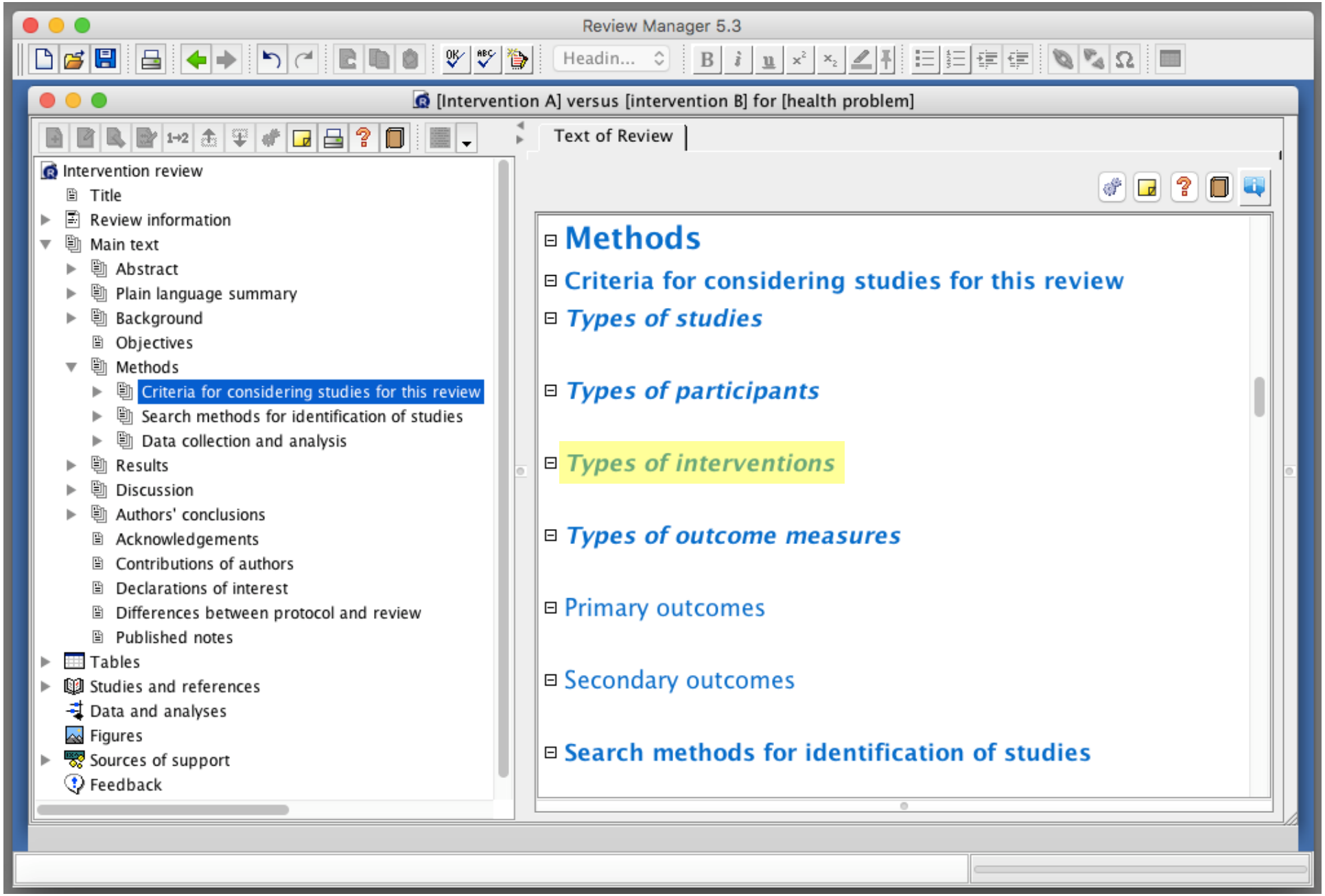



Review Manager 5.3
[Intervention A] versus [intervention B] for [health problem]
Text of Review
Intervention review
Title
Review information
Main text
Abstract
Plain language summary
Background
Objectives
Methods
Criteria for considering studies for this review
Search methods for identification of studies
Data collection and analysis
Results
Discussion
Authors' conclusions
Acknowledgements
Contributions of authors
Declarations of interest
Differences between protocol and review
Published notes
Tables
Studies and references
Data and analyses
Figures
Sources of support
Feedback
Methods
Criteria for considering studies for this review
Types of studies
Types of participants
Types of interventions
Types of outcome measures
Primary outcomes
Secondary outcomes
Search methods for identification of studies

Screening for prostate cancer (Review)
Ilic D, Neuberger MM, Djulbegovic M, Dahm P
Cochrane Database of Systematic Reviews 2013, Issue 1.

Types of participants

All men enrolled in studies of prostate cancer screening were eligible for this review, with no exclusions based on ethnicity, age, or presence of lower urinary tract symptoms. Studies including men with a previous diagnosis and treatment of prostate cancer were excluded.

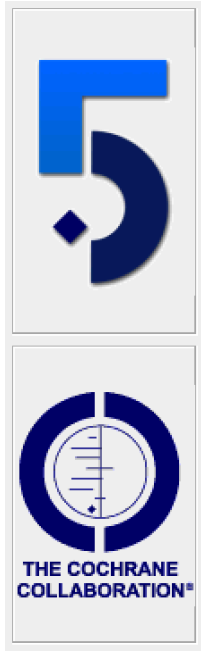

Review Manager 5.3
[Intervention A] versus [intervention B] for [health problem]
Text of Review
Intervention review
Title
Review information
Main text
Abstract
Plain language summary
Background
Objectives
Methods
Criteria for considering studies for this review
Search methods for identification of studies
Data collection and analysis
Results
Discussion
Authors' conclusions
Acknowledgements
Contributions of authors
Declarations of interest
Differences between protocol and review
Published notes
Tables
Studies and references
Data and analyses
Figures
Sources of support
Feedback
Methods
Criteria for considering studies for this review
Types of studies
Types of participants
Types of interventions
Types of outcome measures
Primary outcomes
Secondary outcomes
Search methods for identification of studies

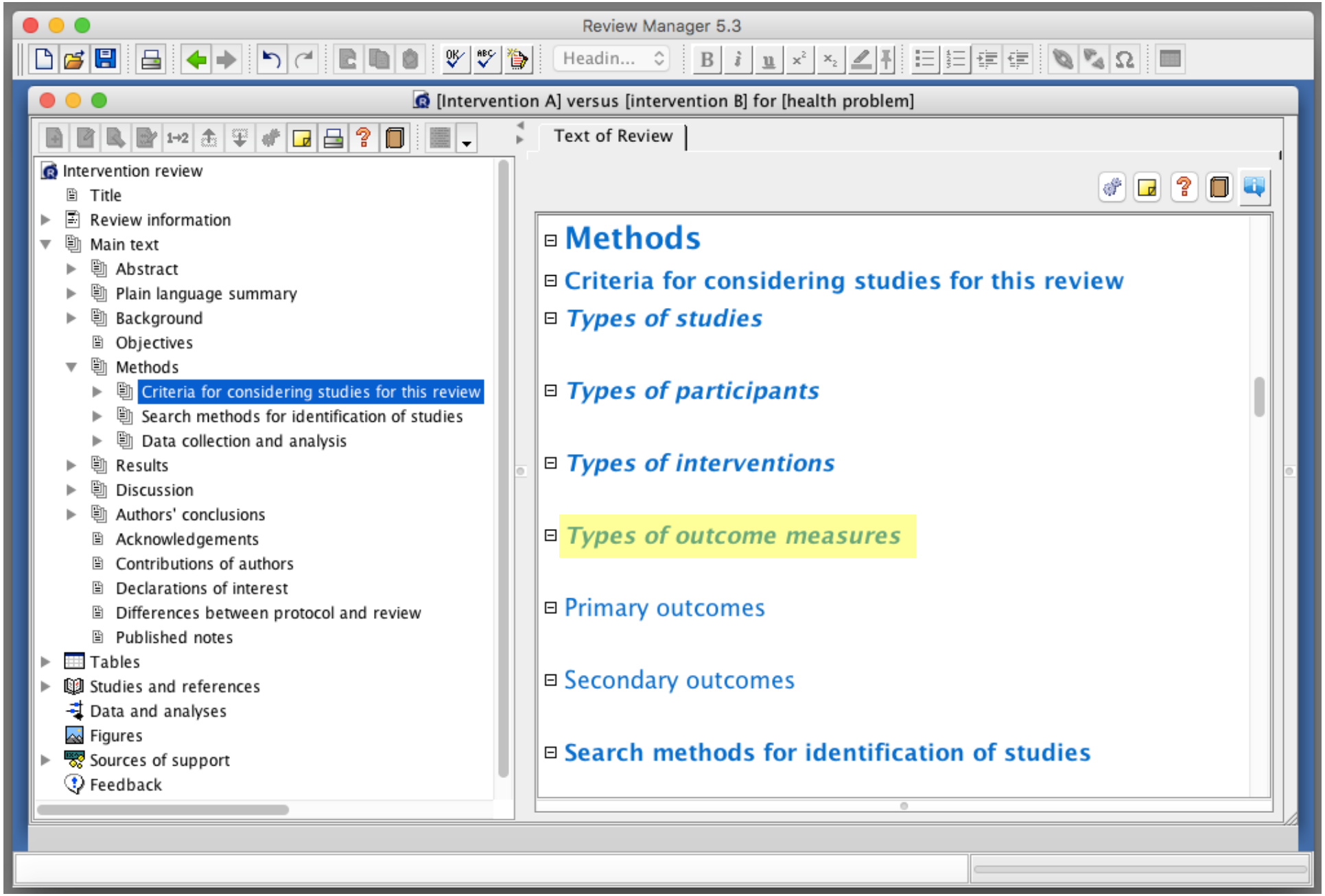
Screening for prostate cancer (Review)
Ilic D, Neuberger MM, Djulbegovic M, Dahm P
Cochrane Database of Systematic Reviews 2013, Issue 1.

Types of interventions

Studies that used any of the following screening procedures, individually or in combination, were included:

- digital rectal examination (DRE);
- prostate-specific antigen (PSA) test (including total, velocity, density, and percentage free and complex); and
- transrectal ultrasound (TRUS)-guided biopsy.


THE COCHRANE
COLLABORATION®


Review Manager 5.3
[Intervention A] versus [intervention B] for [health problem]
Text of Review
Intervention review
Title
Review information
Main text
Abstract
Plain language summary
Background
Objectives
Methods
Criteria for considering studies for this review
Search methods for identification of studies
Data collection and analysis
Results
Discussion
Authors' conclusions
Acknowledgements
Contributions of authors
Declarations of interest
Differences between protocol and review
Published notes
Tables
Studies and references
Data and analyses
Figures
Sources of support
Feedback
Methods
Criteria for considering studies for this review
Types of studies
Types of participants
Types of interventions
Types of outcome measures
Primary outcomes
Secondary outcomes
Search methods for identification of studies

Primary outcomes

Primary outcome measures for this review were prostate cancer-specific and all-cause mortality.

Secondary outcomes

Secondary outcome measures included:

- incident prostate cancers by stage and grade at diagnosis;
- metastatic disease at follow-up;
- quality of life;
- harms of screening (including both adverse outcomes from false-positive or false-negative results and their impact upon resulting treatment procedures); and
- costs associated with screening programs.

Outcomes

Should be importance driven NOT evidence driven

Journal of Clinical Epidemiology 64 (2011) 395–400

GRADE guidelines: 2. Framing the question and deciding on important outcomes

Gordon H. Guyatt[a,*], Andrew D. Oxman[b], Regina Kunz[c], David Atkins[d], Jan Brozek[a], Gunn Vist[b], Philip Alderson[e], Paul Glasziou[f], Yngve Falck-Ytter[g], Holger J. Schünemann[a]

If evidence is lacking for an important outcome, this should be acknowledged, rather than ignoring the outcome - that uncertainty may have a bearing on the ultimate recommendation.

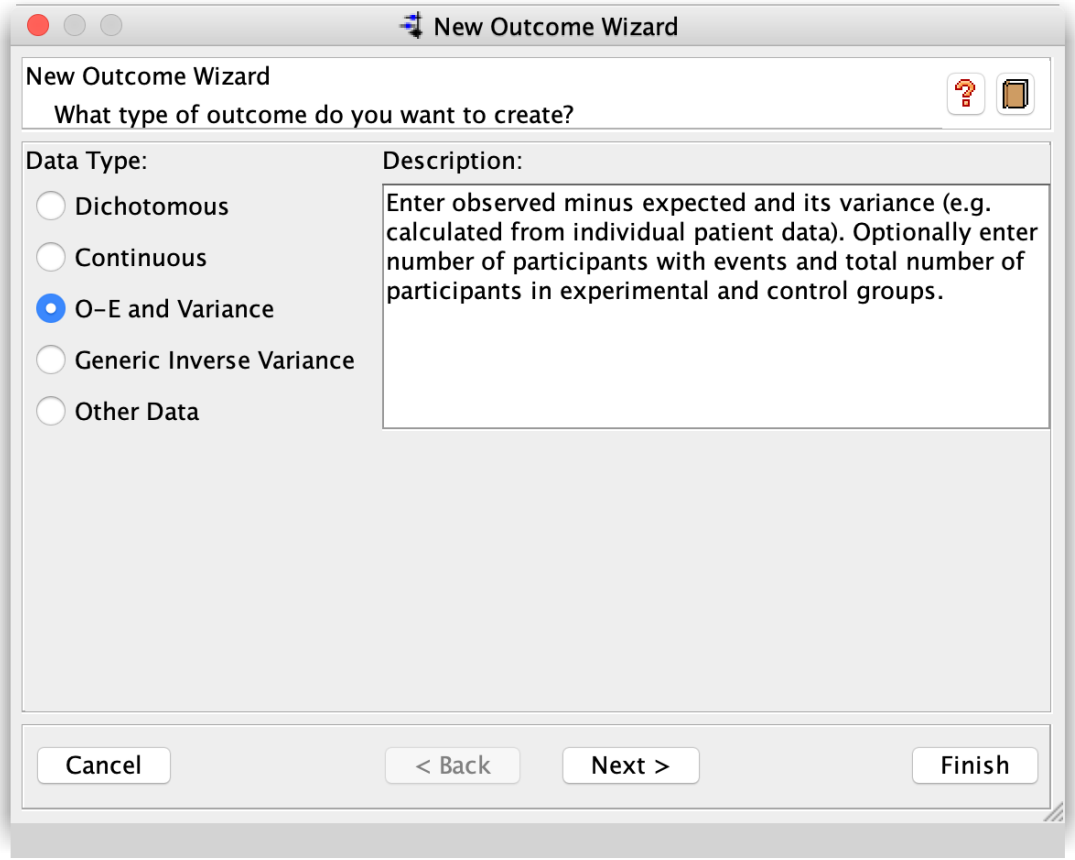
Defining the review question

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

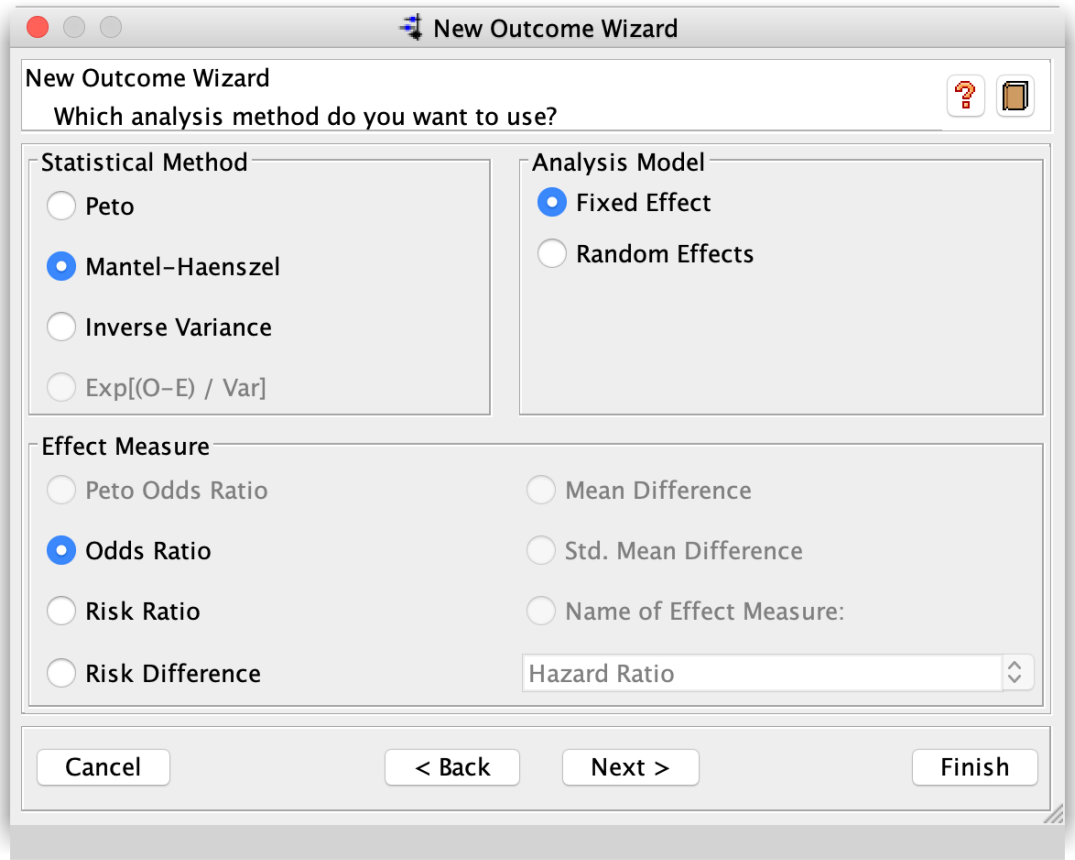
The review question should specify:

- **types of population** (participants),
- **types of interventions** (and comparisons),
- **types of outcomes** that are of interest.

These components of the question, with the additional specification of types of study that will be included, form the basis of the pre-specified eligibility criteria for the review.



variabili di risposta



misure riassuntive di effetto

VARIABILE DI RISPOSTA

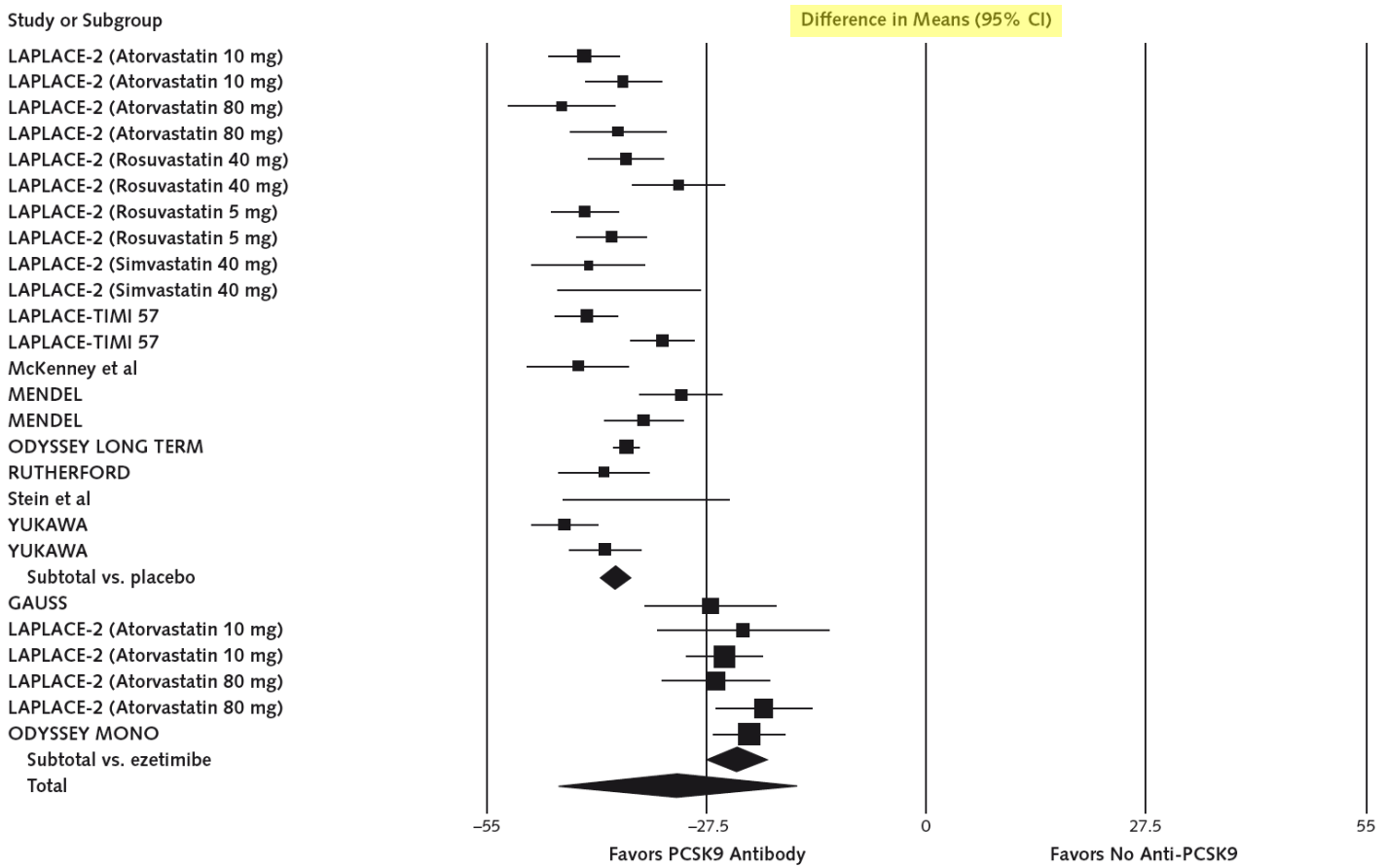
- di tipo **quantitativo**
  - assume uno spettro continuo di valori e viene misurata in riferimento a una scala a intervalli costanti.
- di tipo **qualitativo**
  - esprime categorie di risposta del tipo successo / insuccesso (di un trattamento somministrato).
- del tipo **“tempo a evento”**
  - rappresenta il tempo trascorso fino al verificarsi (o meno) di un evento.

Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia

A Systematic Review and Meta-analysis

Eliano Pio Navarese, MD, PhD; Michalina Kołodziejczak, MD; Volker Schulze, MD; Paul A. Gurbel, MD; Udaya Tantry, PhD; Yingfeng Lin, MD; Maximilian Brockmeyer, MD; David E. Kandzari, MD; Julia M. Kubica, MD; Ralph B. D'Agostino Sr., PhD; Jacek Kubica, MD, PhD; Massimo Volpe, MD; Stefan Agewall, MD; Dean J. Kereiakes, MD; and Malte Kelm, MD

Ann Intern Med. 2015;163:40-51.



Group	Effect Size (95% CI)						Test of Null (2-Tail)		Heterogeneity		
	Number of Studies	Point Estimate	SE	Variance	Lower Limit	Upper Limit	*Z* Value	*P* Value	*Q* Value	*P* Value	I^2
Random-effects analysis											
Overall	26	−31.492	7.580	57.455	−46.348	−16.635	−4.155	0.000	187.788	0.000	86.687

VARIABILE DI RISPOSTA

- di tipo **quantitativo**
  - assume uno spettro continuo di valori e viene misurata in riferimento a una scala a intervalli costanti.
- di tipo **qualitativo**
  - esprime categorie di risposta del tipo successo / insuccesso (di un trattamento somministrato).
- del tipo **“tempo a evento”**
  - rappresenta il tempo trascorso fino al verificarsi (o meno) di un evento.

Risks, Rates and Odds

- ***Risk*** (proportion of persons with disease = *cumulative incidence*)
  - *Risk Ratio* = ratio of 2 cumulative incidence estimates = *Relative Risk*
- ***Rate*** (based on events per person-time = *incidence rate*)
  - ***Rate Ratio*** = ratio of 2 incidence rates = *Relative Rate*
- ***Odds*** (the number of events divided by the number of non events)
  - ***Odds Ratio*** = ratio of 2 odds

Incidenza Cumulativa

Probabilità (rischio) di sviluppare la malattia in uno specifico periodo di tempo *t*

- assume follow-up completo
- è una proporzione perciò può assumere valori da 0 ad 1
- deve riferirsi ad uno specifico periodo di tempo

$$IC = \frac{\text{N° di persone che ammalano tra il } t_0 \text{ e } t_1}{\text{N° di persone non malate all'inizio del periodo } t_0}$$

Es. 5 si ammalano / 10 inizialmente non malati = 0.5

Risks, Rates and Odds

- ***Risk*** (proportion of persons with disease = *cumulative incidence*)
  - ***Risk Ratio*** = ratio of 2 cumulative incidence estimates = *Relative Risk*
- ***Rate*** (based on events per person-time = *incidence rate*)
  - ***Rate Ratio*** = ratio of 2 incidence rates = *Relative Rate*
- ***Odds*** (the number of events divided by the number of non events)
  - ***Odds Ratio*** = ratio of 2 odds

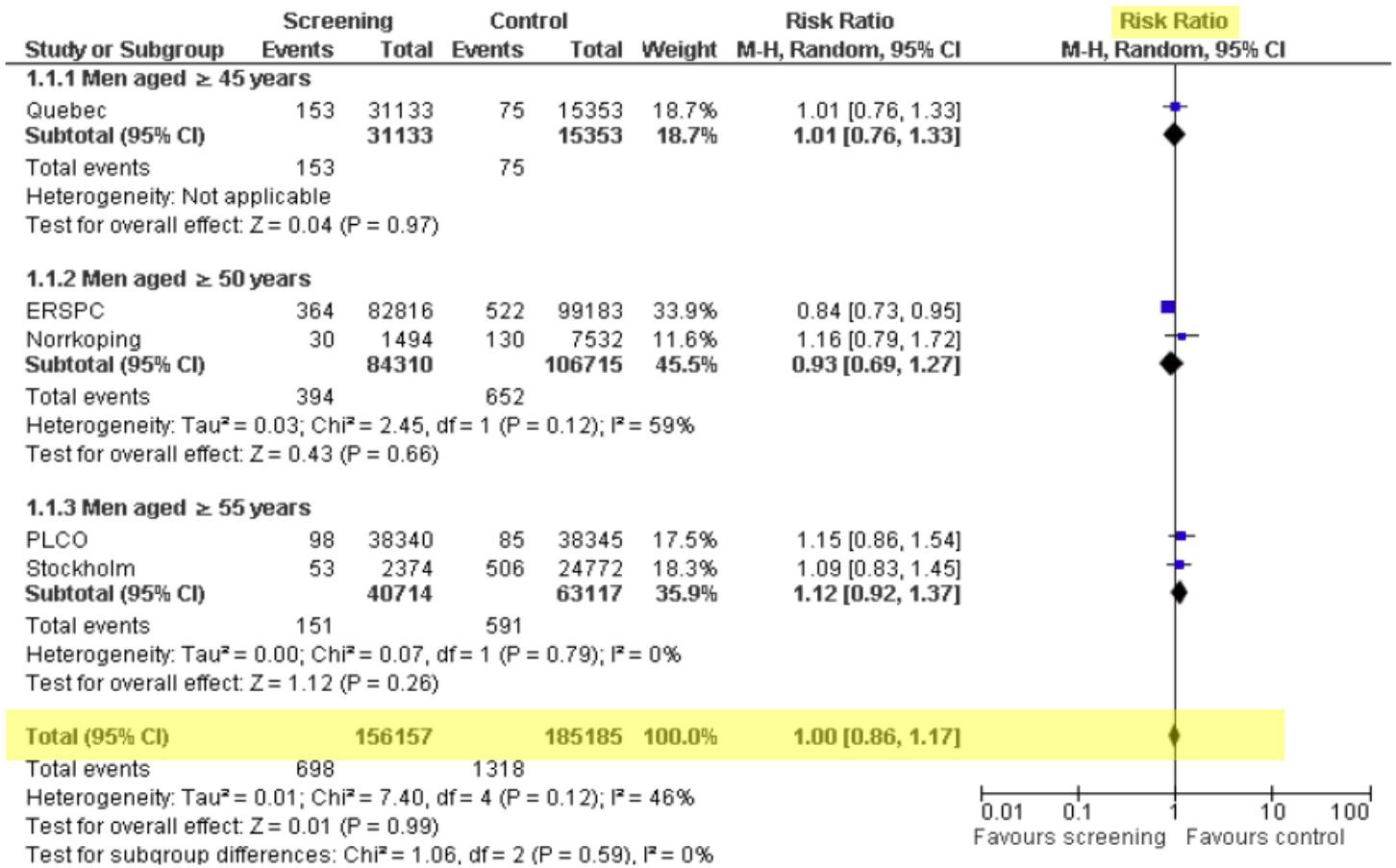
THE COCHRANE COLLABORATION®

Screening for prostate cancer (Review)

Ilic D, Neuberger MM, Djulbegovic M, Dahm P

Cochrane Database of Systematic Reviews 2013, Issue 1. Art. No.: CD004720.

Figure 2. Forest plot of comparison: 1 Screening versus control, outcome: 1.3 Prostate cancer-specific mortality (subgroup analysis age)



Risks, Rates and Odds

- ***Risk*** (proportion of persons with disease = *cumulative incidence*)
  - ***Risk Ratio*** = ratio of 2 cumulative incidence estimates = *Relative Risk*
- ***Rate*** (based on events per person-time = *incidence rate*)
  - ***Rate Ratio*** = ratio of 2 incidence rates = *Relative Rate*
- ***Odds*** (the number of events divided by the number of non events)
  - ***Odds Ratio*** = ratio of 2 odds

Incidence Rate

Incidence rate or person-time rate:

- is a measure of incidence that incorporates time directly into the denominator;
- describes how quickly disease occurs in a population

$$\frac{\textit{Number of new cases of disease or injury during specified period}}{\textit{Time each person was observed, totaled for all persons}}$$

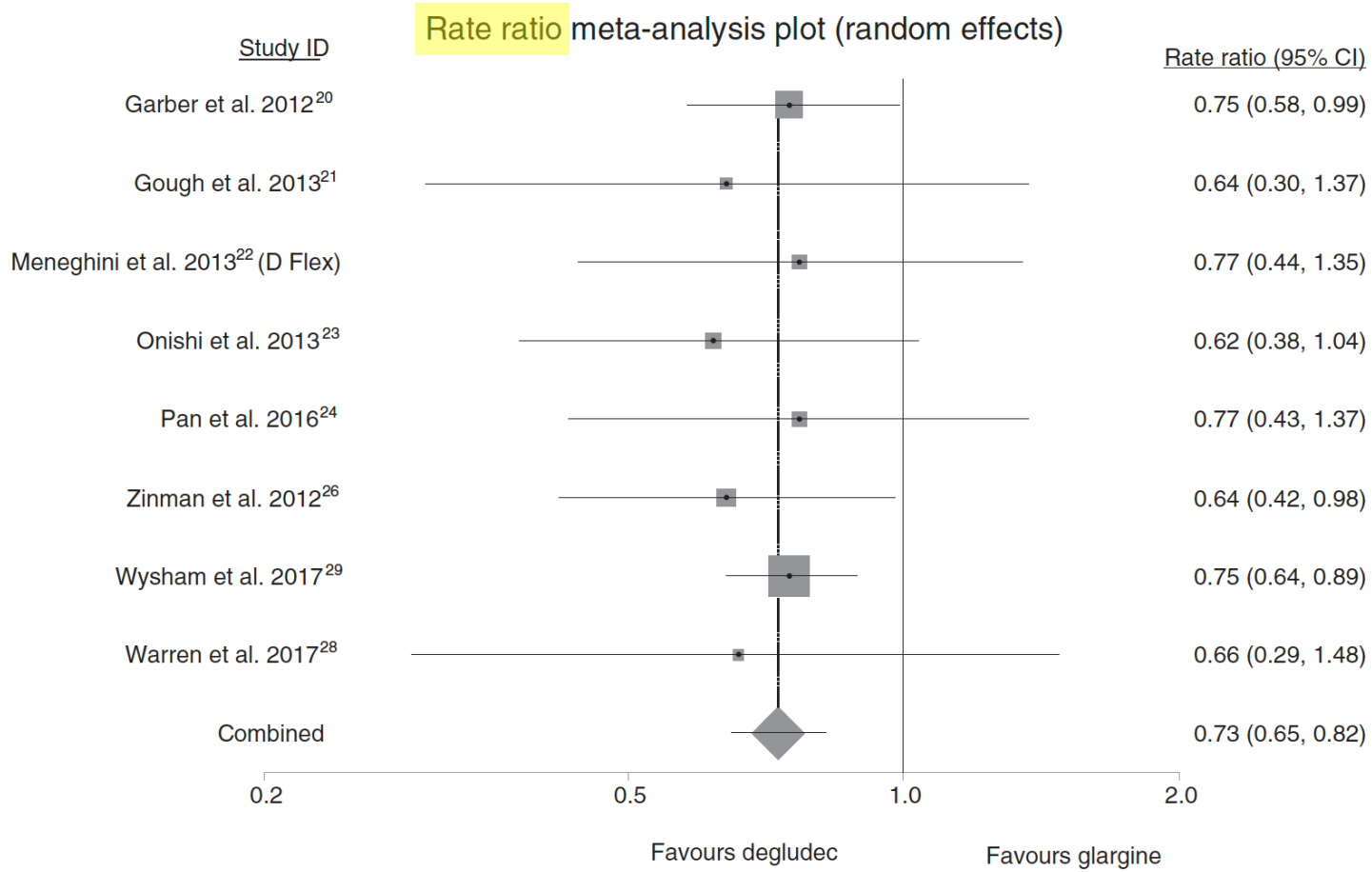
Risks, Rates and Odds

- ***Risk*** (proportion of persons with disease = *cumulative incidence*)
  - ***Risk Ratio*** = ratio of 2 cumulative incidence estimates = *Relative Risk*
- ***Rate*** (based on events per person-time = *incidence rate*)
  - ***Rate Ratio*** = ratio of 2 incidence rates = *Relative Rate*
- ***Odds*** (the number of events divided by the number of non events)
  - ***Odds Ratio*** = ratio of 2 odds

Comparative effectiveness and harms of long-acting insulins for type 1 and type 2 diabetes: A systematic review and meta-analysis

Rebecca S. Holmes MD | Elizabeth Crabtree PhD | Marian S. McDonagh PharmD

Diabetes Obes Metab. 2019;21:984–992.



Nocturnal hypoglycaemia event rates in adult patients with type 2 diabetes treated with daily degludec compared with glargine

Risks, Rates and Odds

- ***Risk*** (proportion of persons with disease = *cumulative incidence*)
  - ***Risk Ratio*** = ratio of 2 cumulative incidence estimates = *Relative Risk*
- ***Rate*** (based on events per person-time = *incidence rate*)
  - ***Rate Ratio*** = ratio of 2 incidence rates = *Relative Rate*
- ***Odds*** (the number of events divided by the number of non events)
  - ***Odds Ratio*** = ratio of 2 odds

Risks, Rates and Odds

- ***Risk*** (proportion of persons with disease = *cumulative incidence*)
- ***R*** …es =
- ***Odds*** (the … events divided by the number of non events)
  - ***Odds Ratio*** = ratio of 2 odds

Odds Ratios are used to compare the occurrence of the outcome of interest (e.g. disease or unfavourable event), given exposure to the variable of interest (e.g. health characteristic, or intervention).

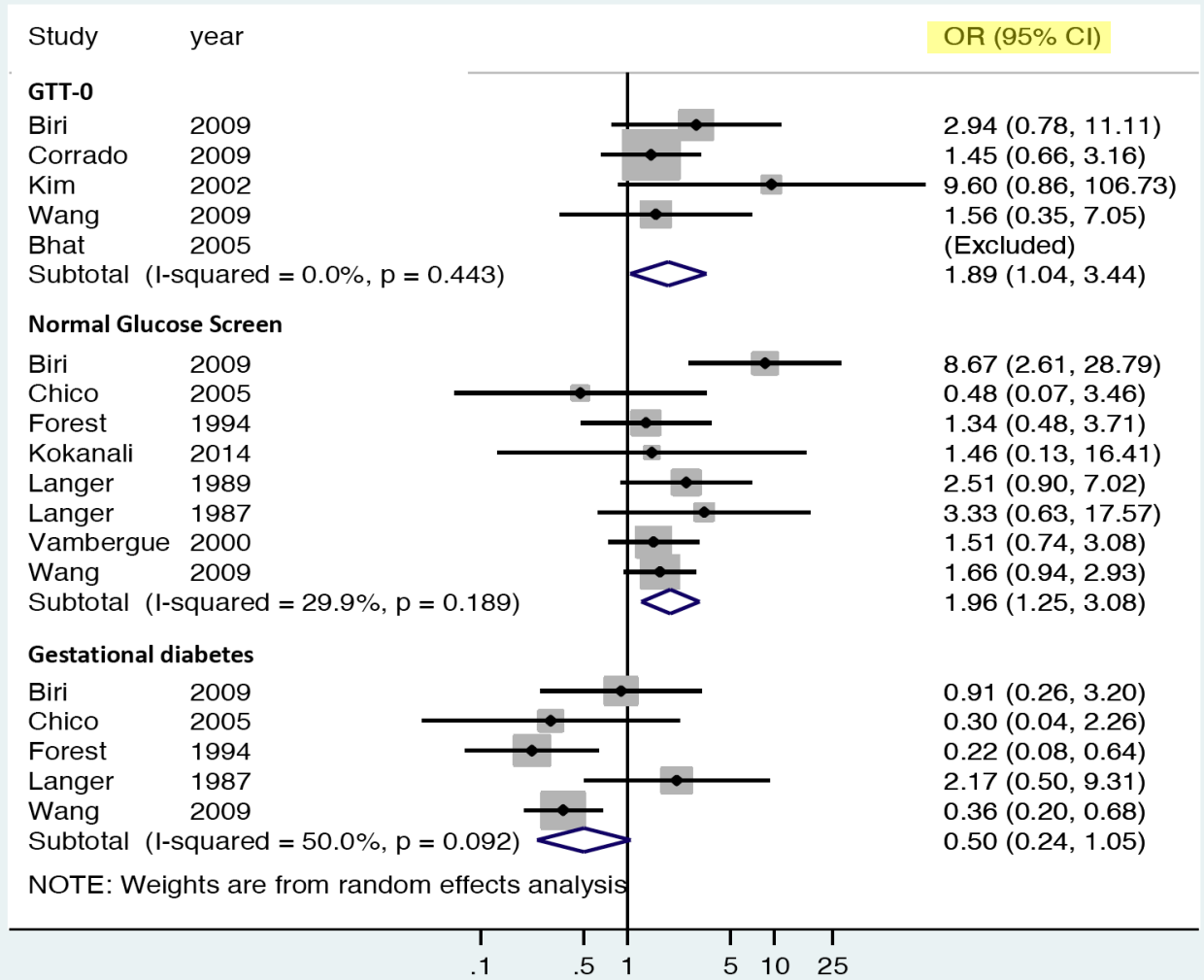
Most commonly used in **case-control studies**

Accepted Manuscript

Single abnormal value on 3 hour oral glucose tolerance test during pregnancy is associated with adverse maternal and neonatal outcomes: A systematic review and meta-analysis

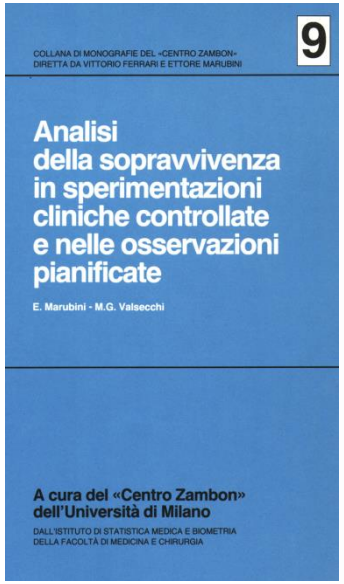
Jared T. Roeckner, MD, Luis Sanchez-Ramos, MD, Rubymel Jijon-Knupp, MD, Andrew M. Kaunitz, MD

Neonatal Hypoglycemia



VARIABILE DI RISPOSTA

- di tipo quantitativo
  - assume uno spettro continuo di valori e viene misurata in riferimento a una scala a intervalli costanti.
- di tipo qualitativo
  - esprime categorie di risposta del tipo successo / insuccesso (di un trattamento somministrato).
- del tipo “**tempo a evento**”
  - rappresenta il tempo trascorso fino al verificarsi (o meno) di un evento.



Tempi di risposta $t_{(j)}$	Tempi troncati* t^*	N° soggetti esposti a rischio n_j	N° eventi terminali d_j	Rischio istantaneo di "morte" $\hat{\lambda}(t_{(j)})$	Probabilità cumulativa di sopravvivere $t_{(j)}$ $\hat{P}_j$
9		20	1	1/20 = .050	(1 – 1/20) × 1 = .9500
13		19	1	1/19 = .053	(1 – 1/19) × .9500 = .8996
20		18	1	1/18 = .055	(1 – 1/18) × .8996 = .8501
26		17	1	1/17 = .059	(1 – 1/17) × .8501 = .7999
27		16	1	1/16 = .062	(1 – 1/16) × .7999 = .7503
28		15	1	1/15 = .067	(1 – 1/15) × .7503 = .7000
30		14	1	1/14 = .071	(1 – 1/14) × .7000 = .6503
32		13	2	2/13 = .154	(1 – 2/13) × .6503 = .5502
75		11	1	1/11 = .091	(1 – 1/11) × .5502 = .5001
79		10	1	1/10 = .100	(1 – 1/10) × .5001 = .4501
91		9	1	1/9 = .111	(1 – 1/9) × .4501 = .4001
	177*	8	0	0/8 = .0	(1 – 0/8) × .4001 = .4001
193		7	1	1/7 = .143	(1 – 1/7) × .4001 = .3429
541		6	1	1/6 = .167	(1 – 1/6) × .3429 = .2856
1129		5	1	1/5 = .200	(1 – 1/5) × .2856 = .2285
	1499*	4	0	0/4 = .0	(1 – 0/4) × .2285 = .2285
1585		3	1	1/3 = .333	(1 – 1/3) × .2285 = .1524

TABELLA 10.
Calcolo secondo Kaplan e Meier della curva di sopravvivenza del rene trapiantato nei pazienti di tabella 6.

Indicatori riassuntivi di effetto di variabili tempo-a-evento

- Differenza tra stime della mediana di sopravvivenza (KM)
- Differenza media di sopravvivenza (*restricted means*) al tempo *t*
- Differenza tra stime di sopravvivenza (KM) al tempo *t* (*Milestone* Survival)
- Hazard Ratio (KM+Cox)

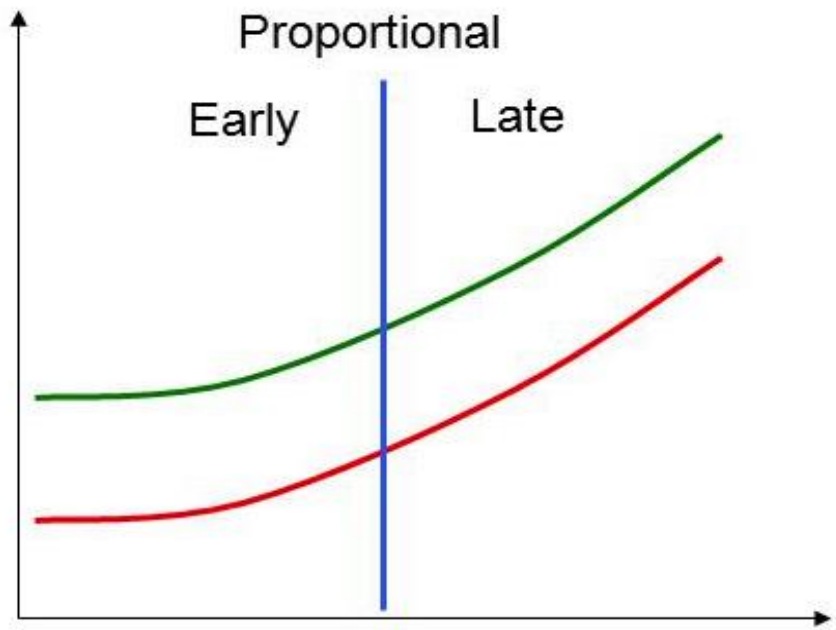
Indicatori riassuntivi di effetto di variabili tempo-a-evento

- Differenza tra stime della mediana di s
- D *ted m*
- D tempo *t estone* Survival)
- **Hazard Ratio** (KM+Cox)

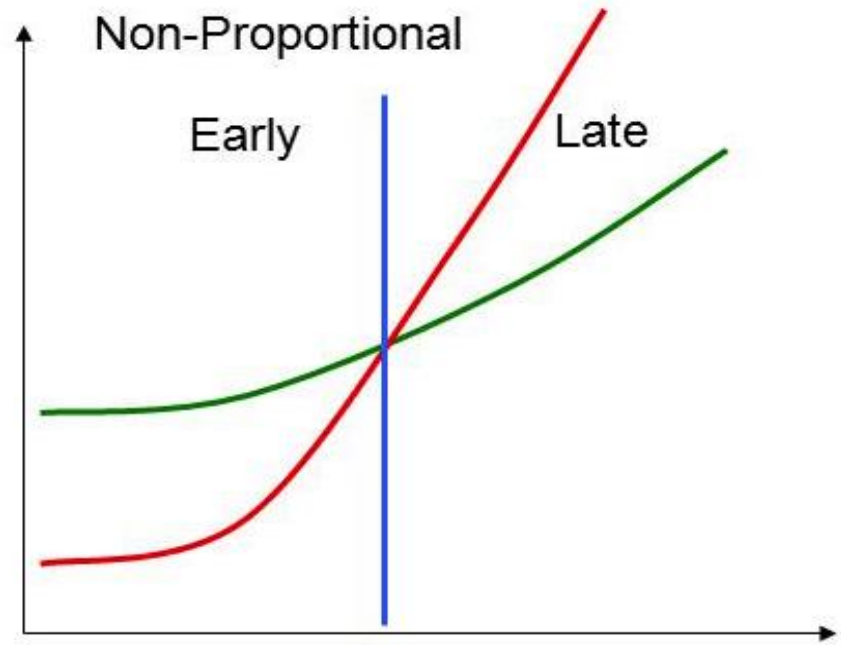
Appropriato quando il rapporto tra gli *hazard* dei due gruppi si mantiene (relativamente) costante

Proportional Hazard Assumption

If we are comparing a new treatment with the standard treatment, it is assumed that the ratio of the hazard for an individual on a new treatment to that for an individual on the standard treatment remains constant over time



Here, the effect is the same in both time periods



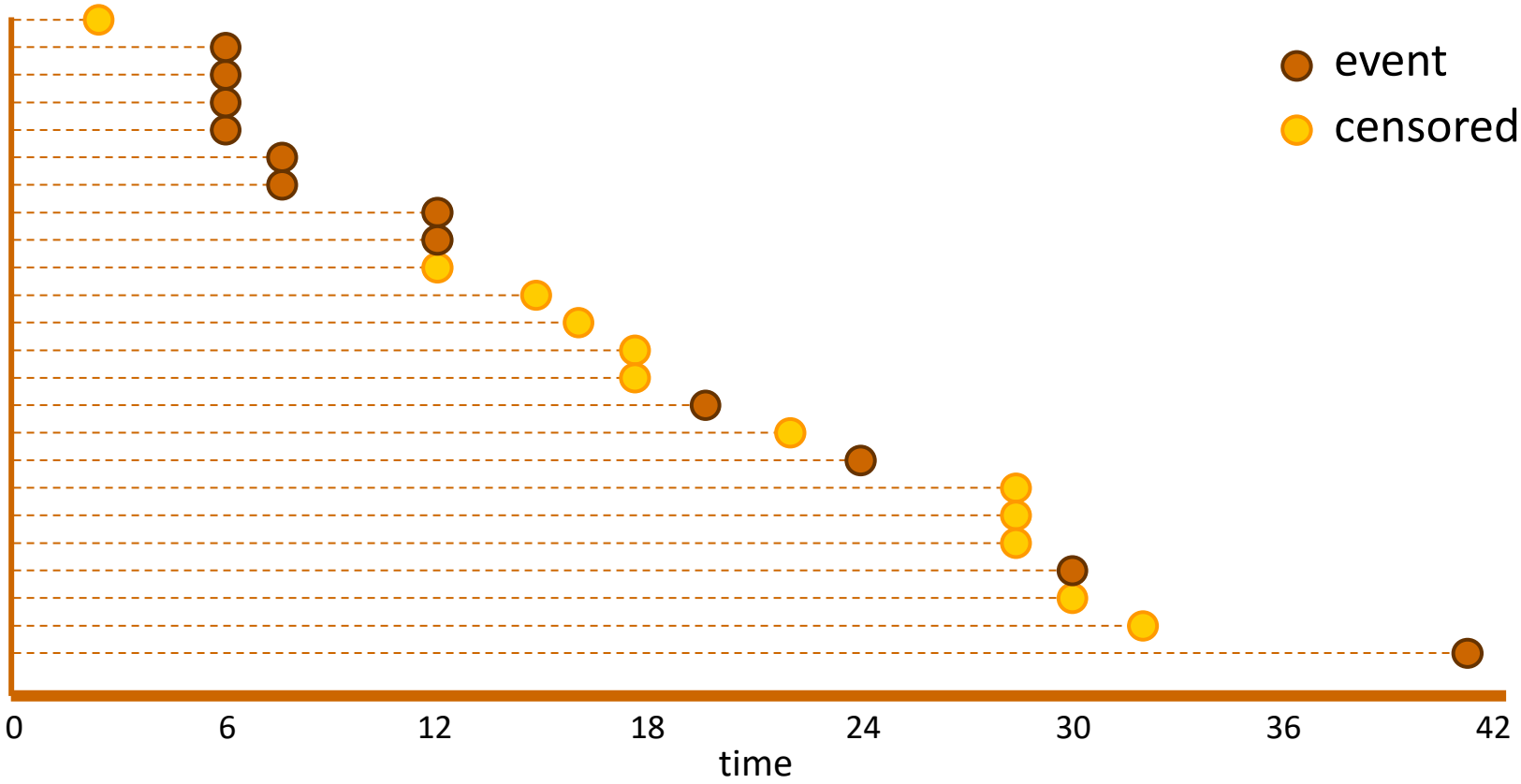
Here, the effect is negative in the early period and positive in the late period

Defining a Hazard Ratio (HR)

- Compares risk of event in two populations or samples
- The ratio of risk (*hazard rate*) in experimental group to risk (*hazard rate*) in control group
  - *The Hazard Rate (λ)* is the rate at which events happen
- Assumption: *proportional hazards (PH),* i.e. the risk does not depend on time, that is, "risk is constant over time"
  - If non PH is present, the HR is actually time-dependent and the estimated HR that is obtained is some type of average over the event times
  - The *restricted mean survival time* is as a possible alternative tool in the analysis of these trials

$$\lambda = \frac{d}{f + F}$$

d = number of events
f = sum of follow-up times for patients with event
F = sum of follow-up times for patients with no event (censored)



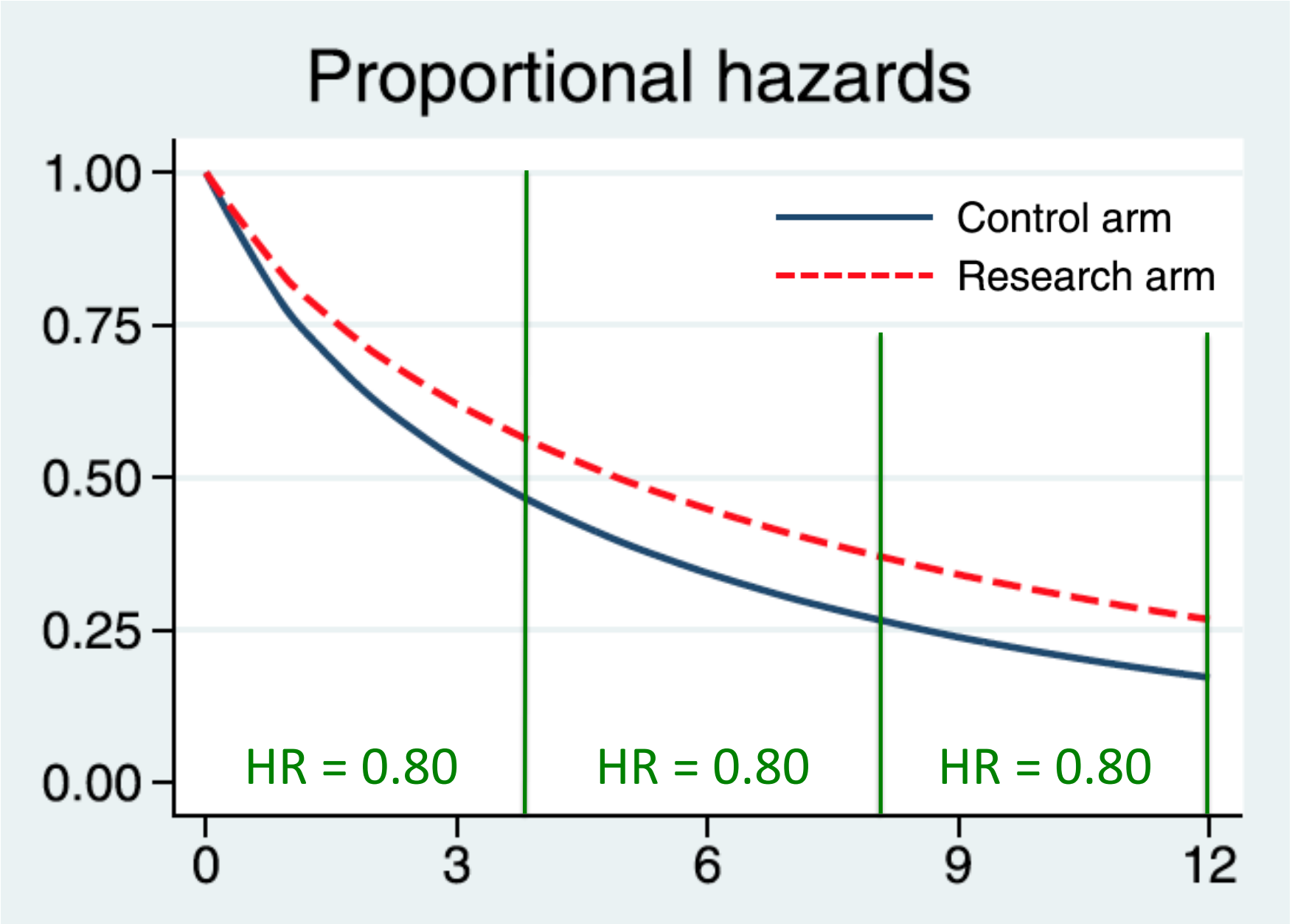
d = 12
f = 6+6+6+6+8+8+12+12+20+24+30+42 = 180
F = 3+12+15+16+18+18+22+28+28+28+30+33 = 251

$$\lambda = \frac{12}{431} = 0.0278$$

R. D'Amico 2009, modif.

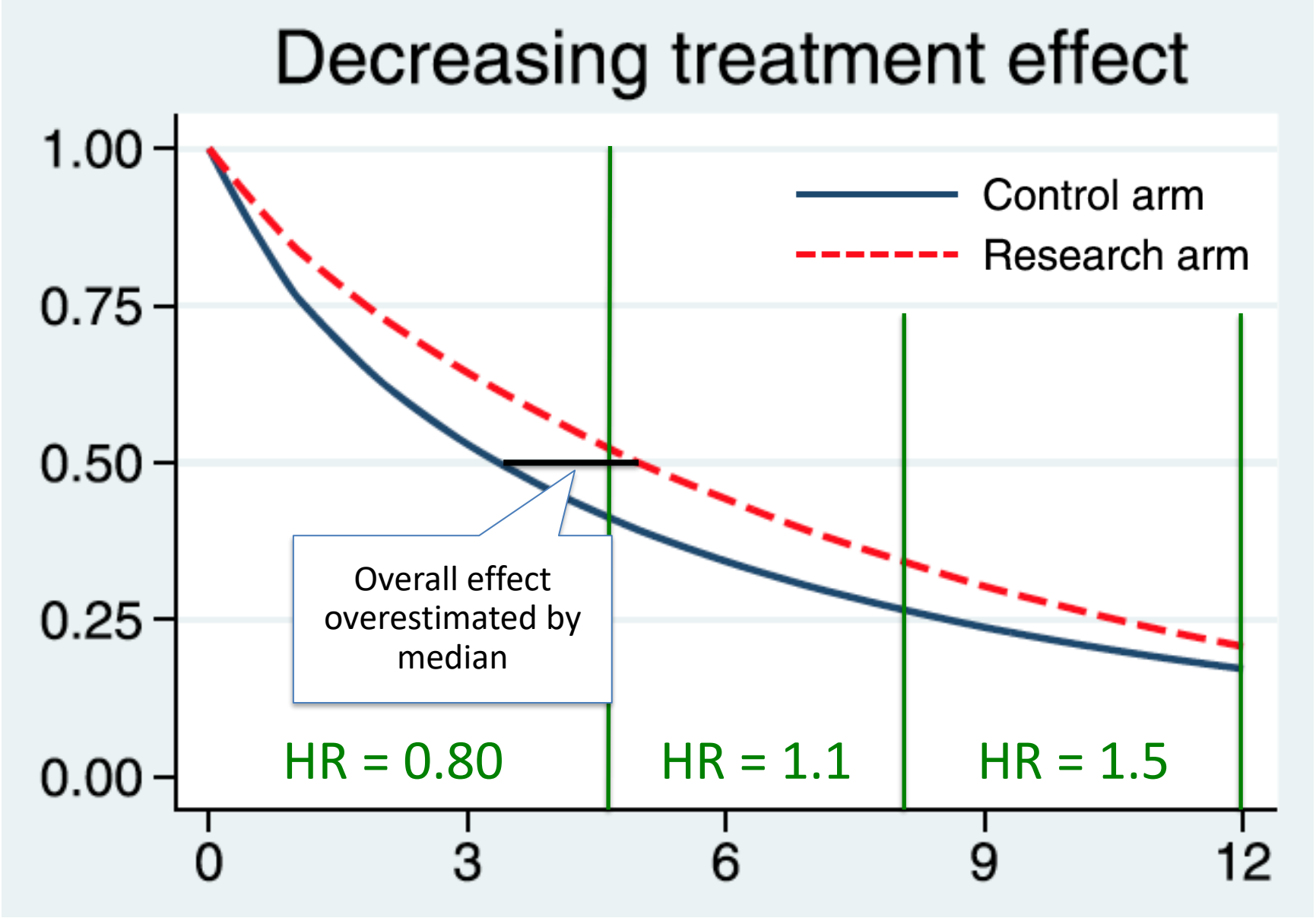
Defining a Hazard Ratio (HR)

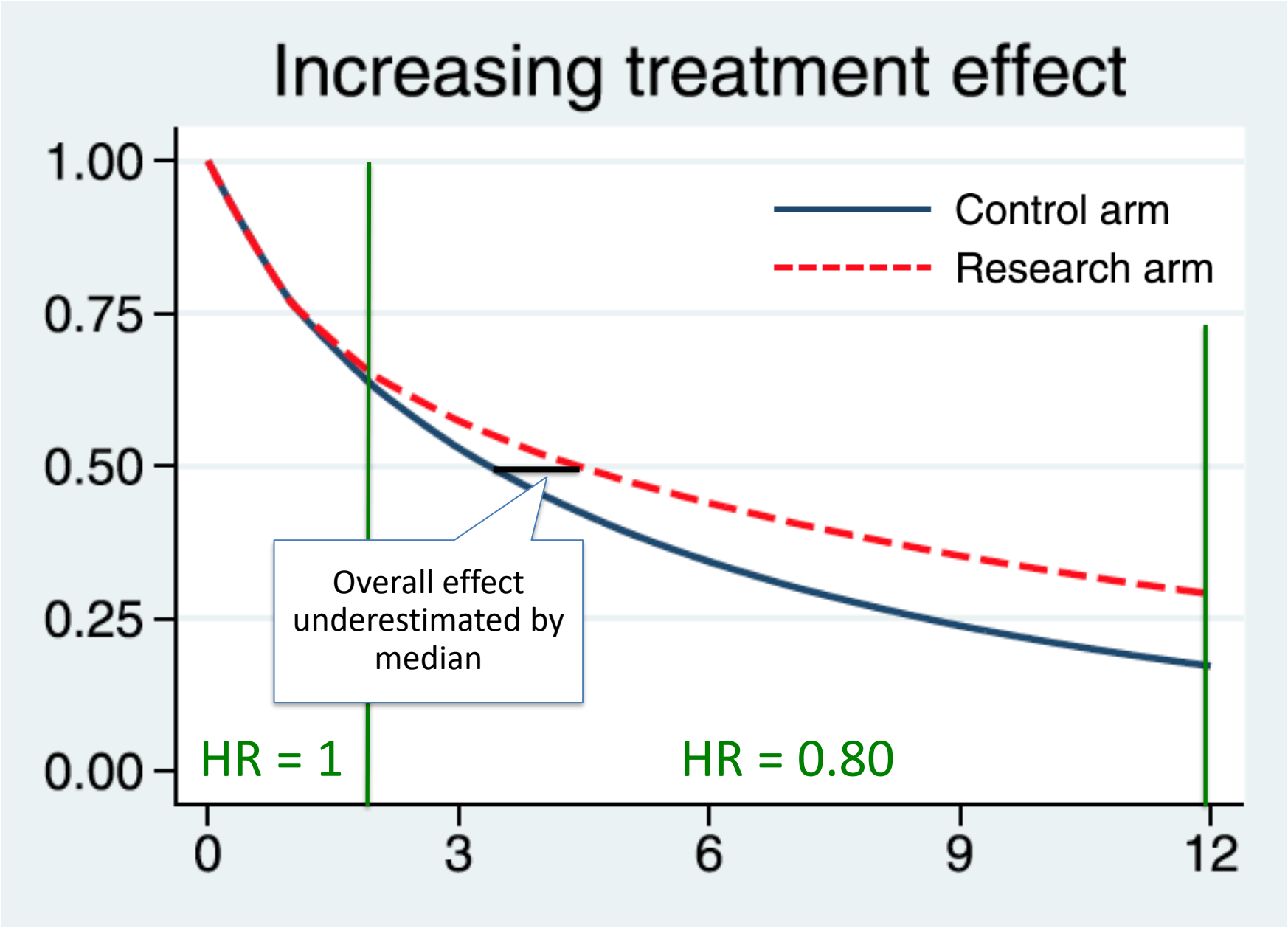
- Compares risk of event in two populations or samples
- The ratio of risk (*hazard rate*) in experimental group to risk (*hazard rate*) in control group
  - *The Hazard Rate (λ)* is the rate at which events happen
- Assumption: *proportional hazards (PH),* i.e. the risk does not depend on time, that is, "risk is constant over time"
  - If non PH is present, the HR is actually time-dependent and the estimated HR that is obtained is some type of average over the event times
  - The *restricted mean survival time* is as a possible alternative tool in the analysis of these trials


Proportional hazards
1.00
0.75
0.50
0.25
0.00
0
3
6
9
12
Control arm
Research arm
HR = 0.80
HR = 0.80
HR = 0.80

Defining a Hazard Ratio (HR)

- Compares risk of event in two populations or samples
- The ratio of risk (*hazard rate*) in experimental group to risk (*hazard rate*) in control group
  - *The Hazard Rate (λ)* is the rate at which events happen
- Assumption: *proportional hazards (PH),* i.e. the risk does not depend on time, that is, "risk is constant over time"
  - If non PH is present, the HR is actually time-dependent and the estimated HR that is obtained is some type of average over the event times
  - The *restricted mean survival time* is as a possible alternative tool in the analysis of these trials


Decreasing treatment effect
1.00
0.75
0.50
0.25
0.00
0
3
6
9
12
Control arm
Research arm
Overall effect overestimated by median
HR = 0.80
HR = 1.1
HR = 1.5


Increasing treatment effect
1.00
0.75
0.50
0.25
0.00
0
3
6
9
12
Control arm
Research arm
Overall effect underestimated by median
HR = 1
HR = 0.80

Defining a Hazard Ratio (HR)

- Compares risk of event in two populations or samples
- The ratio of risk (*hazard rate*) in experimental group to risk (*hazard rate*) in control group
  - *The Hazard Rate (λ)* is the rate at which events happen
- Assumption: *proportional hazards (PH),* i.e. the risk does not depend on time, that is, "risk is constant over time"
  - If non PH is present, the HR is actually time-dependent and the estimated HR that is obtained is some type of average over the event times
  - The *restricted mean survival time* is as a possible alternative tool in the analysis of these trials

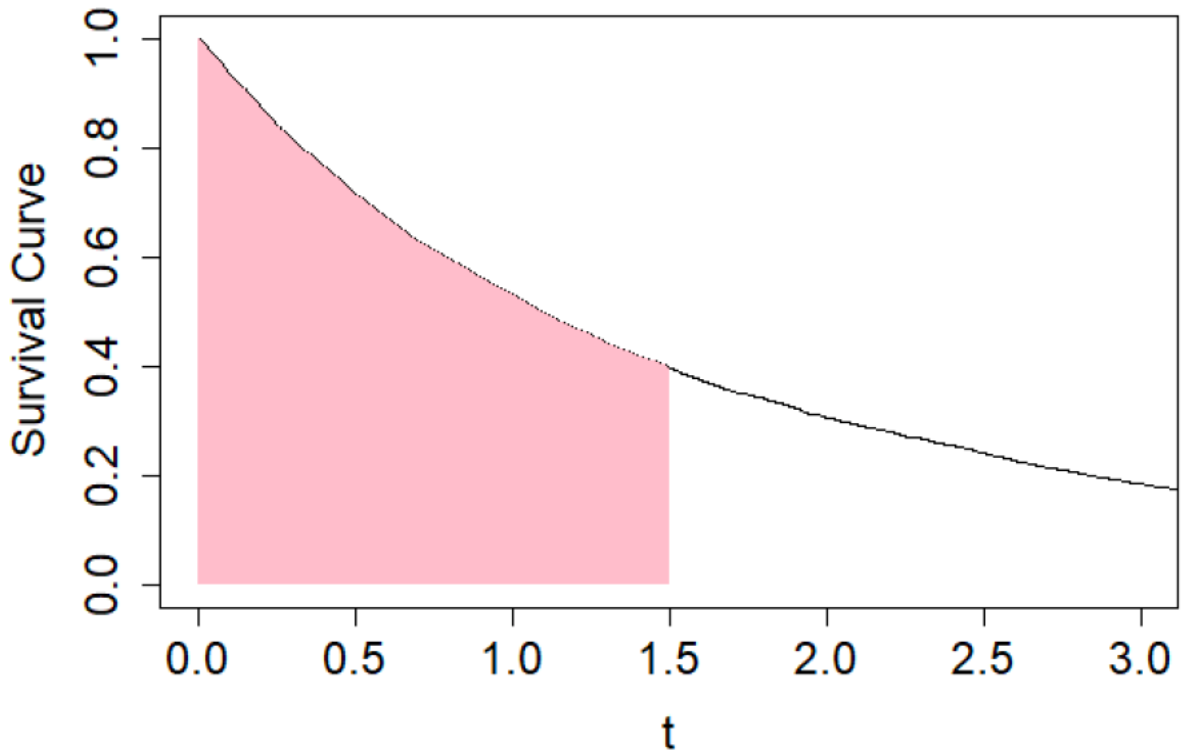
Indicatori riassuntivi di effetto di variabili tempo-a-evento

- Differenza tra stime della mediana di sopravvivenza (KM)
- **Differenza media di sopravvivenza (*restricted means*) al tempo *t***
- Differenza tra stime di sopravvivenza (KM) al tempo *t* (*Milestone* Survival)
- Hazard Ratio (KM+Cox)

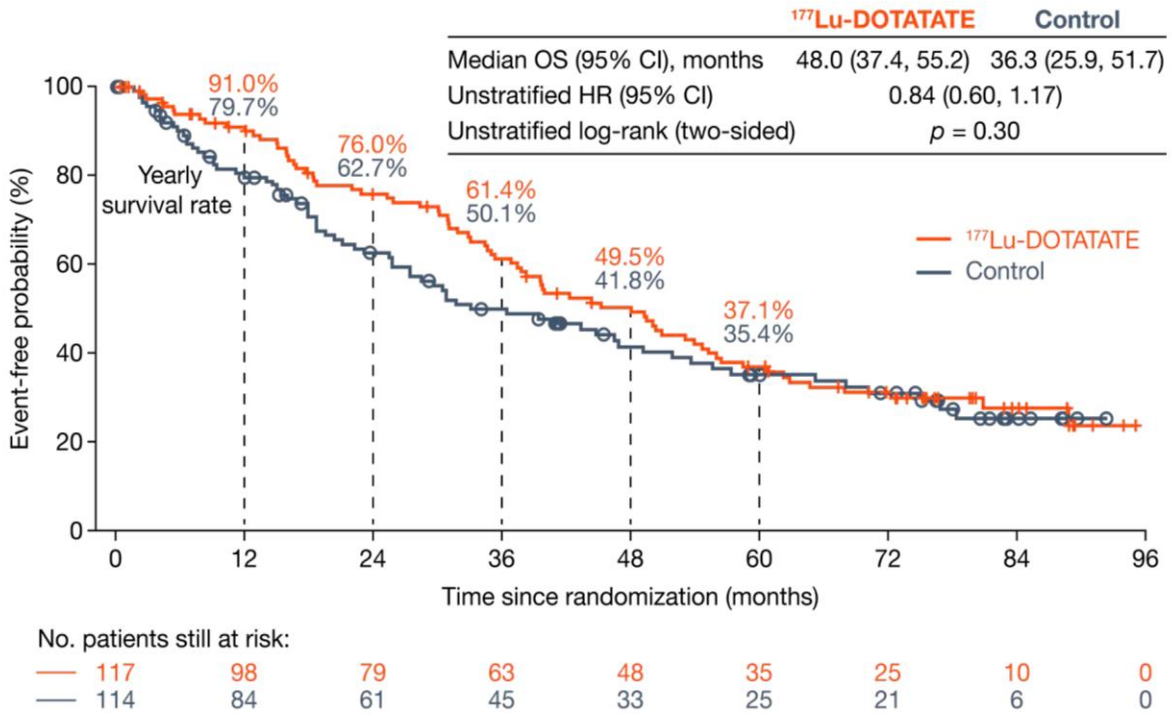
Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome

Patrick Royston* and Mahesh KB Parmar

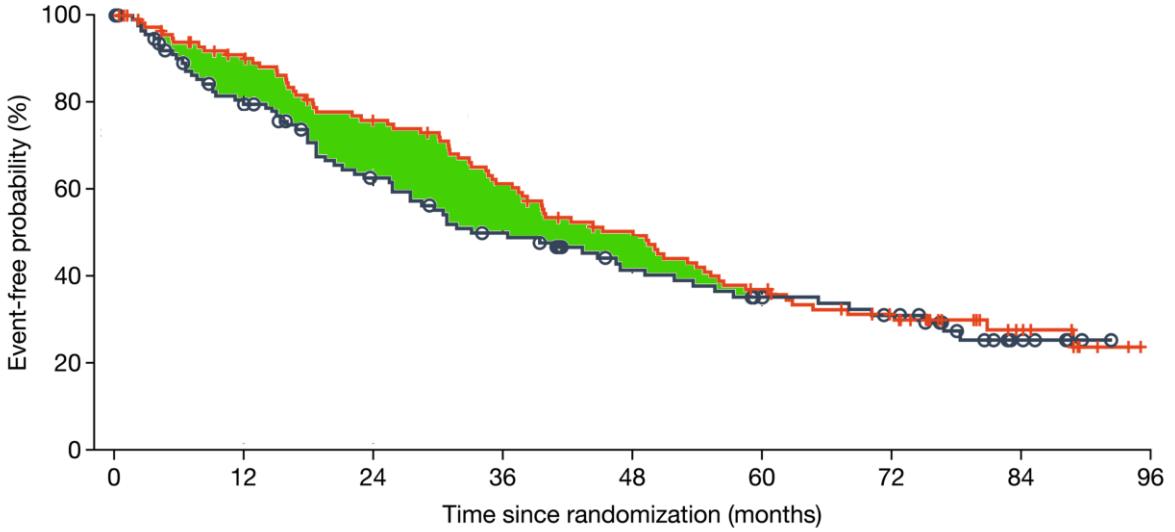
BMC Medical Research Methodology 2013, **13**:152



The phase 3 NETTER-1 study of 177Lu-DOTATATE in patients with midgut neuroendocrine tumours: further survival analyses



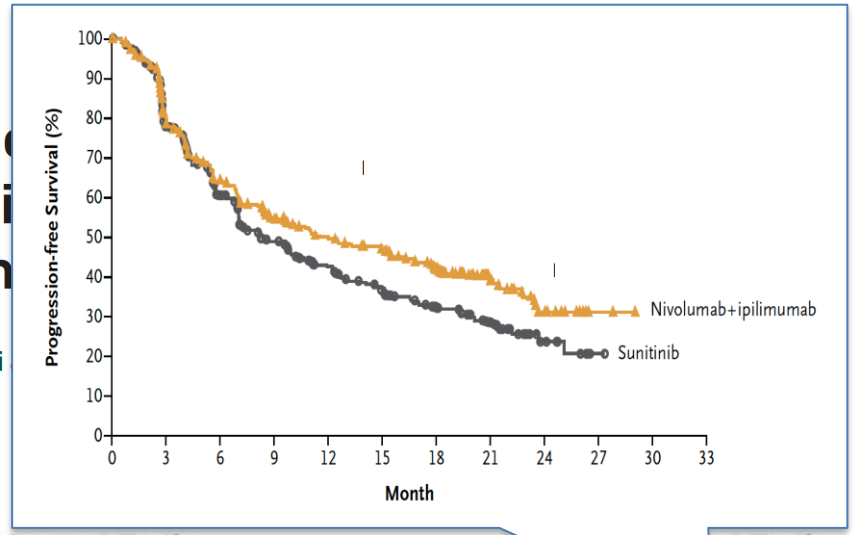
Deaths, n (%)	65 (55.6)	63 (55.3)
RMST, months (95% CI)	41.2 (37.6, 44.9)	36.1 (31.9, 40.4)
Difference, months (95% CI)	**5.1 (–0.5, 10.7)**	



Ruszniewski PB, et al. ESMO 2021

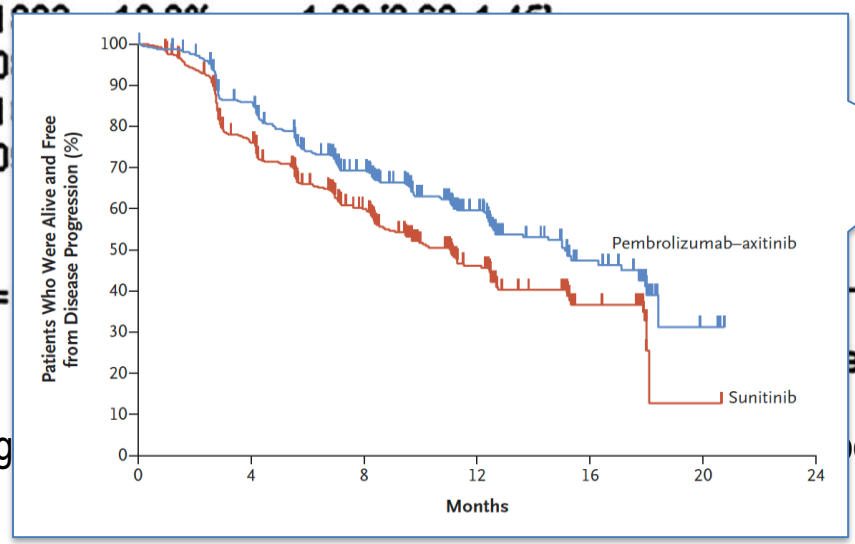
Results from a meta-analysis
checkpoint inhibitors in first-li
cancer patients: does PD-L1 m

Giandomenico Roviello, Silvia Paola Corona, Gabriella Nesi



Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
CheckMate 214	-0.0202	0.11	18.4%	0.98 [0.79, 1.22]
Immotion 150 (Atezo vs SUN)	0.174	0.19	10.9%	1.19 [0.82, 1.73]
IMmotion 150 (BEV+Atezo vs SUN)	0	0.1		
Immotion 151	-0.1863	0.0		
JAVELIN Renal101	-0.3711	0.1		
KEYNOTE-426	-0.3711	0.0		
Total (95% CI)				

Heterogeneity: Tau² = 0.02; Chi² = 13.35, df = 5 (P = 0.02); I² =
Test for overall effect: Z = 2.10 (P = 0.04)



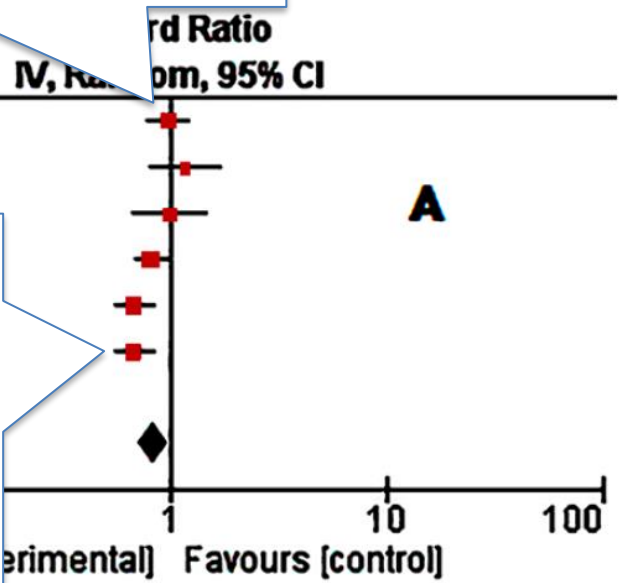


Figure 2. Forest plots of hazard ratios (HRs) for prog oint inhibitors with sunitinib.

NEGRAR DI VALPOLICELLA
11-12 FEBBRAIO 2022

Centro Formazione IRCCS "Sacro Cuore-Don Calabria"

11 Febbraio 2022

10.30-10.45	Presentazione ed obiettivi del Corso Stefania GORI - Fabrizio NICOLIS Giovanni L. PAPPAGALLO
10.45-11.30	Tipologia delle Revisioni della Letteratura Scientifica Obiettivi di una Revisione Sistematica Michela CINQUINI
11.30-12.00	Definizione del quesito clinico e degli outcome di interesse; misure di associazione Giovanni L. PAPPAGALLO
12.00-13.00	Lavoro di gruppo *Summing-Up* (metodo: *What? So What? Now What?*) (valido come prova ECM)
13.000-14.00	Colazione di lavoro
14.00-14.45	Come trovare informazioni - I database bibliografici, i siti di linee guida e studi clinici... Veronica Andrea FITTIPALDO
14.45-15.30	Definizione della strategia di ricerca e di selezione degli studi; *study flow* Michela CINQUINI
15.30-16.00	Metodi di valutazione di autori e riviste scientifiche: indici bibliometrici classici e innovativi Giulio ZUANETTI
16.00-16.30	Coffee Break
16.30-17.30	Valutazione del rischio di *bias* negli studi selezionati Ivan MOSCHETTI
17.30-18.30	Lavoro di gruppo *Summing-Up* (metodo: *What? So What? Now What?*) (valido come prova ECM)

NEGRAR DI VALPOLICELLA
11-12 FEBBRAIO 2022

Centro Formazione IRCCS "Sacro Cuore-Don Calabria"

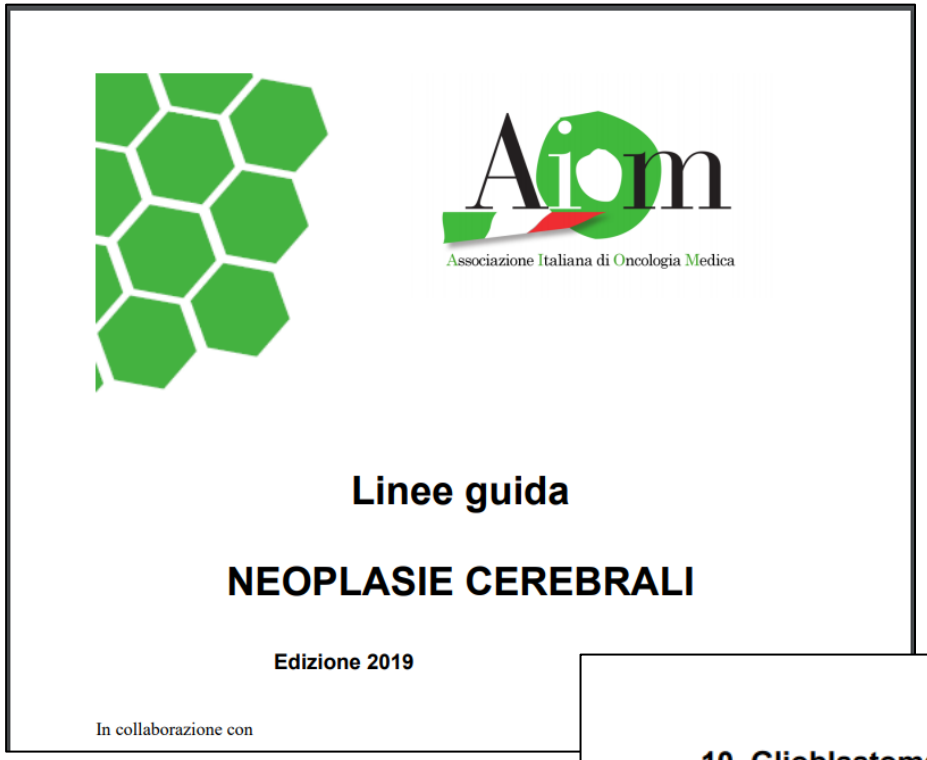
11 Febbraio 2022

10.30-10.45	Presentazione ed obiettivi del Corso Stefania GORI - Fabrizio NICOLIS Giovanni L. PAPPAGALLO
10.45-11.30	Tipologia delle Revisioni della Letteratura Scientifica Obiettivi di una Revisione Sistematica Michela CINQUINI
11.30-12.00	Definizione del quesito clinico e degli outcome di interesse; misure di associazione Giovanni L. PAPPAGALLO
12.00-13.00	Lavoro di gruppo *Summing-Up* (metodo: *What? So What? Now What?*) (valido come prova ECM)
13.000-14.00	Colazione di lavoro
14.00-14.45	Come trovare informazioni - I database bibliografici, i siti di linee guida e studi clinici... **Veronica Andrea FITTIPALDO**
14.45-15.30	Definizione della strategia di ricerca e di selezione degli studi; *study flow* Michela CINQUINI
15.30-16.00	Metodi di valutazione di autori e riviste scientifiche: indici bibliometrici classici e innovativi Giulio ZUANETTI
16.00-16.30	Coffee Break
16.30-17.30	Valutazione del rischio di *bias* negli studi selezionati Ivan MOSCHETTI
17.30-18.30	Lavoro di gruppo *Summing-Up* (metodo: *What? So What? Now What?*) (valido come prova ECM)

Obiettivo Generale

Prendere decisioni nella pratica clinica rispondendo a quesiti attraverso il reperimento delle evidenze disponibili

Quesito clinico



Associazione Italiana di Oncologia Medica

Linee guida

NEOPLASIE CEREBRALI

Edizione 2019

In collaborazione con

10. Glioblastoma di nuova diagnosi

Il glioblastoma è la neoplasia cerebrale più aggressiva e più frequente: la sua incidenza media è di 5-8 casi ogni 100.000 abitanti e rappresenta il 54% rispetto al totale di tutti i gliomi diagnosticati (41, 42).

Quesito 2: Nei pazienti con meno di 70 anni alla radioterapia (60 Gy/30 frazioni) dovrebbe essere associato un trattamento con temozolomide concomitante (75 mg/m^2/die) ed adiuvante (150-200 mg/m^2 per 5 giorni, ogni 28)?
Descrizione delle evidenze: *Lo studio pubblicato da:* – Stupp, R, New England Journal of Medicine, 2005 (13). *condotto in termini di:* – singolo studio randomizzato

Elaborazione del modello PICO

Articolare il quesito clinico col modello PICO risulta molto efficace per ritrovare evidenze clinicamente rilevanti in letteratura

Elaborazione del modello PICO

P = paziente o popolazione

I = intervento

C = confronto

O = outcome (esito)

Nei pazienti affetti da glioblastoma di nuova diagnosi, con meno di 70 anni, alla radioterapia deve essere associato un trattamento con temozolomide concomitante o adiuvante?

Linee guida «Neoplasie cerebrali». AIOM (Associazione Italiana Oncologia Medica) Edizione 2018.

Elaborazione del modello PICO

P = soggetti affetti di glioblastoma <70anni

I = radioterapia

C = temozolamide

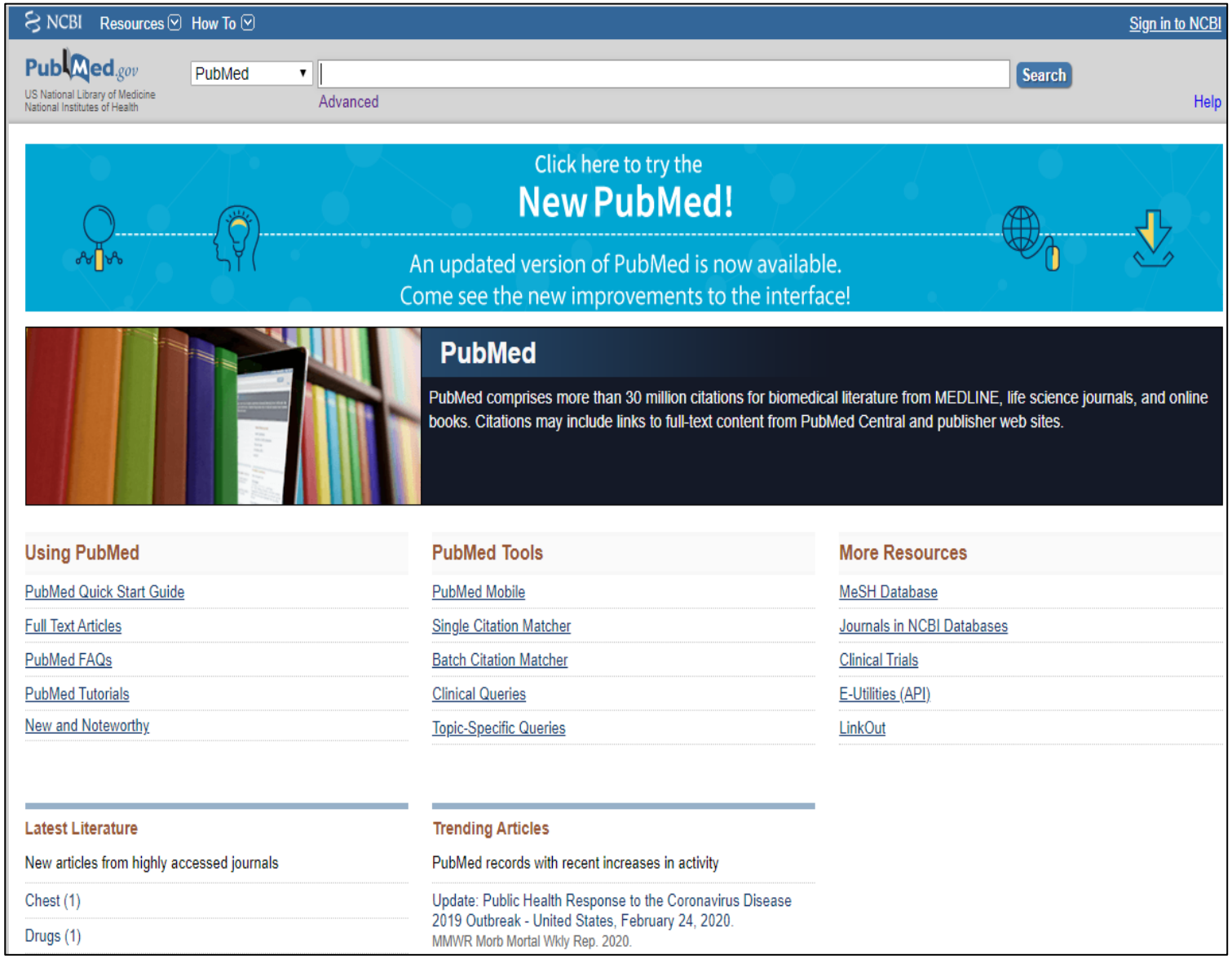
Nei ***pazienti affetti da glioblastoma di nuova diagnosi, con meno di 70 anni,*** alla ***radioterapia*** deve essere associato un trattamento con ***temozolomide*** concomitante o adiuvante?

Linee guida «Neoplasie cerebrali». AIOM (Associazione Italiana Oncologia Medica) Edizione 2018.

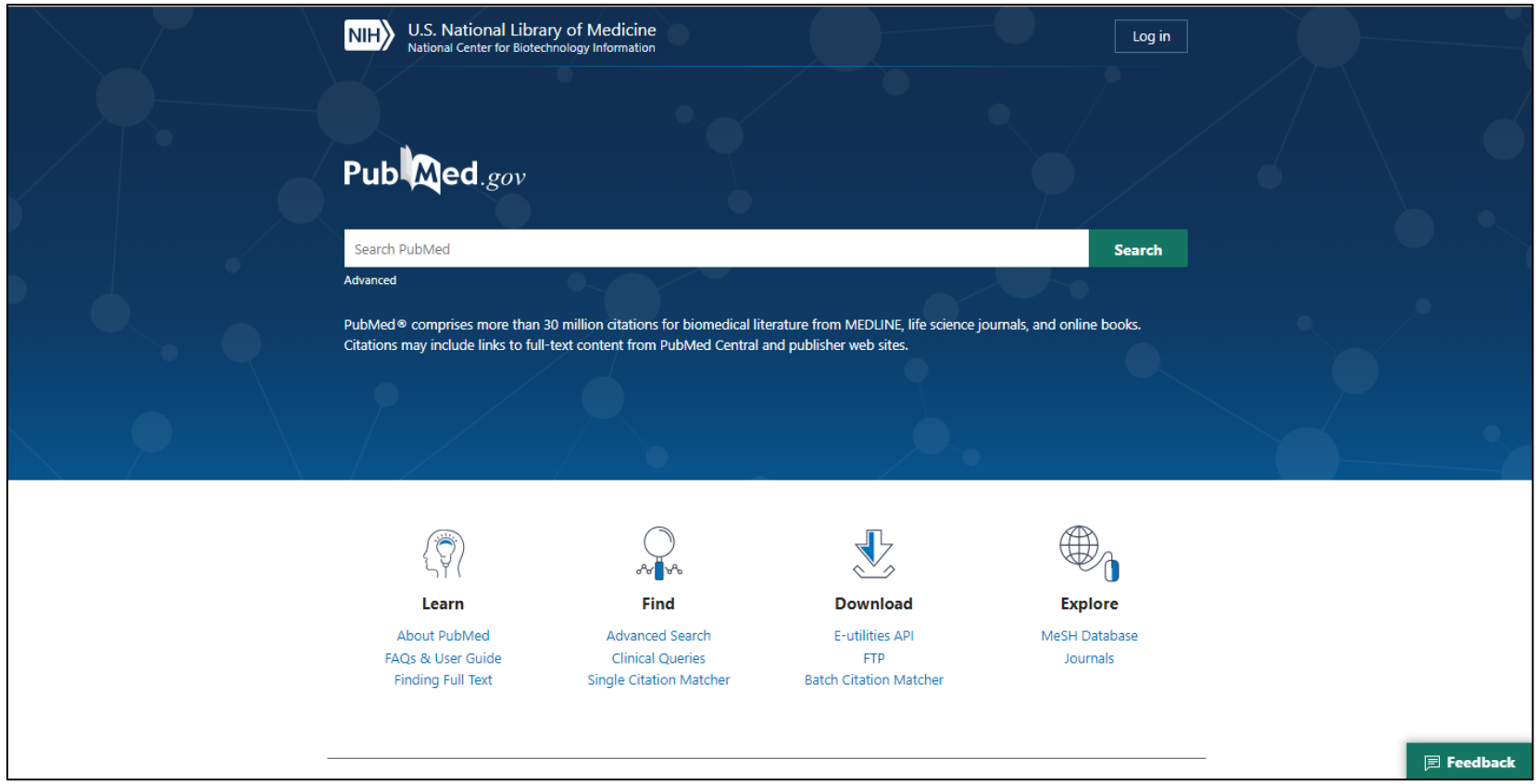
Creare la stringa di ricerca

Interrogare le diverse banche dati

Trovare gli studi randomizzati (RCT)



https://www.ncbi.nlm.nih.gov/pubmed/


U.S. National Library of Medicine
National Center for Biotechnology Information
Log in
PubMed.gov
Search PubMed
Search
Advanced
PubMed® comprises more than 30 million citations for biomedical literature from MEDLINE, life science journals, and online books.
Citations may include links to full-text content from PubMed Central and publisher web sites.
Learn
About PubMed
FAQs & User Guide
Finding Full Text
Find
Advanced Search
Clinical Queries
Single Citation Matcher
Download
E-utilities API
FTP
Batch Citation Matcher
Explore
MeSH Database
Journals
Feedback

Pubmed: Banca dati bibliografica

- Archivio di **citazioni**, curato dal National Center of Biotechnology (NCBI) presso la National Library of Medicine di Bethesda e messo a disposizione gratuitamente nel 1996 tramite la piattaforma PubMed disponibile sul Web.

- L'Index Medicus, pubblicata dalla National Library of Medicine (NLM) nel 1879, ha indicizzato le principali riviste di medicina e di scienze biomediche, all'inizio negli Stati Uniti e dopo in tutto il mondo diventando il database ora conosciuto come MEDLINE®.

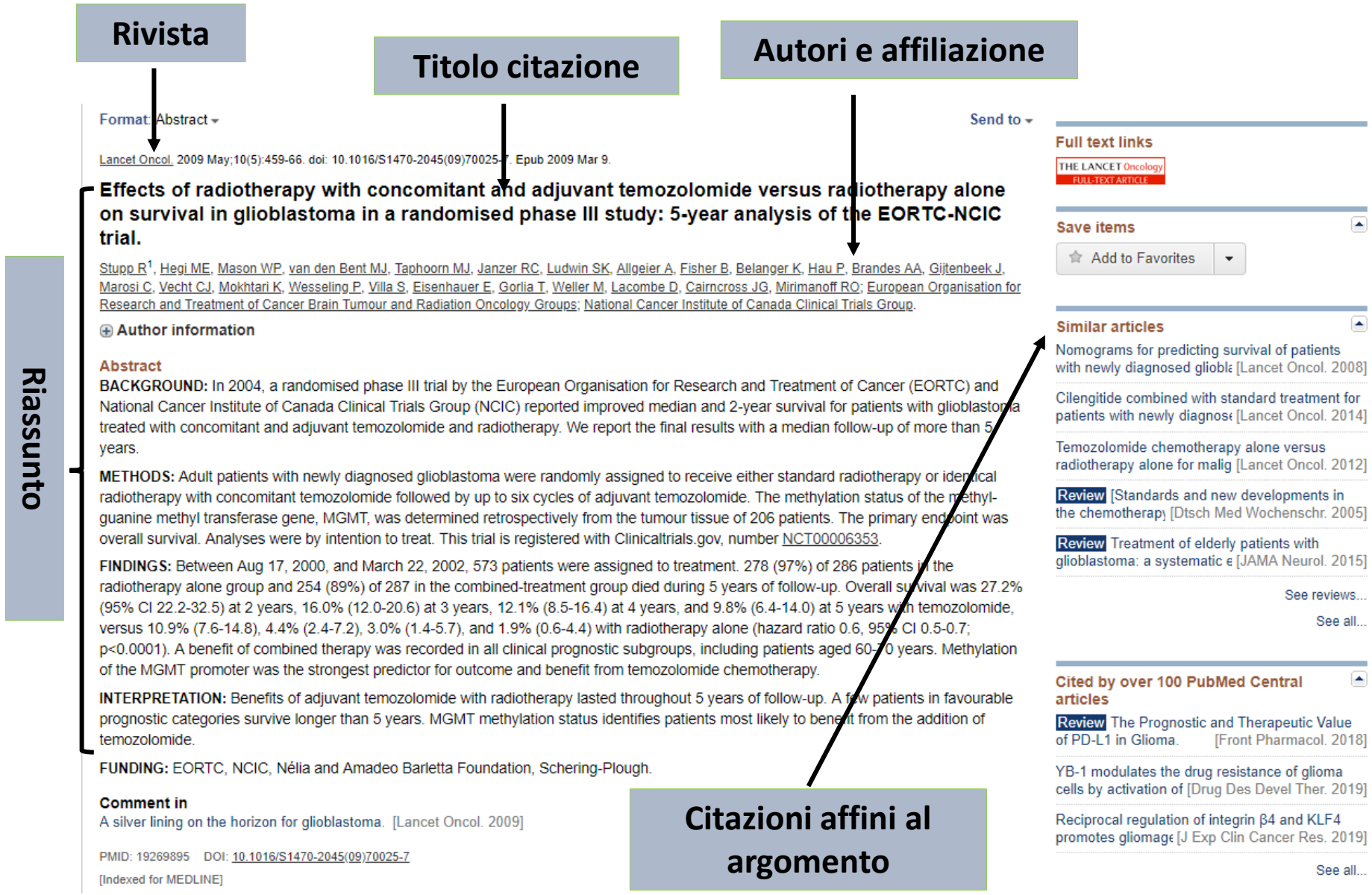
MEDLINE®
(*Medical Literature Analysis and Retrieval System Online*)

- Contiene più di 29 milioni di **citazioni** di riviste e abstract di letteratura biomedica da tutto il mondo.
- Medline contiene più di 5 milla journals indexati.
- Offre strumenti di ricerca attraverso parole chiavi su più campi (autore, titolo, abstract).
- Consente l'uso di operatori logici e la modalità di ricerca libera e con i termine MeSH.

Citazione bibliografica

- Ogni citazione bibliografica rappresenta un articolo di rivista.
- È composta da campi che forniscono informazioni sull’articolo.

I campi della citazione bibliografica



Sensibilità

30 records utili su 3000 ritrovati su PubMed

- ✓ Ricerca completa
- X Alto numero di records non rilevanti alla nostra ricerca

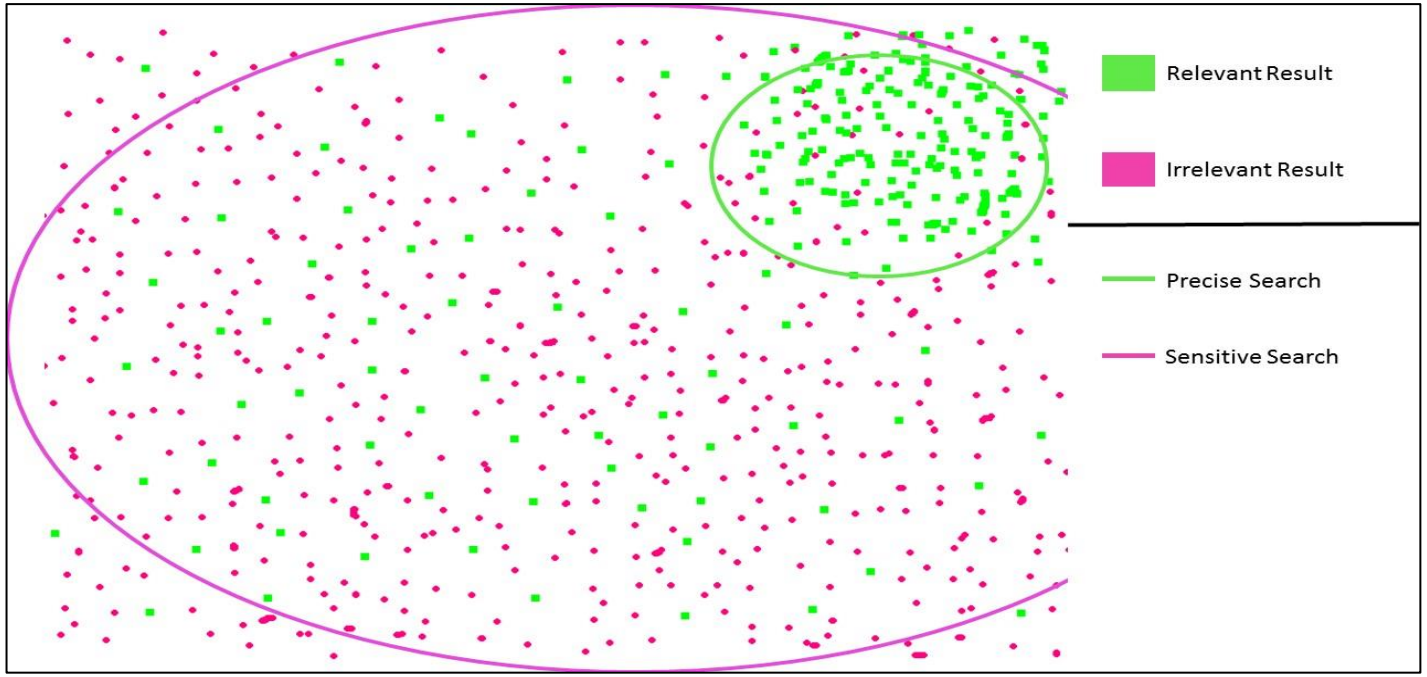
Precisione

10 records utili su 30 ritrovati su PubMed

- ✓ Trova i records rilevanti
- X Pericolo di perdere records, ricerca incompleta

Quindi … sensibilità o precisione?

Alta precisione e sensibilità allo stesso tempo … impossibile



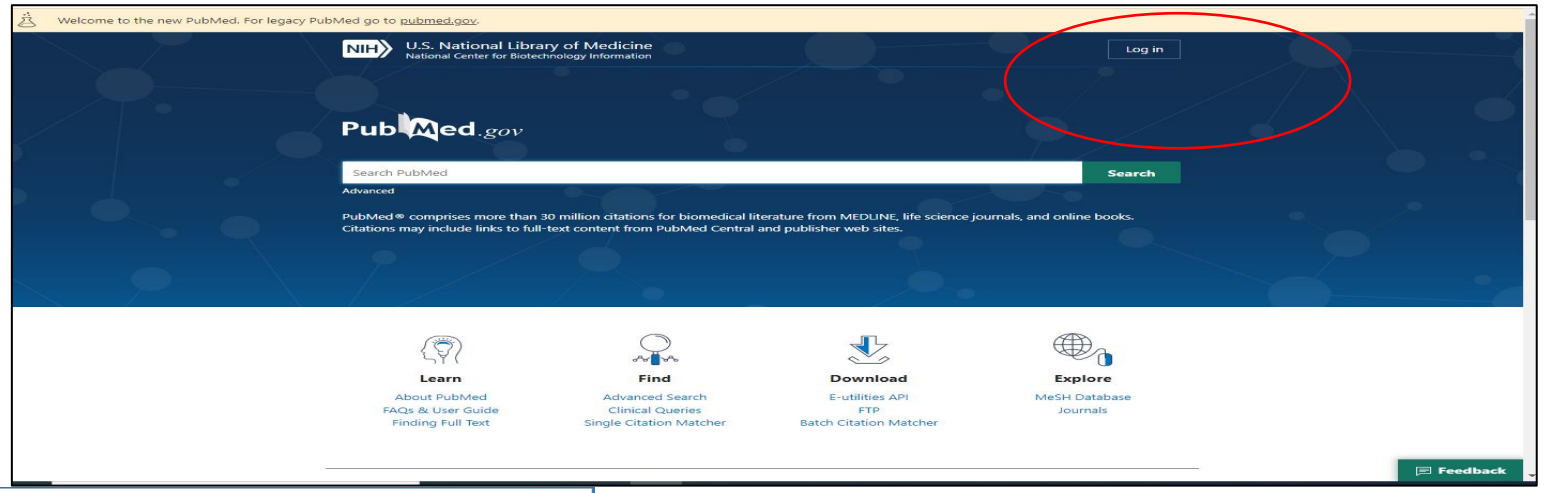
Fonte: University of Toronto https://guides.library.utoronto.ca/c.php?g=577919&p=4304403

Per fare una revisione sistematica → **sensibilità**

Per il clinico, che deve rispondere ad un quesito clinico → **Precisione**

Guida per una ricerca su PubMed

- Pubmed: Registrarsi e creare un account
- Ricerca libera
- Gli operatori booleani
- Creare una stringa di ricerca
- Mesh: utilizzo
- Risultati: conservazione e rilancio della ricerca
- Scaricare i risultati

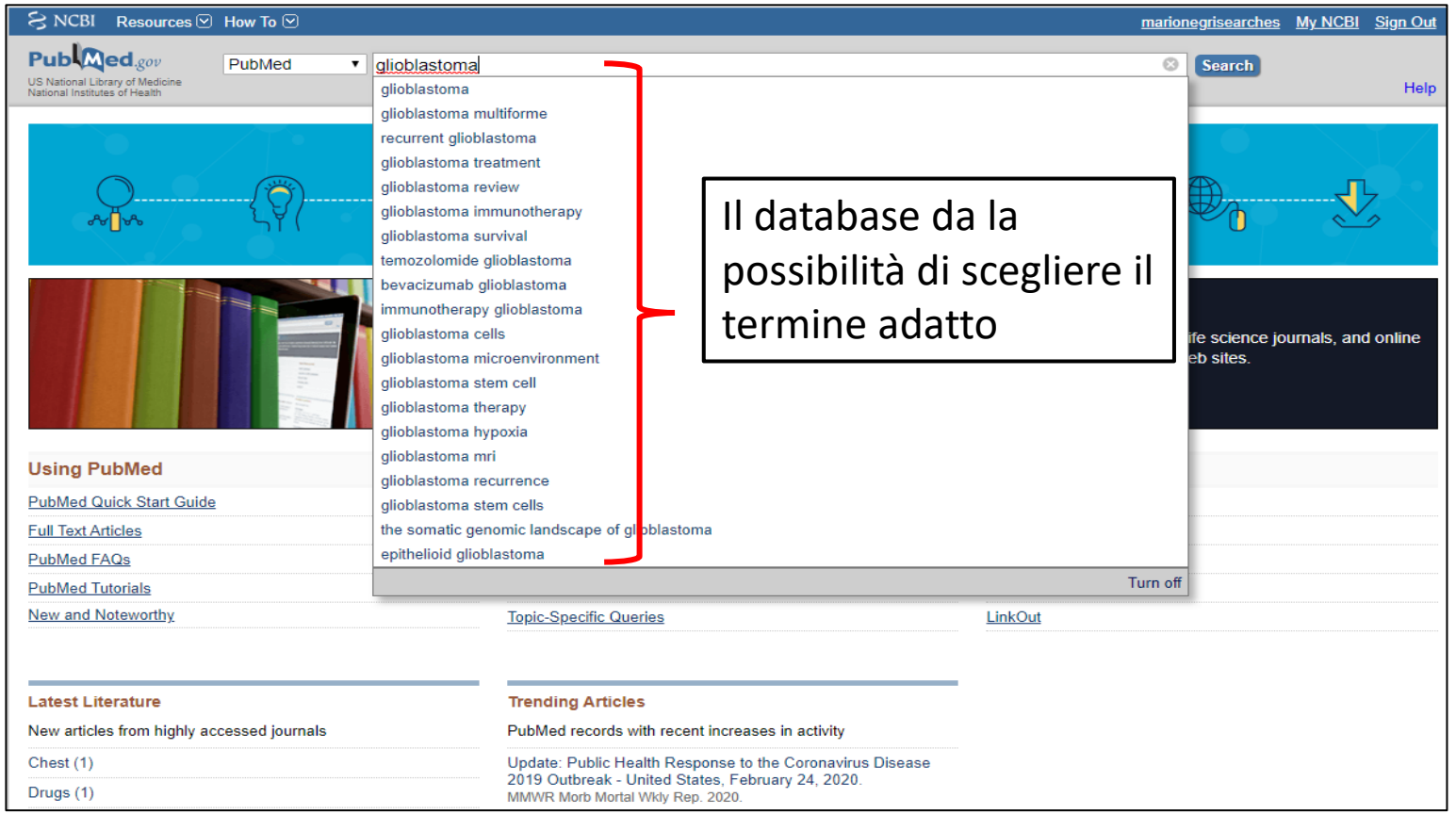


1

2

Registrarsi sul sito di PubMed e creare una utenza permette di salvare le ricerche e richiamarli per aggiornarli.

Ricerca libera

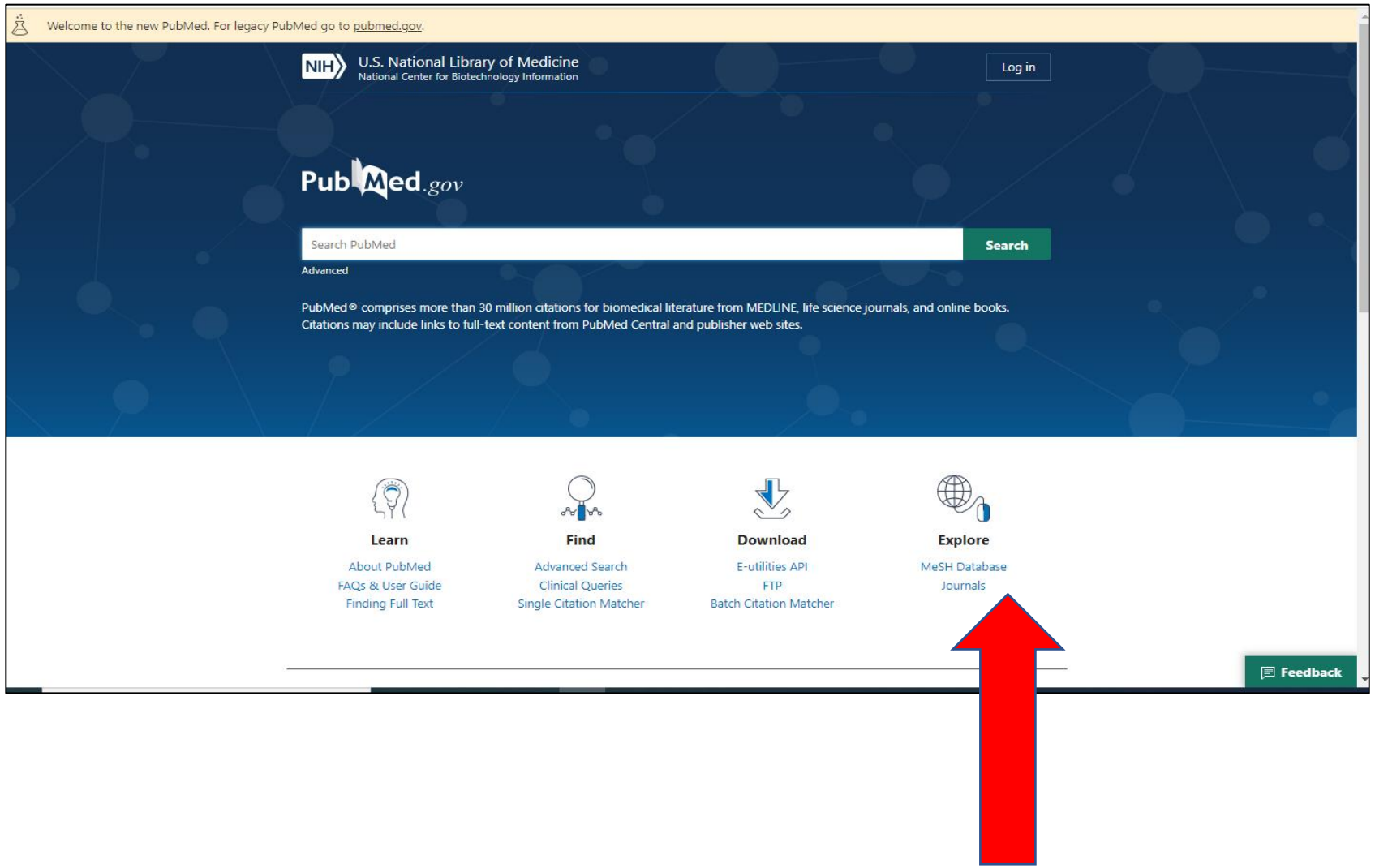


Il database e formato da diversi campi: autore, data, nome del journal, ecc.
Inserendo solo una parola chiave, in questo caso glioblastoma, la ricerca verrà fatta in tutti i campi, la chiamata “ricerca libera”

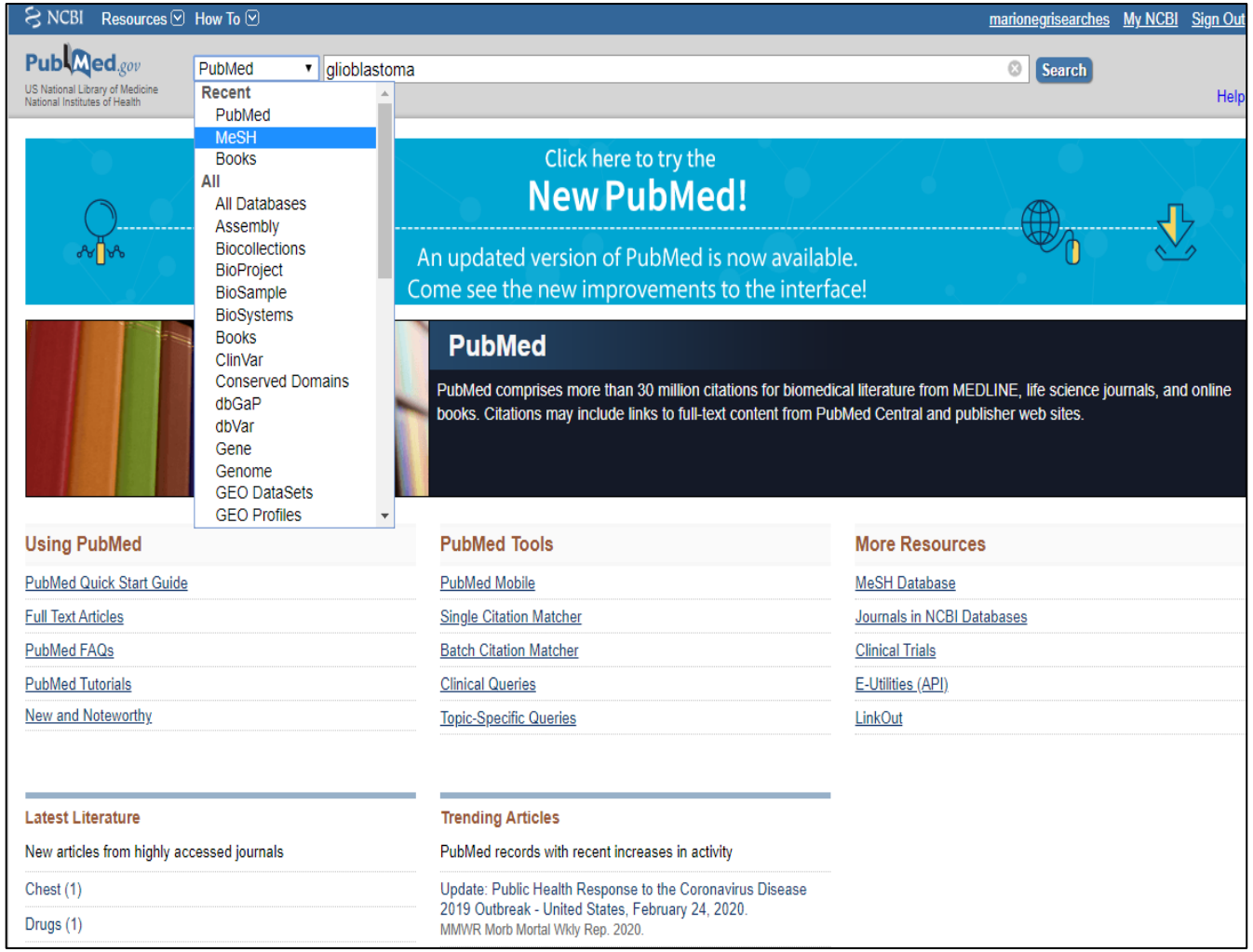
Più di 35.000 risultati e
1.790 pagine da controllare!

La ricerca libera e semplice da fare ma il risultato ritrova un alto numero di records e, nella maggior parte dei casi, poco attinenti alla nostra ricerca.

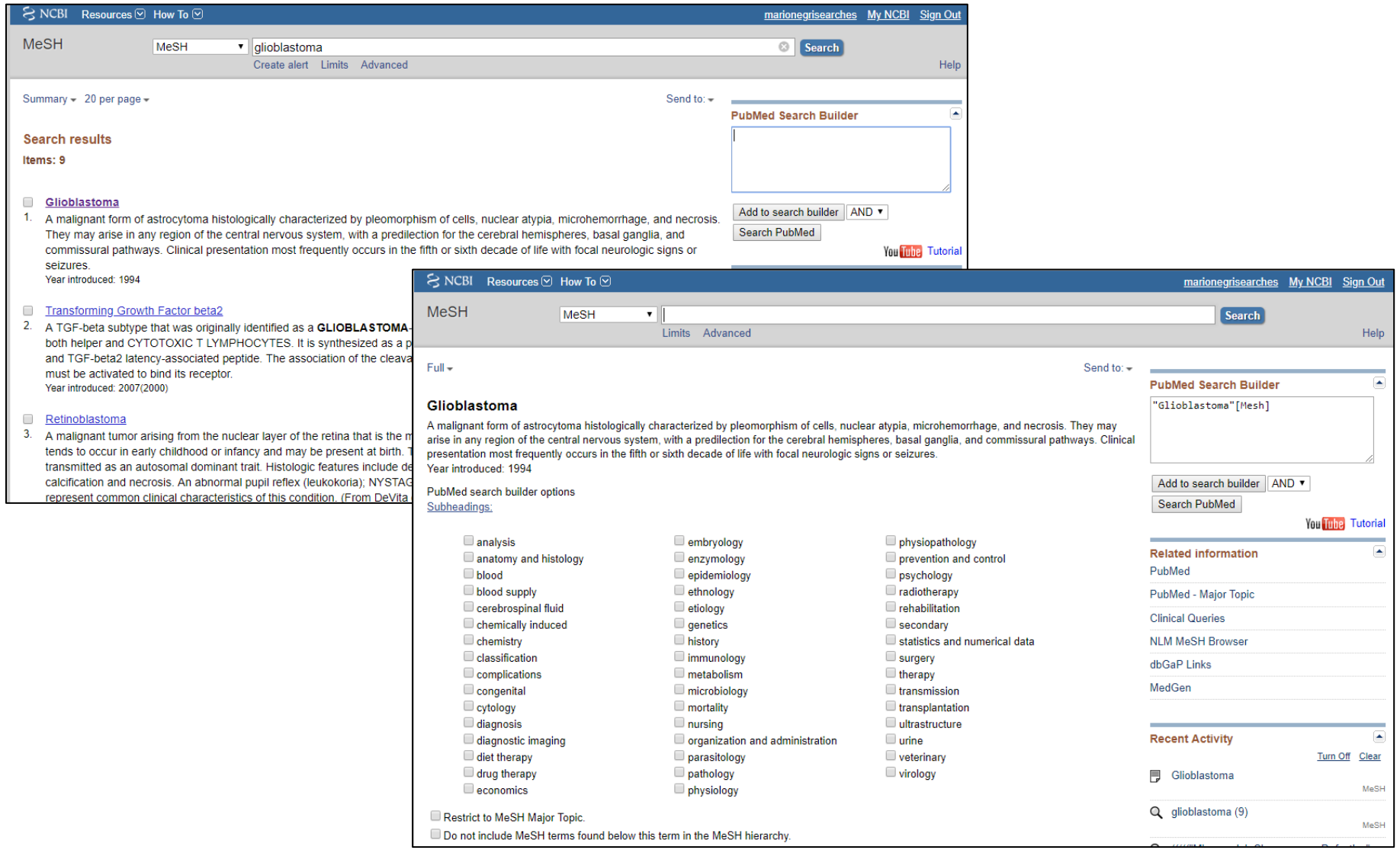
MeSH: Medical Subject Headings



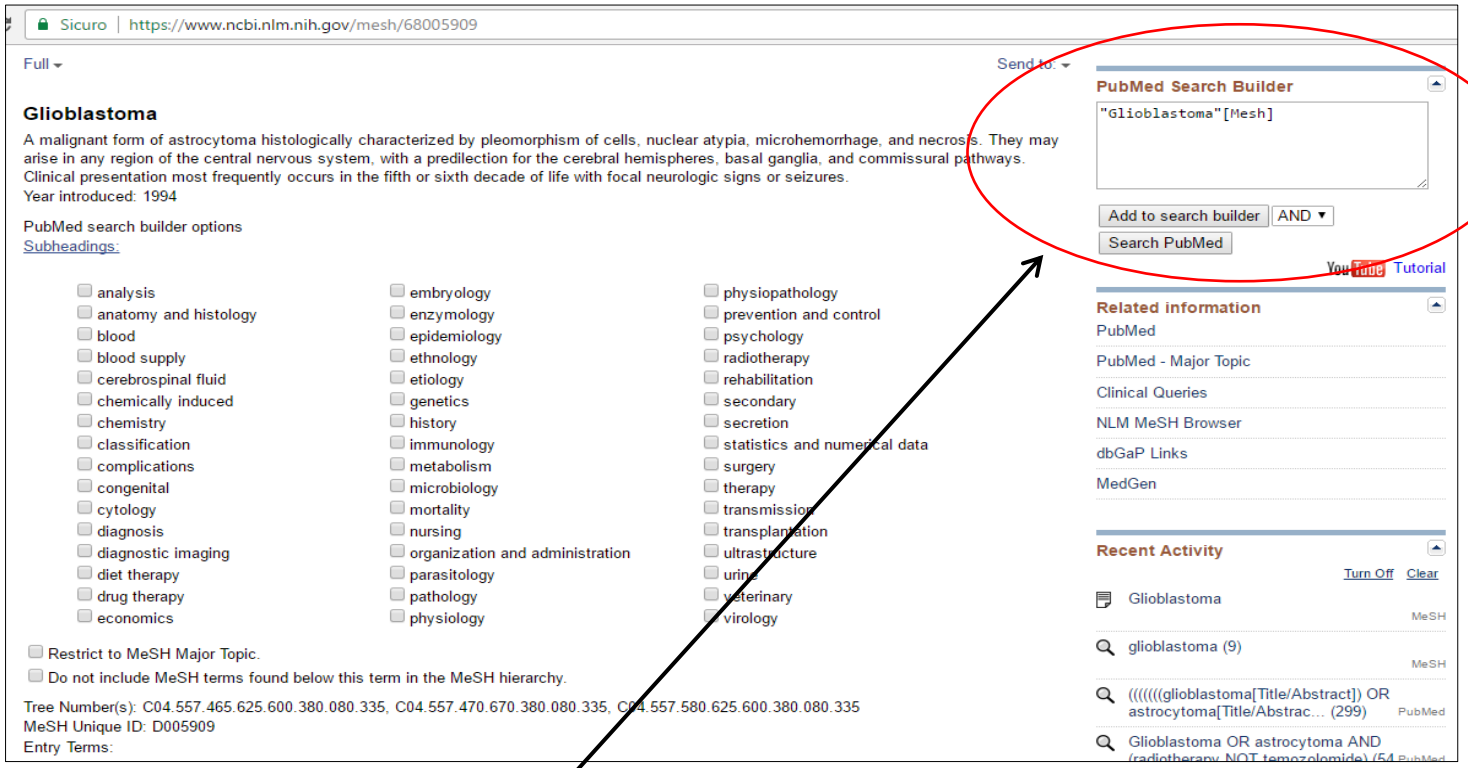
MeSH: Medical Subject Headings



Con il vocabolario controllato possiamo costruire una ricerca più mirata.



Il vocabolario controllato da la possibilità di scegliere
il termine più attinente alla nostra ricerca

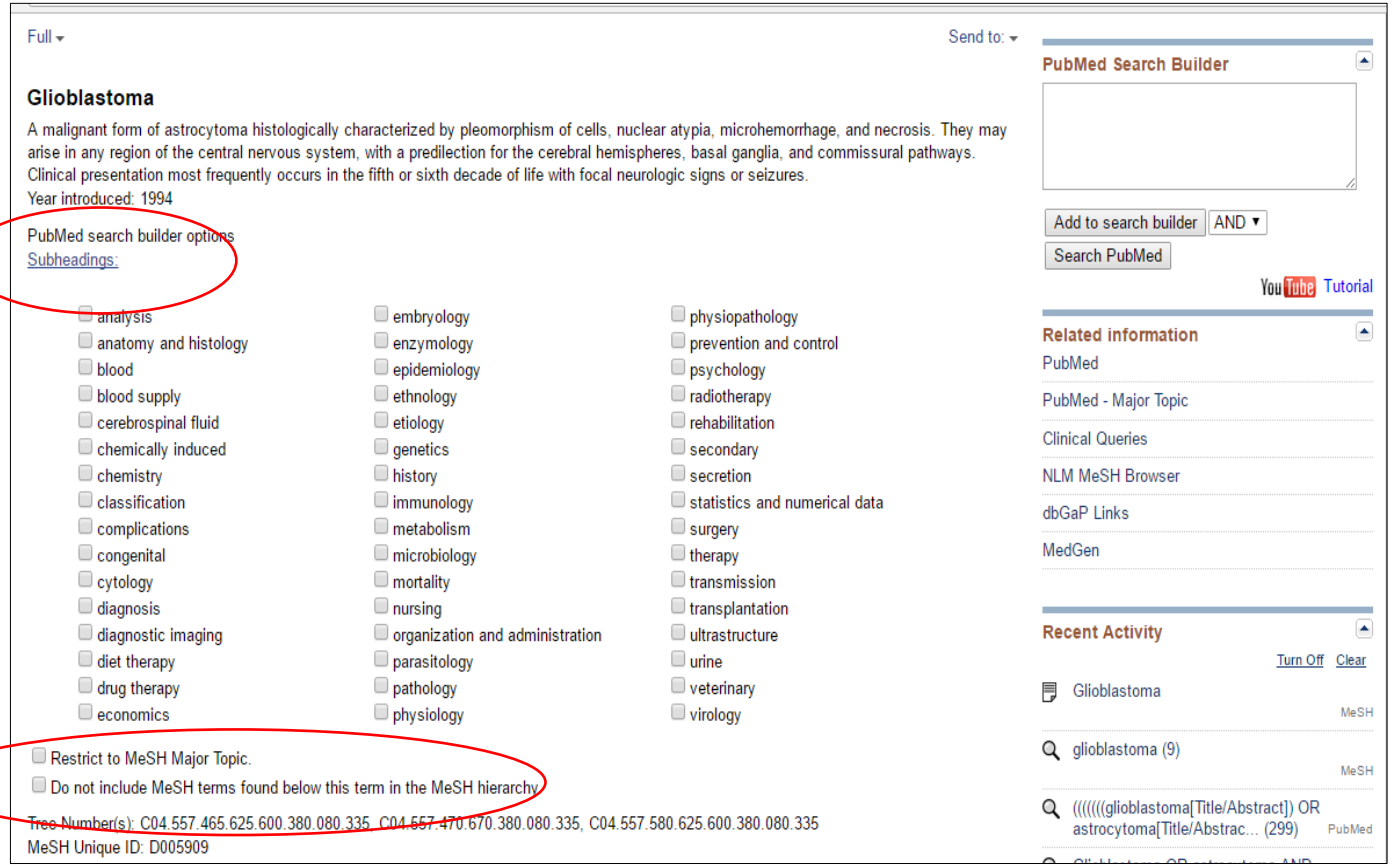


Impostato il termine da cercare se inserisce nella maschera di ricerca

P = soggetti affetti di **glioblastoma** <70anni

I = radioterapia

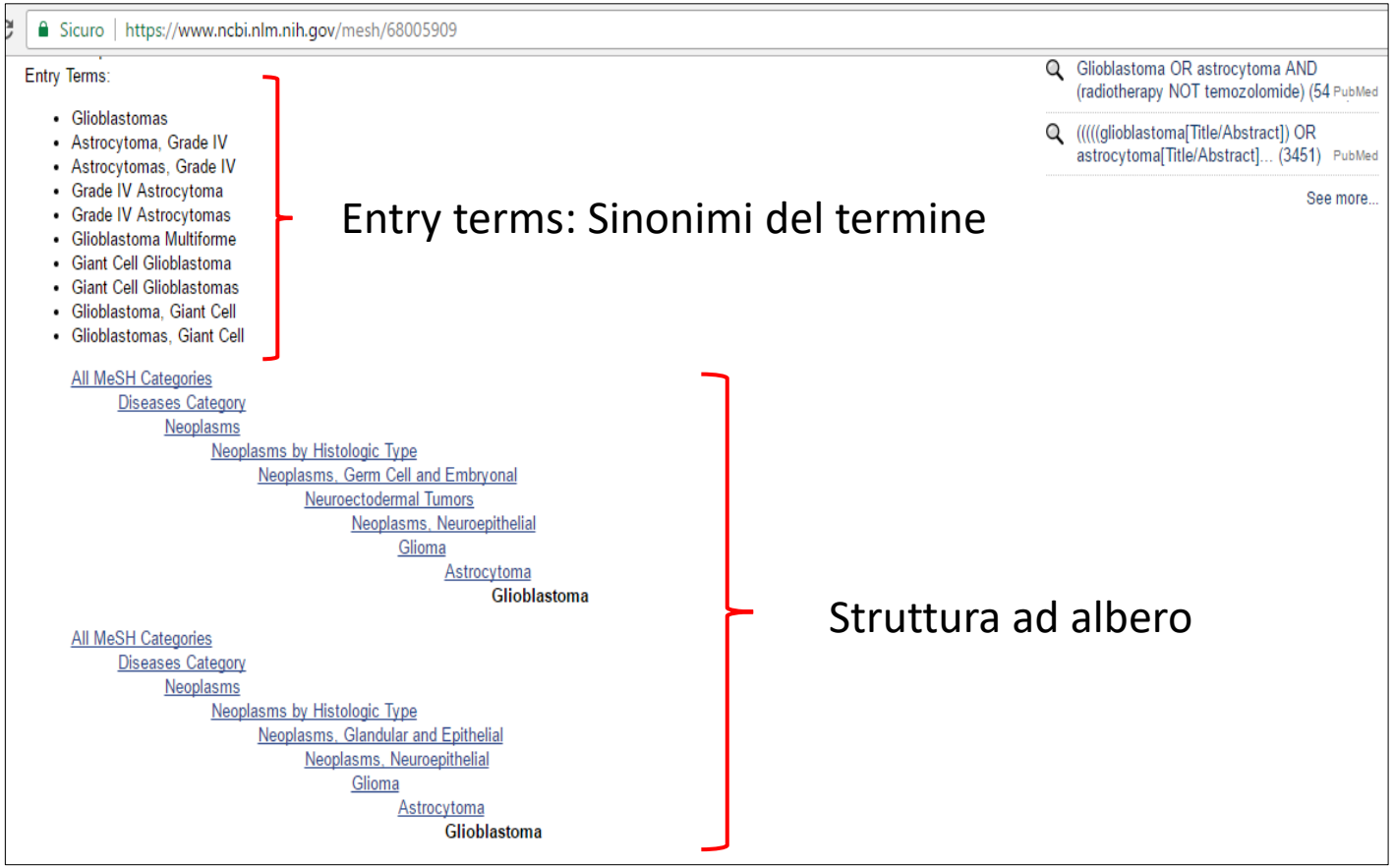
C = temozolamide



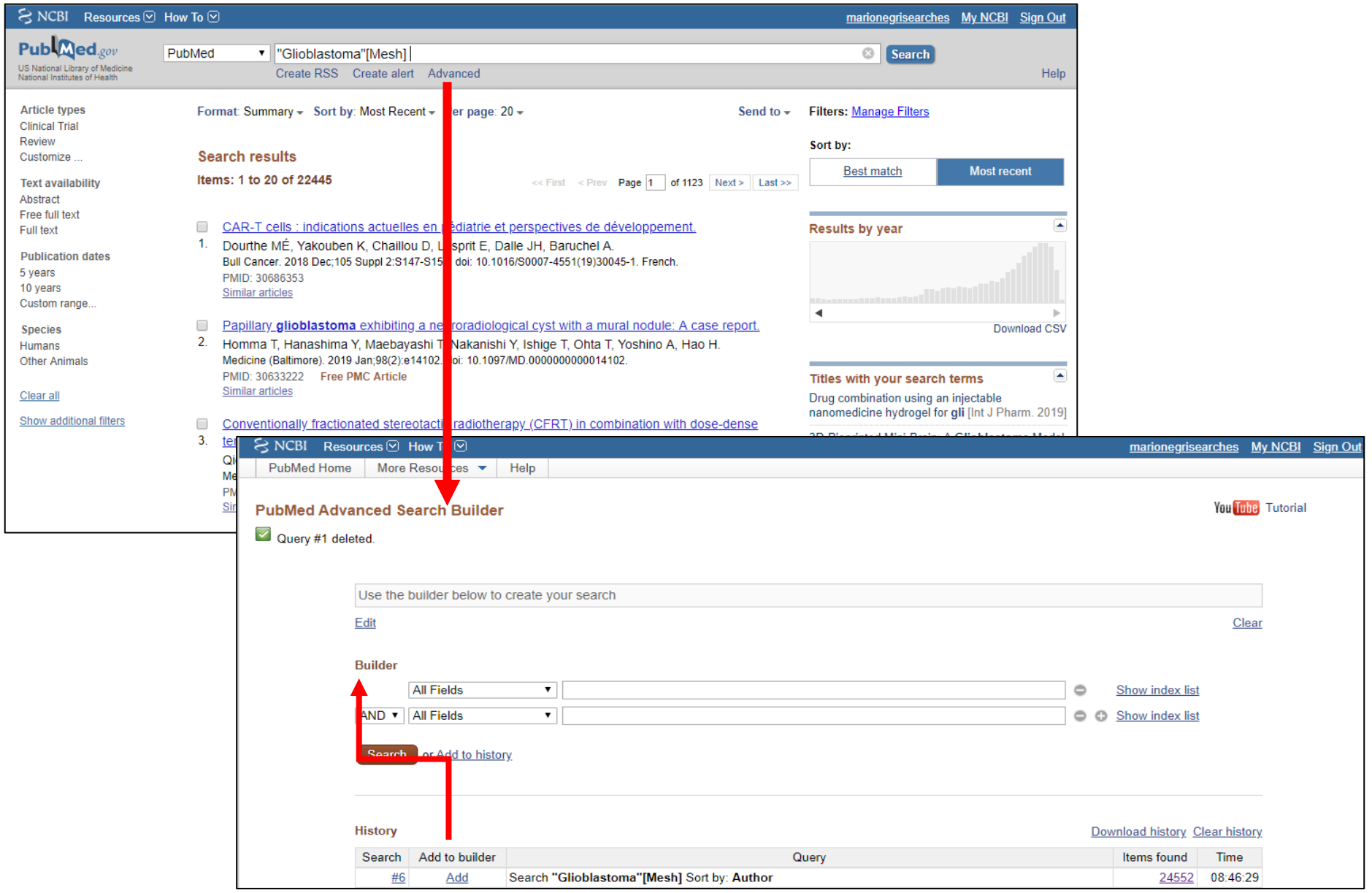
I **subheadings**: restringono il campo ad un aspetto più specifico ed è possibile scegliere più di uno.

Restrict to MeSH Major Topic: con questa opzione i risultati ottenuti ricadranno sul termine MeSH cercato.

Do not include MeSH terms found below this term in the MeSH hierarchy: esplodere o no il termine, I risultati non includeranno i termini al di sotto della nostra parola chiave nella struttura ad albero.

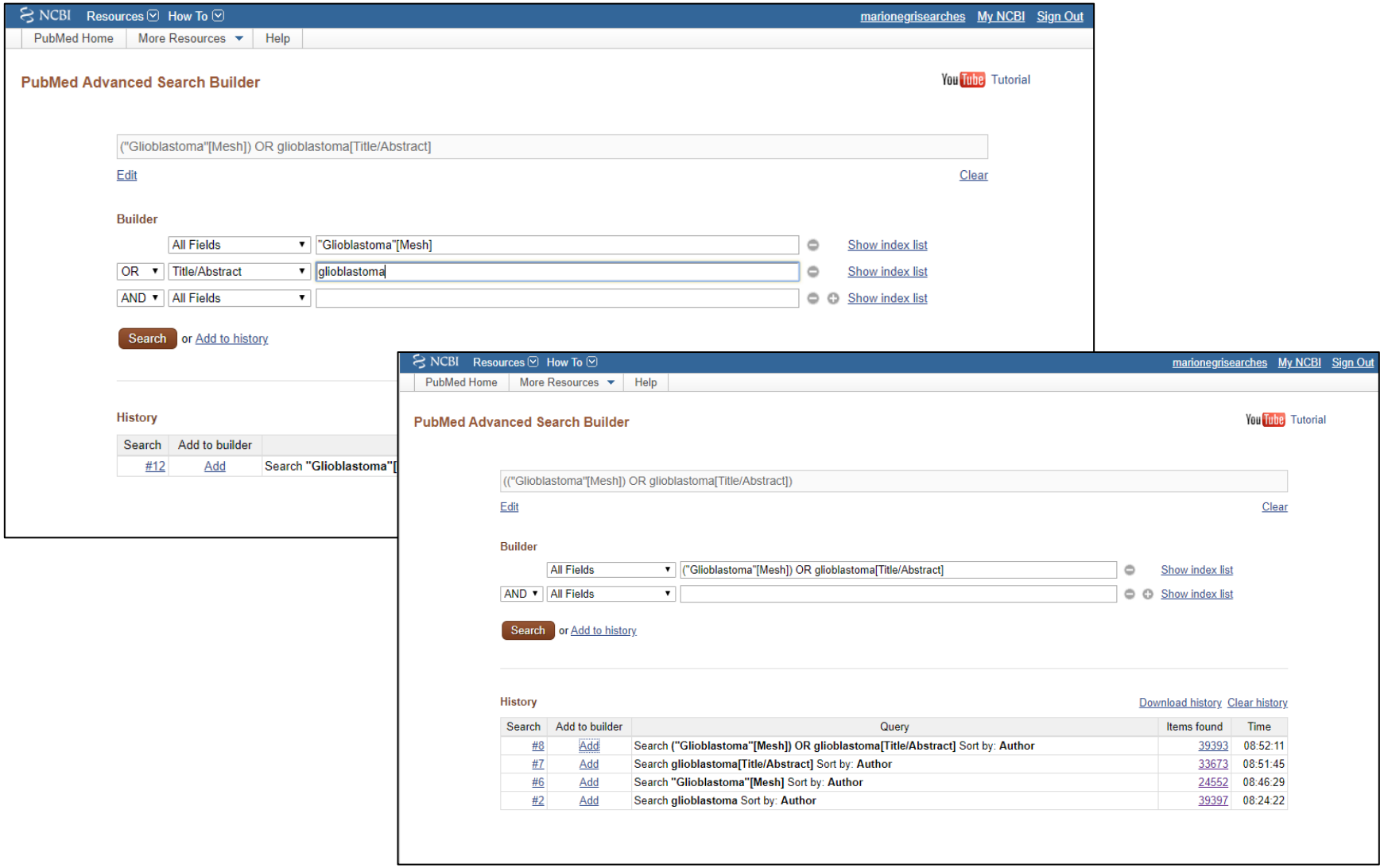


Struttura ad albero: qui si vede a che punto dell'albero è il nostro termine di interesse

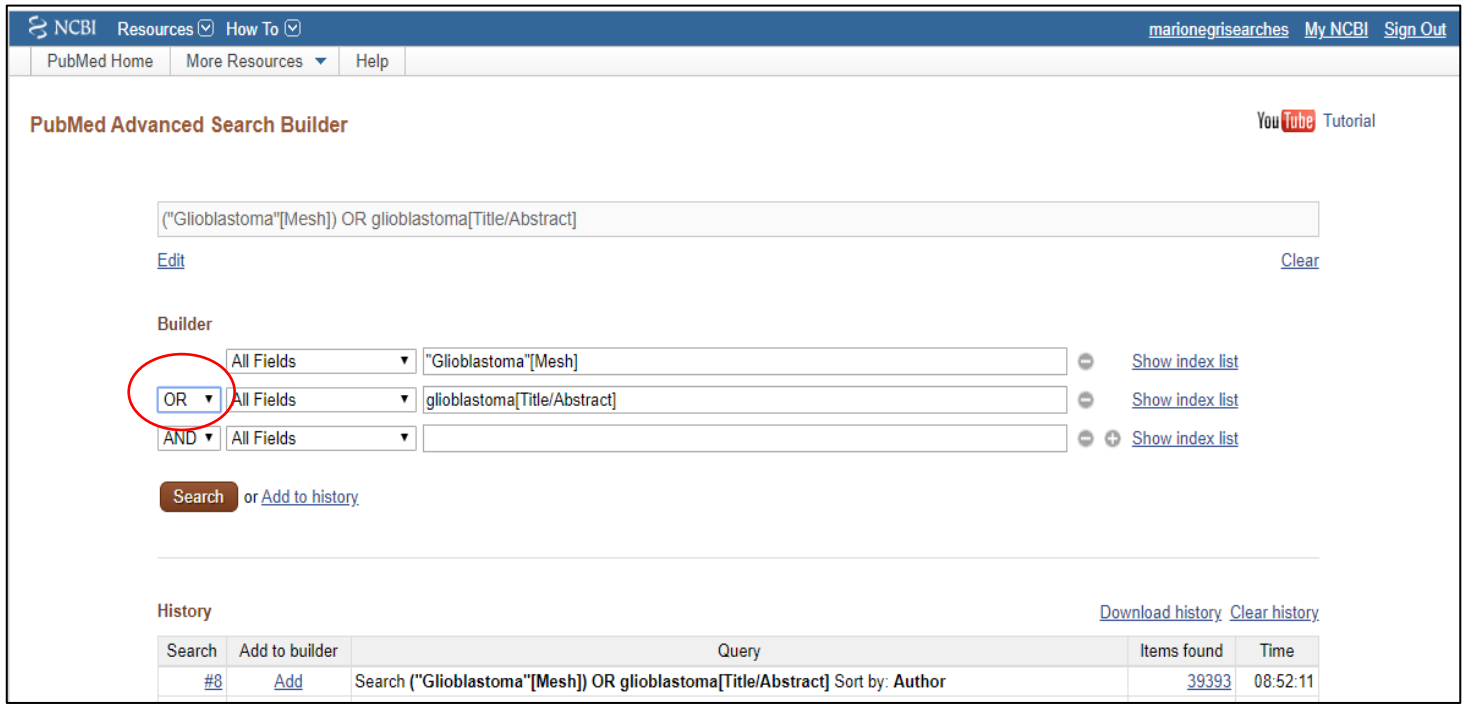


Cliccando su **Advanced** se accede alla pagina che ci permette di costruire una strategia di ricerca.

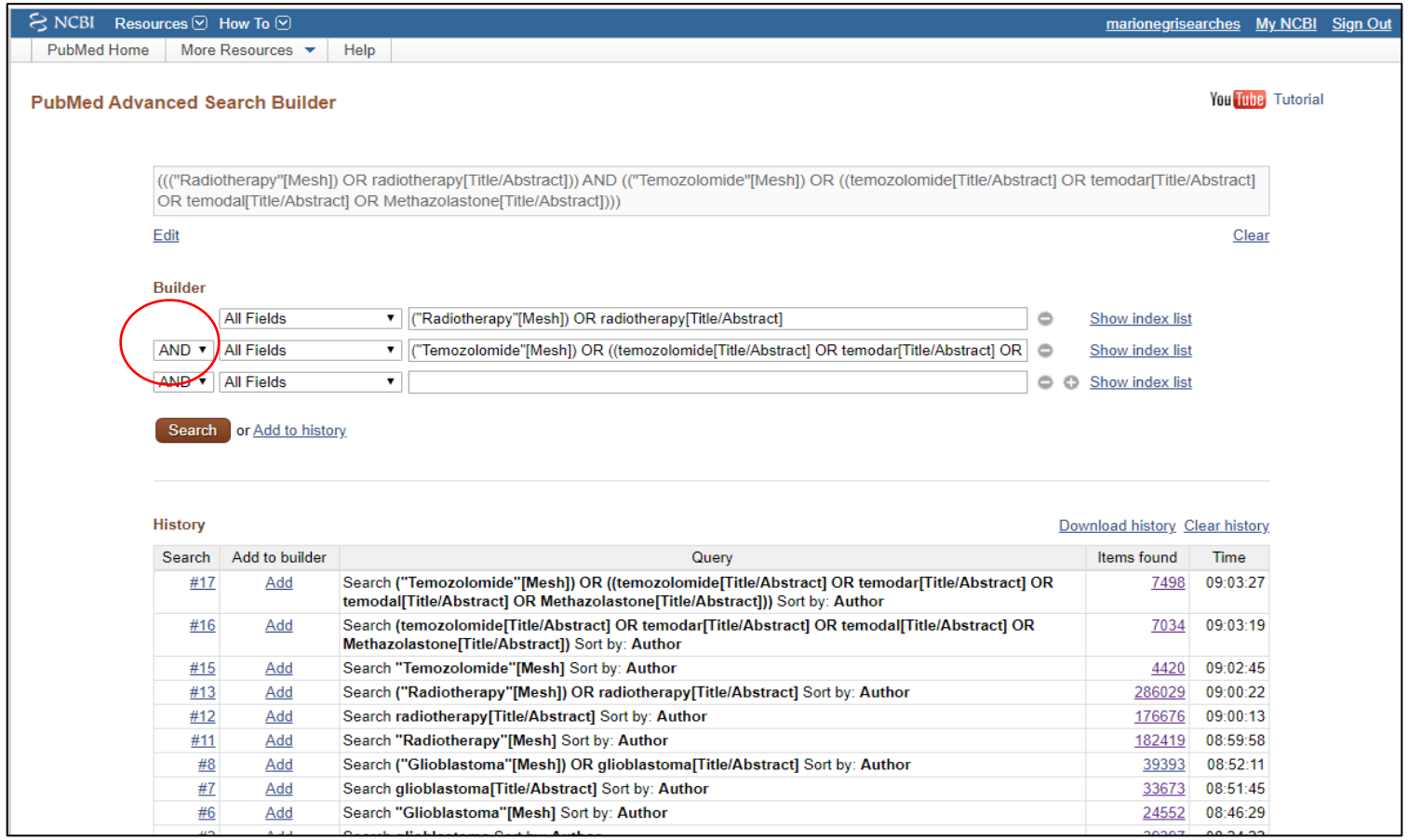
Operatori booleani



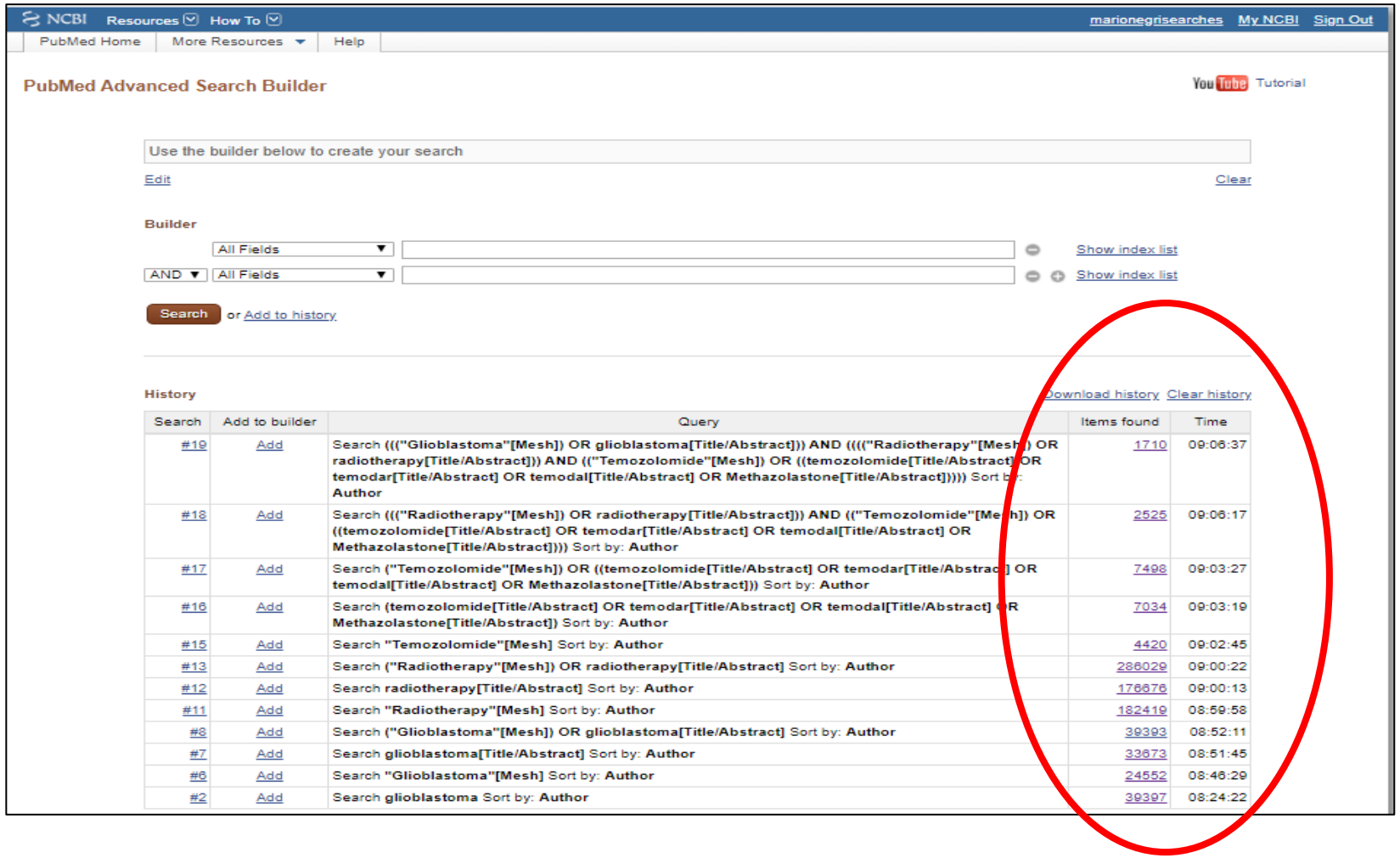
Utilizzando gli operatori logici: OR – AND – NOT
si può stabilire una relazione tra i termini da ricercare.



Con **OR** il database ricercherà i documenti che contengano la parola glioblastoma come termine MeSH o nei titoli e abstract.

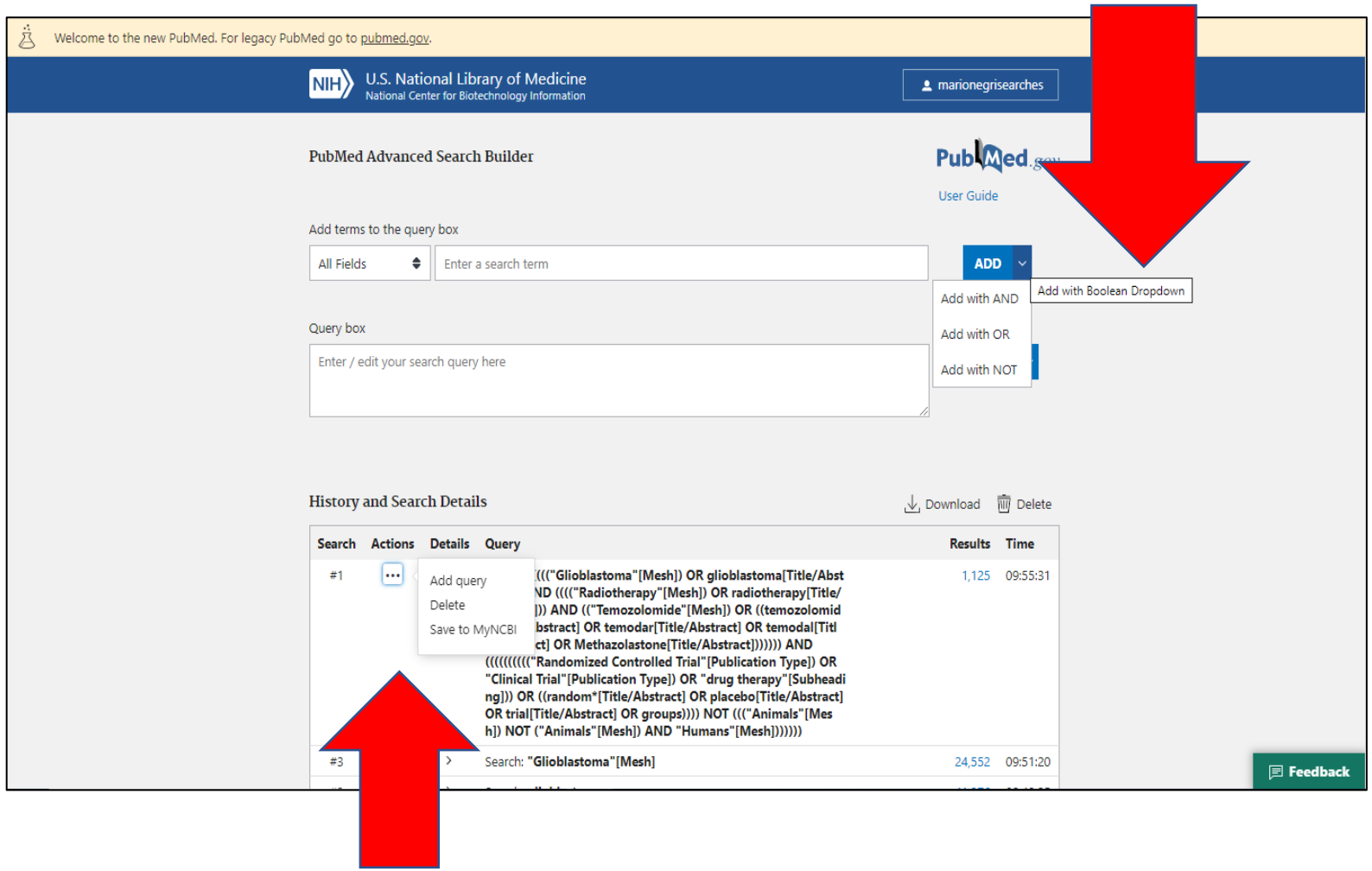


Con **AND** il database ricercherà i documenti che contengano le parole radiotherapy e temozolomide contemporaneamente.



Con una ricerca più elaborata
Il numero dei risultati diminuiscono


Click here to try the
New PubMed!
An updated version of PubMed is now available.
Come see the new improvements to the interface!


Welcome to the new PubMed. For legacy PubMed go to pubmed.gov.
NIH U.S. National Library of Medicine
National Center for Biotechnology Information
marionegrisearches
PubMed Advanced Search Builder
PubMed.gov
User Guide
Add terms to the query box
All Fields
Enter a search term
ADD
Add with Boolean Dropdown
Add with AND
Add with OR
Add with NOT
Query box
Enter / edit your search query here
History and Search Details
Download
Delete
Search Actions Details Query Results Time
#1
Add query
Delete
Save to MyNCBI
(((("Glioblastoma"[Mesh]) OR glioblastoma[Title/Abst
ND ((((("Radiotherapy"[Mesh]) OR radiotherapy[Title/
])) AND (("Temozolomide"[Mesh]) OR ((temozolomid
bstract] OR temodar[Title/Abstract] OR temodal[Titl
ct] OR Methazolastone[Title/Abstract])))))) AND
((((((((("Randomized Controlled Trial"[Publication Type]) OR
"Clinical Trial"[Publication Type]) OR "drug therapy"[Subheadi
ng])) OR ((random*[Title/Abstract] OR placebo[Title/Abstract]
OR trial[Title/Abstract] OR groups)))) NOT ((("Animals"[Mes
h]) NOT ("Animals"[Mesh]) AND "Humans"[Mesh])))))
1,125 09:55:31
#3
Search: "Glioblastoma"[Mesh]
24,552 09:51:20
Feedback

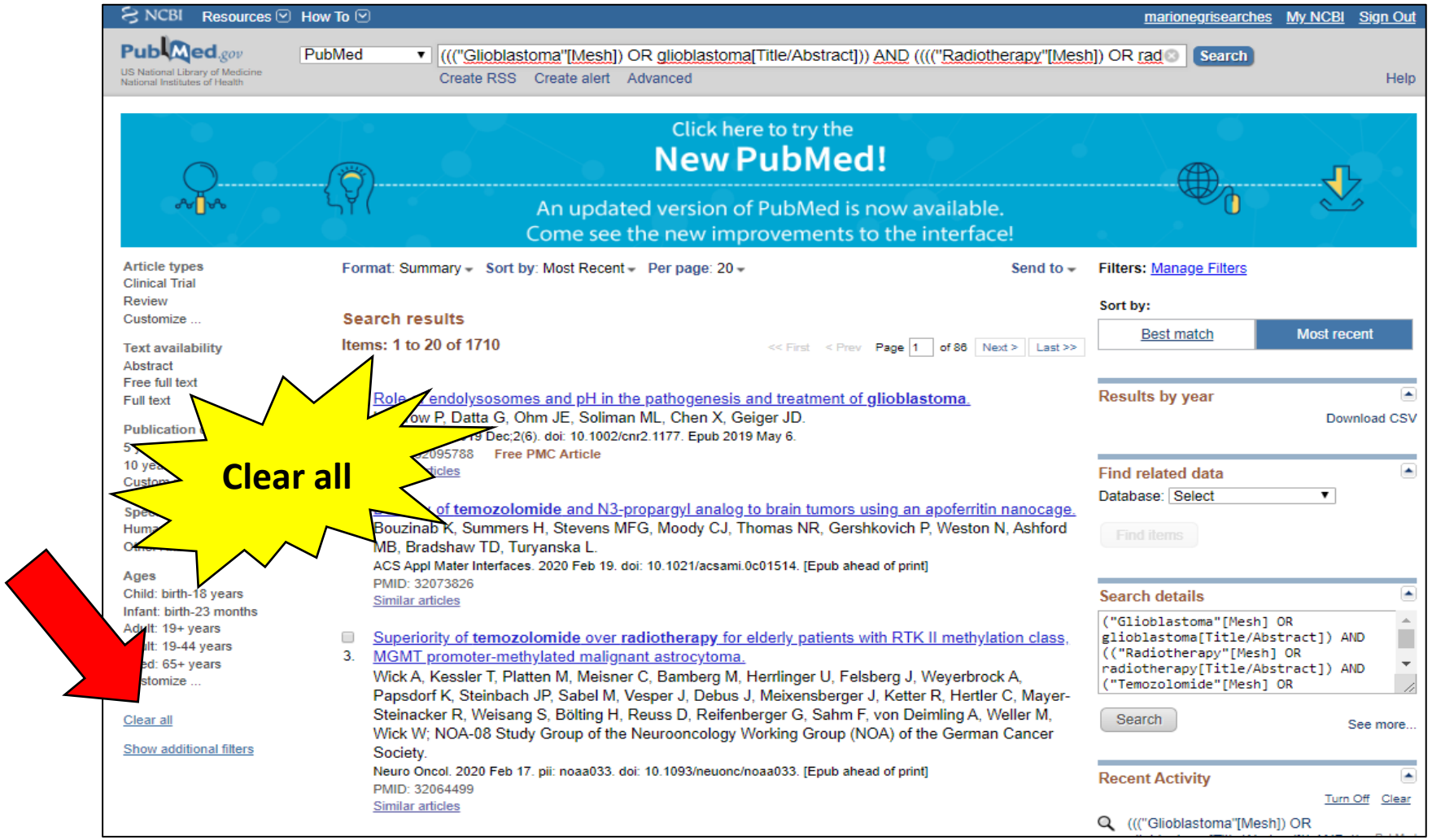
Precisione nella ricerca

P = soggetti affetti di glioblastoma **<70anni**

I = radioterapia

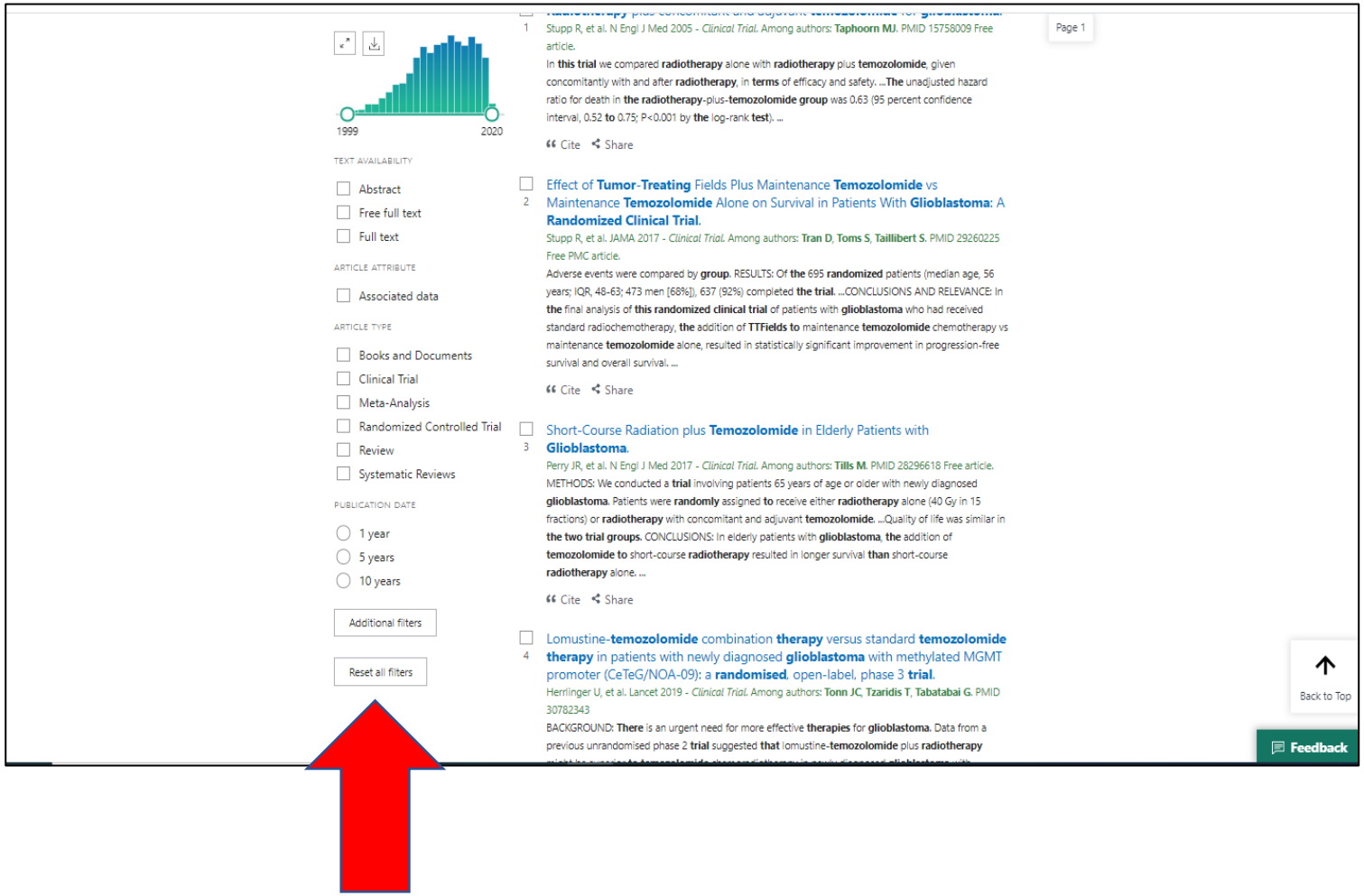
C = temozolamide

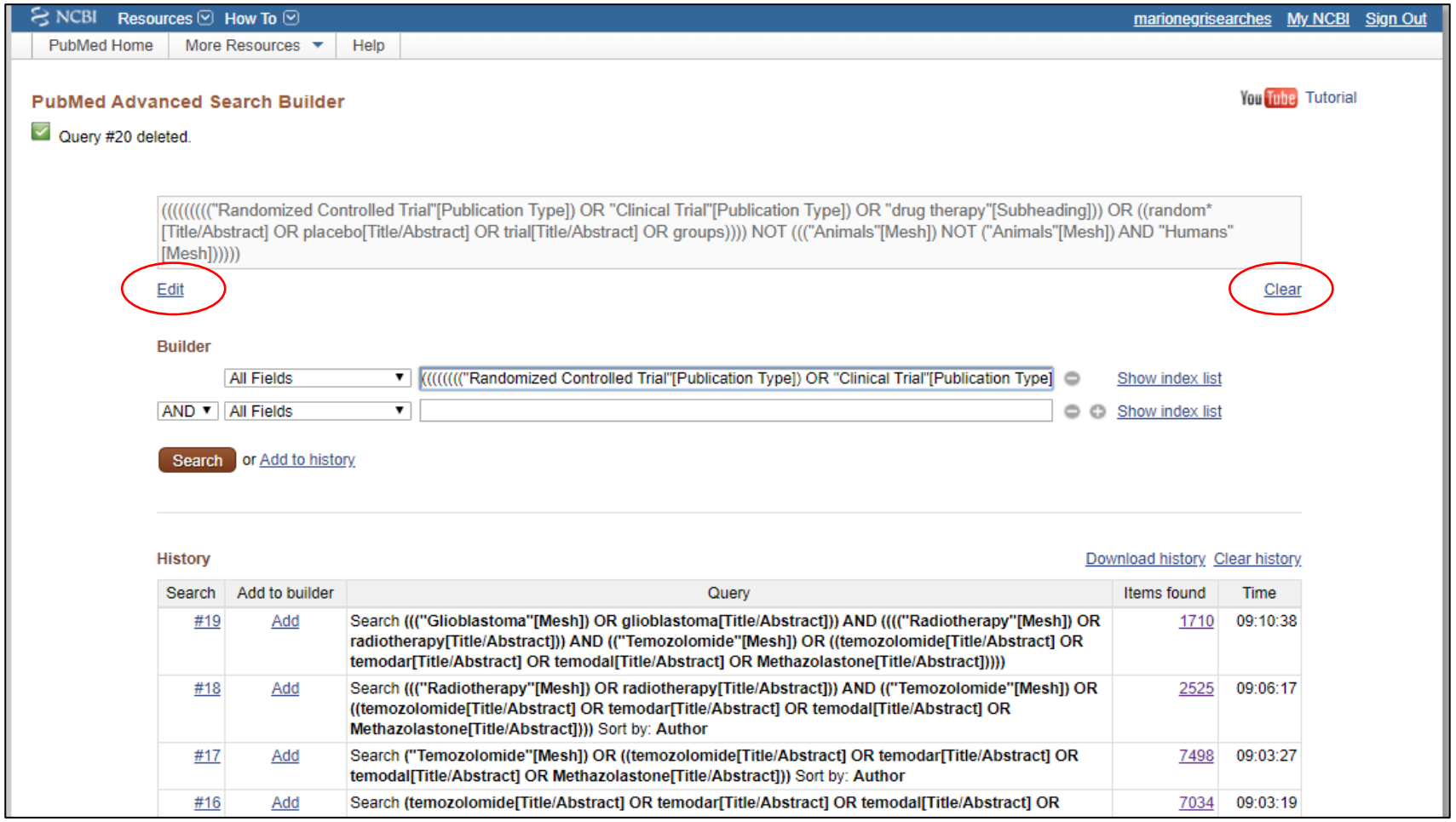
I filtri (limits) delimitano la nostra ricerca



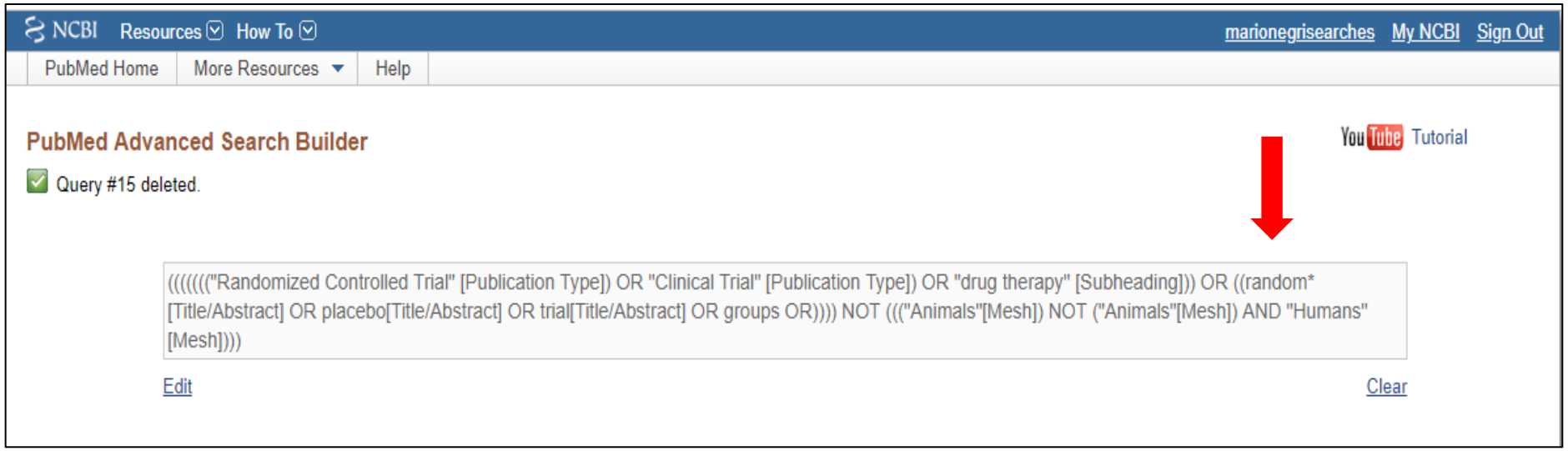
E molto importante ricordarci che i limiti impostati vengono mantenuti in memoria nelle ricerche successive, quindi una volta finita la ricerca bisogna disattivarli.


Click here to try the
New PubMed!
An updated version of PubMed is now available.
Come see the new improvements to the interface!


1999
2020
TEXT AVAILABILITY
Abstract
Free full text
Full text
ARTICLE ATTRIBUTE
Associated data
ARTICLE TYPE
Books and Documents
Clinical Trial
Meta-Analysis
Randomized Controlled Trial
Review
Systematic Reviews
PUBLICATION DATE
1 year
5 years
10 years
Additional filters
Reset all filters
Page 1
1 Stupp R, et al. N Engl J Med 2005 - Clinical Trial. Among authors: Taphoorn MJ. PMID 15758009 Free article.
In this trial we compared radiotherapy alone with radiotherapy plus temozolomide, given concomitantly with and after radiotherapy, in terms of efficacy and safety. ...The unadjusted hazard ratio for death in the radiotherapy-plus-temozolomide group was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001 by the log-rank test). ...
Cite Share
2 Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial.
Stupp R, et al. JAMA 2017 - Clinical Trial. Among authors: Tran D, Toms S, Taillibert S. PMID 29260225 Free PMC article.
Adverse events were compared by group. RESULTS: Of the 695 randomized patients (median age, 56 years; IQR, 48-63; 473 men [68%]), 637 (92%) completed the trial. ...CONCLUSIONS AND RELEVANCE: In the final analysis of this randomized clinical trial of patients with glioblastoma who had received standard radiochemotherapy, the addition of TTFields to maintenance temozolomide chemotherapy vs maintenance temozolomide alone, resulted in statistically significant improvement in progression-free survival and overall survival. ...
Cite Share
3 Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma.
Perry JR, et al. N Engl J Med 2017 - Clinical Trial. Among authors: Tills M. PMID 28296618 Free article.
METHODS: We conducted a trial involving patients 65 years of age or older with newly diagnosed glioblastoma. Patients were randomly assigned to receive either radiotherapy alone (40 Gy in 15 fractions) or radiotherapy with concomitant and adjuvant temozolomide. ...Quality of life was similar in the two trial groups. CONCLUSIONS: In elderly patients with glioblastoma, the addition of temozolomide to short-course radiotherapy resulted in longer survival than short-course radiotherapy alone. ...
Cite Share
4 Lomustine-temozolomide combination therapy versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with methylated MGMT promoter (CeTeG/NOA-09): a randomised, open-label, phase 3 trial.
Herrlinger U, et al. Lancet 2019 - Clinical Trial. Among authors: Tonn JC, Tzaridis T, Tabatabai G. PMID 30782343
BACKGROUND: There is an urgent need for more effective therapies for glioblastoma. Data from a previous unrandomised phase 2 trial suggested that lomustine-temozolomide plus radiotherapy
Back to Top
Feedback



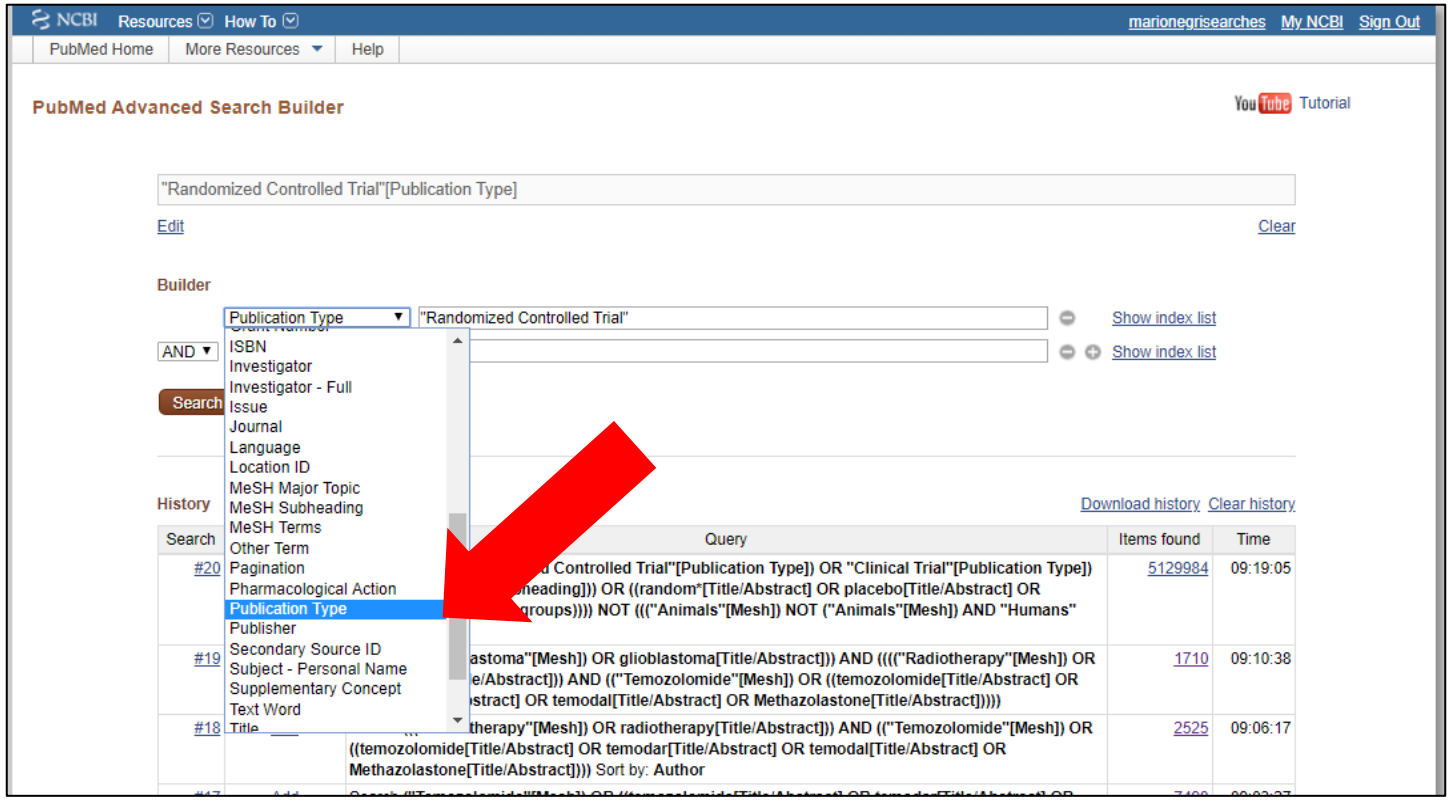
Edit e **clear** permettono correggere e cancellare velocemente la stringa di ricerca



Troncare le parole con l'asterisco (*): verranno ricercate tutte le varianti che iniziano con la stessa radice.
random* (randomized, randomizes, randomizing, randomization, randomised, randomises, randomising and randomisation)

Le **parentesi** stabiliscono un ordine di priorità nei termini da cercare, in questo caso il database non cercherà gli studi sugli animali e neanche quelli su umani e animali

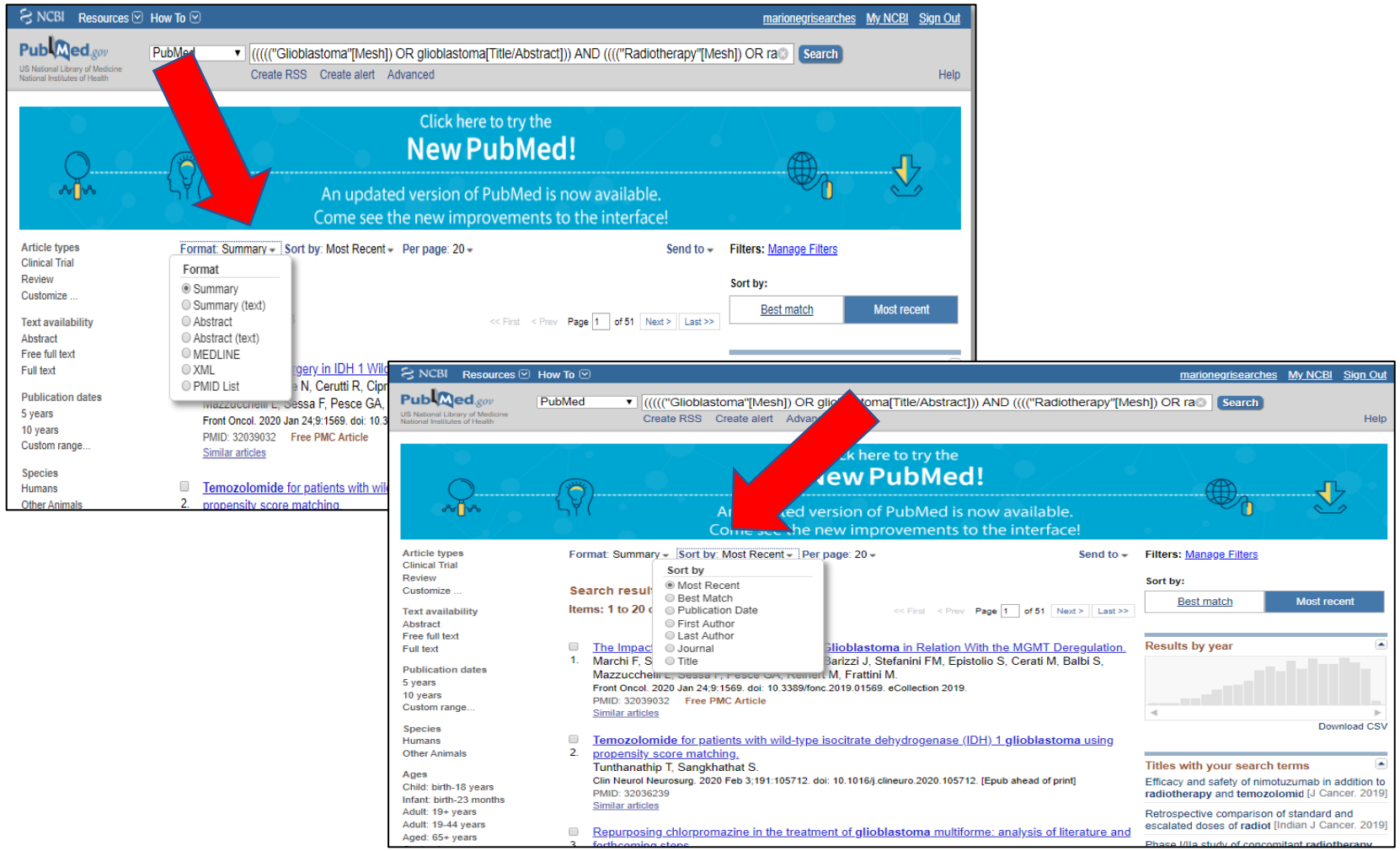
… NOT (("Animals"[Mesh]) NOT ("Animals"[Mesh] AND "Humans"[Mesh]))



"Clinical Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type])

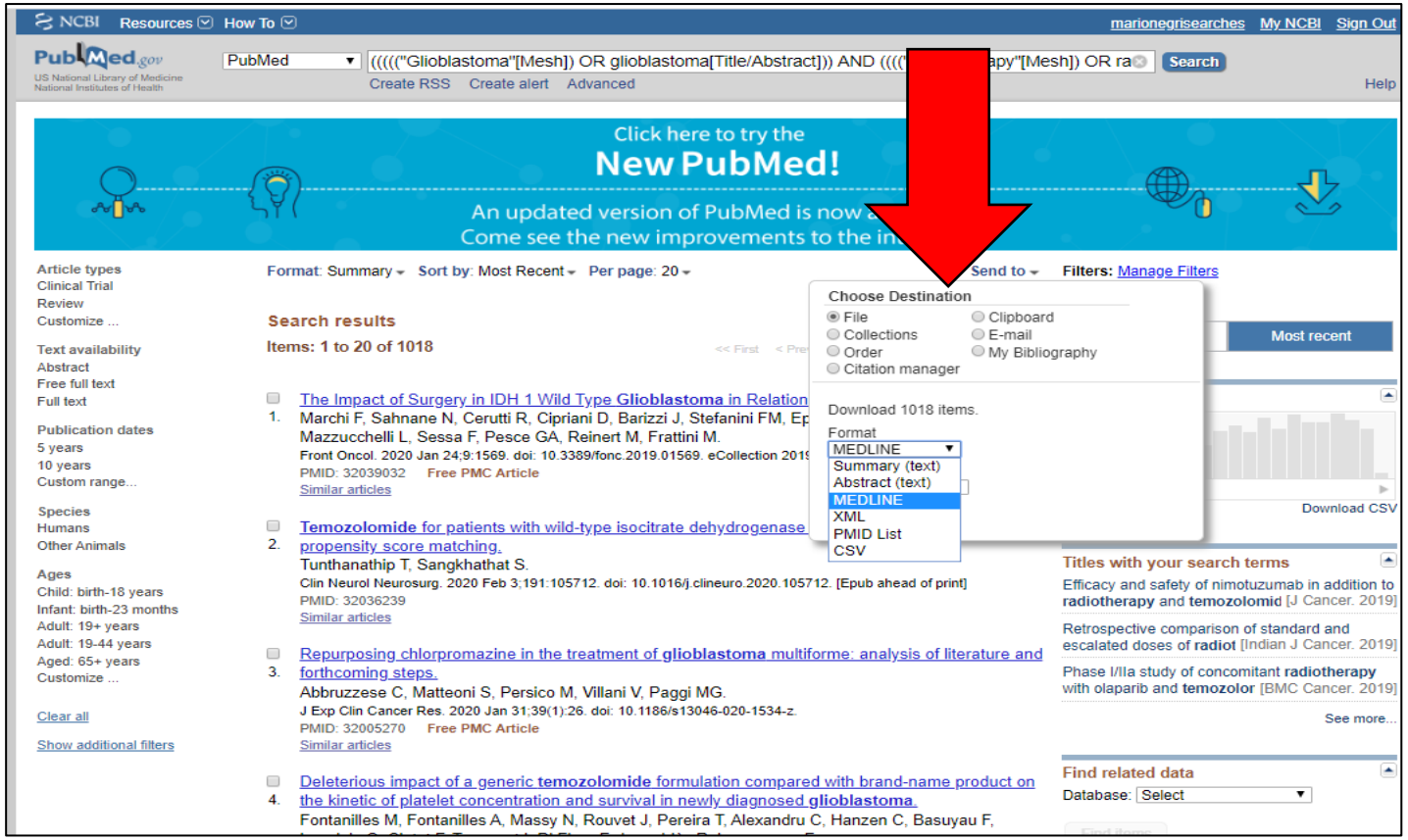
Ricerca per frase: Inserendo più termini nella maschera di ricerca, il database cercherà ogni singolo termine combinandolo con l'operatore AND.
Se invece si vuole trovare un risultato come frase, i termini devono essere racchiusi tra virgolette.

Risultati

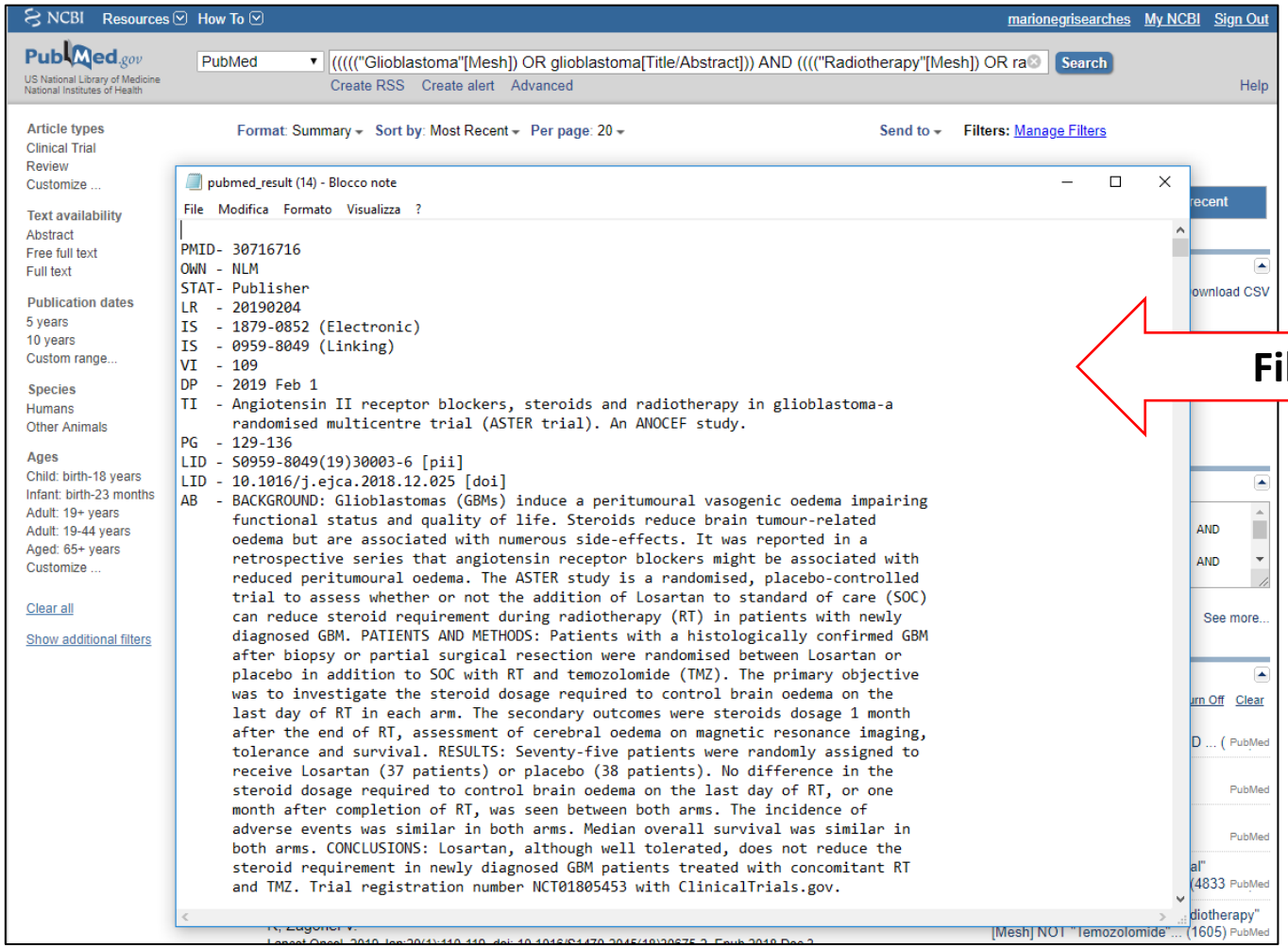


Dalle tendine si può scegliere sia il formato che l'ordine da dare all'elenco dei risultati

Scaricare i risultati

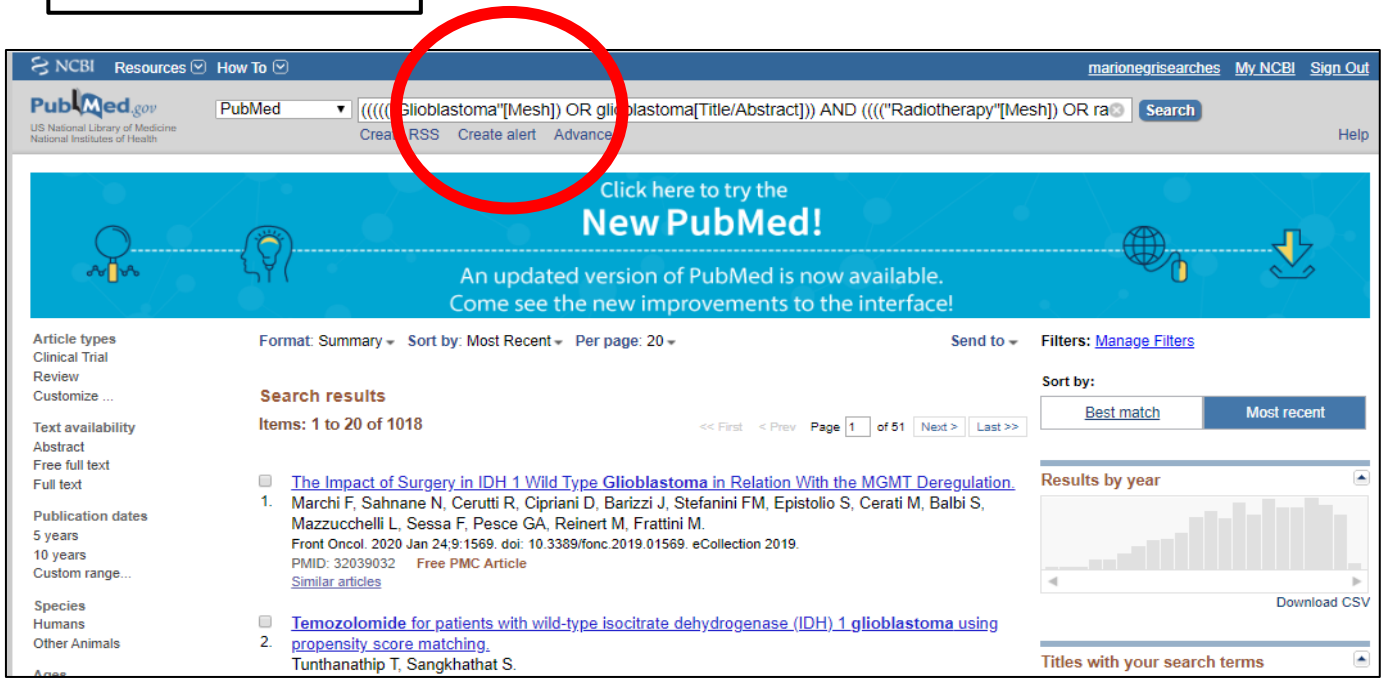


Send to: scegliere la destinazione dell'elenco di risultati che la ricerca ha trovato



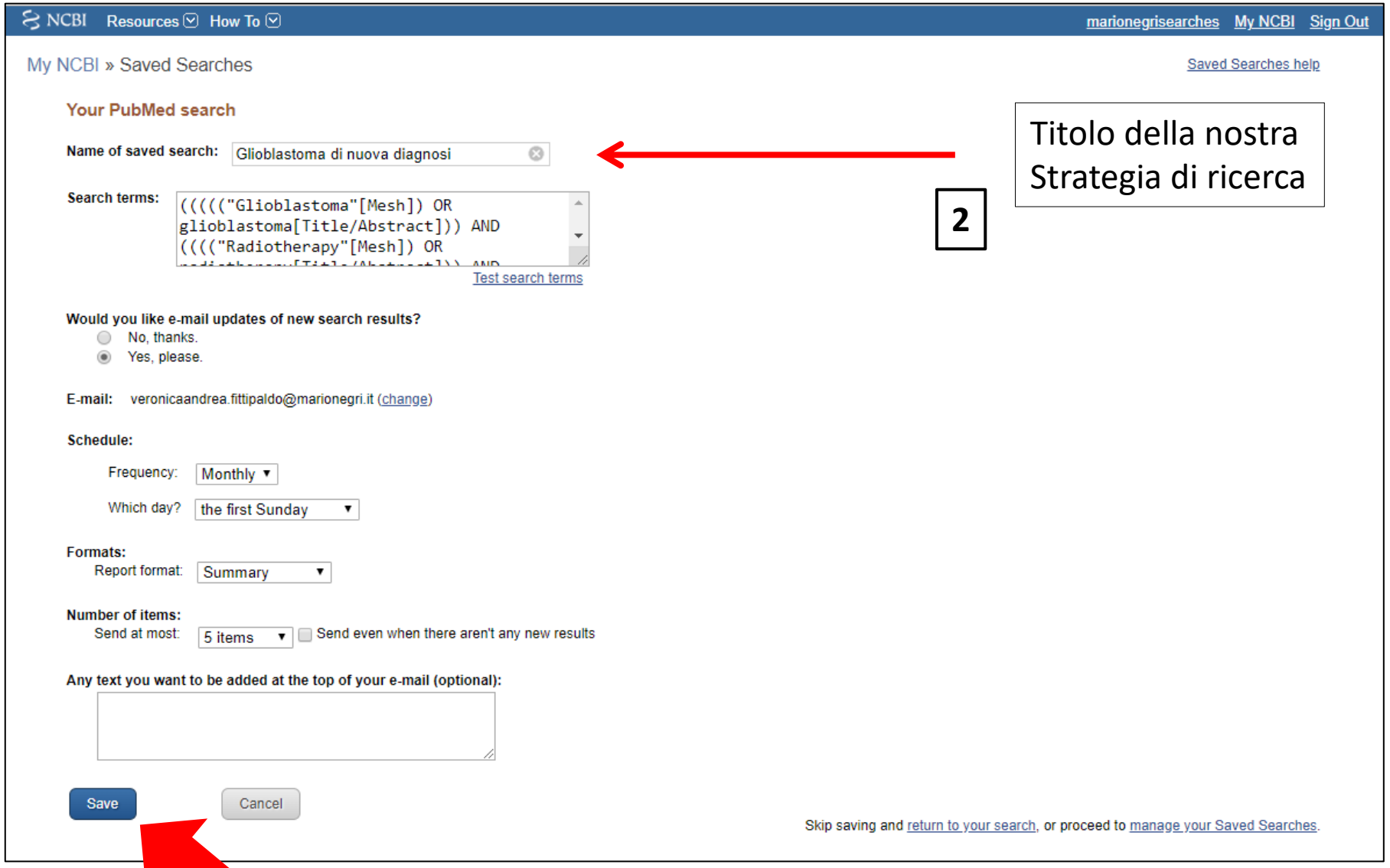
Questo formato di file mi permette di caricarlo in un software che serve alla gestione e condivisione di documenti: **Mendeley e Zotero (gratuiti), Endnote e Refworks (a pagamento)**

Salvare i risultati



1

Create alert: l'elenco dei risultati verranno conservati nell'account Pubmed che abbiamo creato.



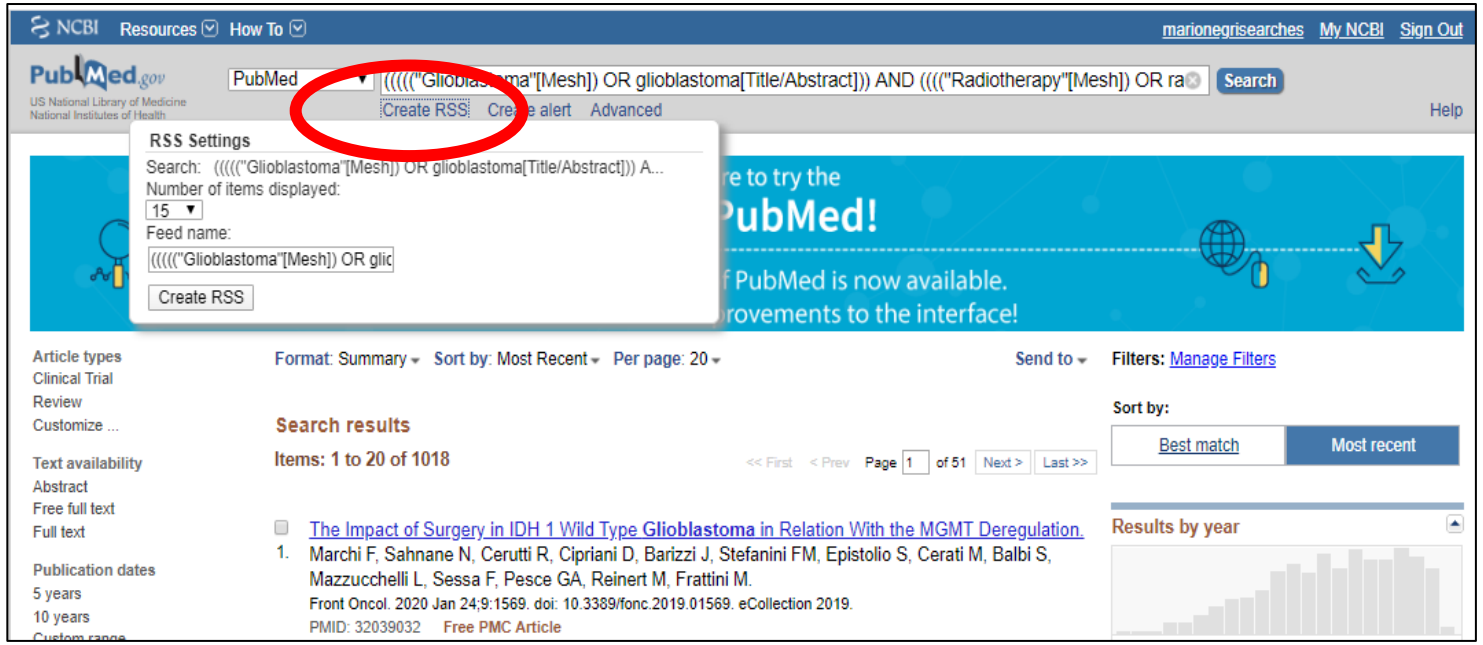
Titolo della nostra Strategia di ricerca

2

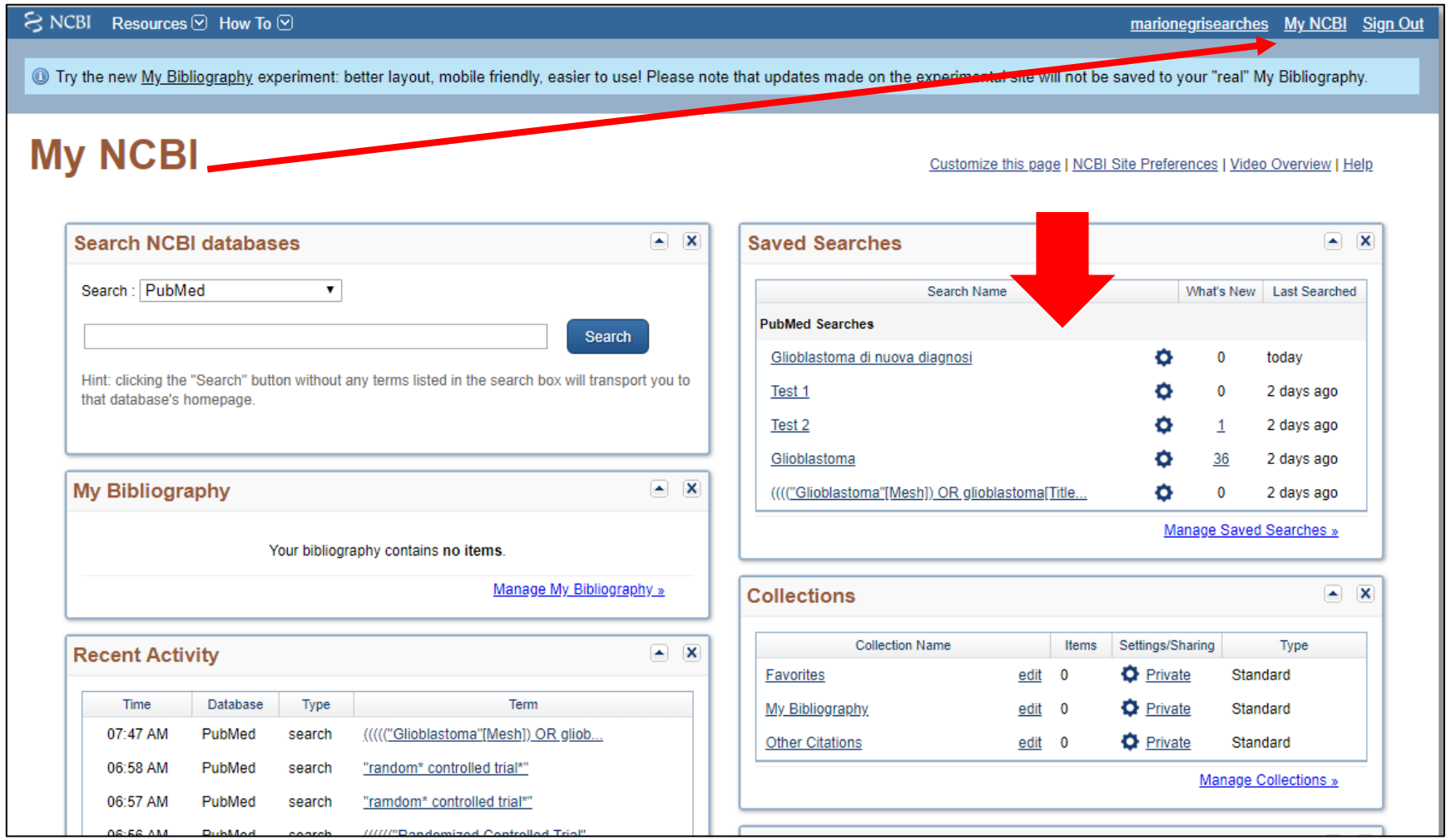
3

Cliccare per salvare

Creare RSS (Really Simple Syndication)

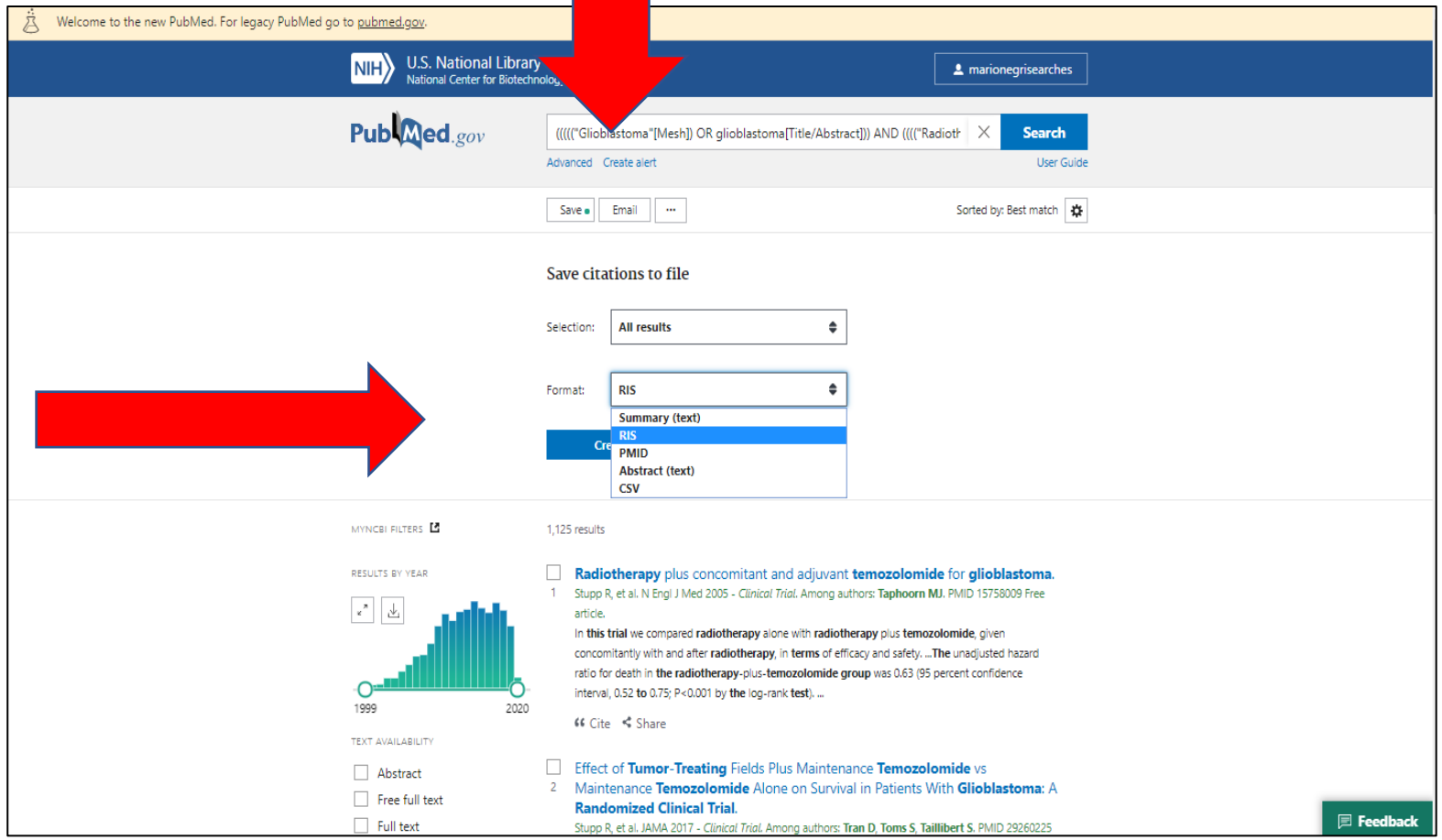


Create RSS: Questa funzione ci permette di ricevere gli aggiornamenti della ricerca.



La ricerca verrà mantenuta nel nostro account per rilanciarla e aggiornare i risultati


Click here to try the
New PubMed!
An updated version of PubMed is now available.
Come see the new improvements to the interface!


Welcome to the new PubMed. For legacy PubMed go to pubmed.gov.
U.S. National Library
National Center for Biotechnology
marionegrisearches
PubMed.gov
((((("Glioblastoma"[Mesh]) OR glioblastoma[Title/Abstract])) AND ((((("Radiotl
Search
Advanced
Create alert
User Guide
Save
Email
Sorted by: Best match
Save citations to file
Selection:
All results
Format:
RIS
Summary (text)
RIS
PMID
Abstract (text)
CSV
MYNCBI FILTERS
1,125 results
RESULTS BY YEAR
1999
2020
TEXT AVAILABILITY
Abstract
Free full text
Full text
Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma.
1
Stupp R, et al. N Engl J Med 2005 - Clinical Trial. Among authors: Taphoorn MJ. PMID 15758009 Free article.
In this trial we compared radiotherapy alone with radiotherapy plus temozolomide, given concomitantly with and after radiotherapy, in terms of efficacy and safety. ...The unadjusted hazard ratio for death in the radiotherapy-plus-temozolomide group was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001 by the log-rank test). ...
Cite
Share
Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial.
2
Stupp R, et al. JAMA 2017 - Clinical Trial. Among authors: Tran D, Toms S, Taillibert S. PMID 29260225
Feedback

GRAZIE PER L’ATTENZIONE

NEGRAR DI VALPOLICELLA
11-12 FEBBRAIO 2022

Centro Formazione IRCCS "Sacro Cuore-Don Calabria"

11 Febbraio 2022

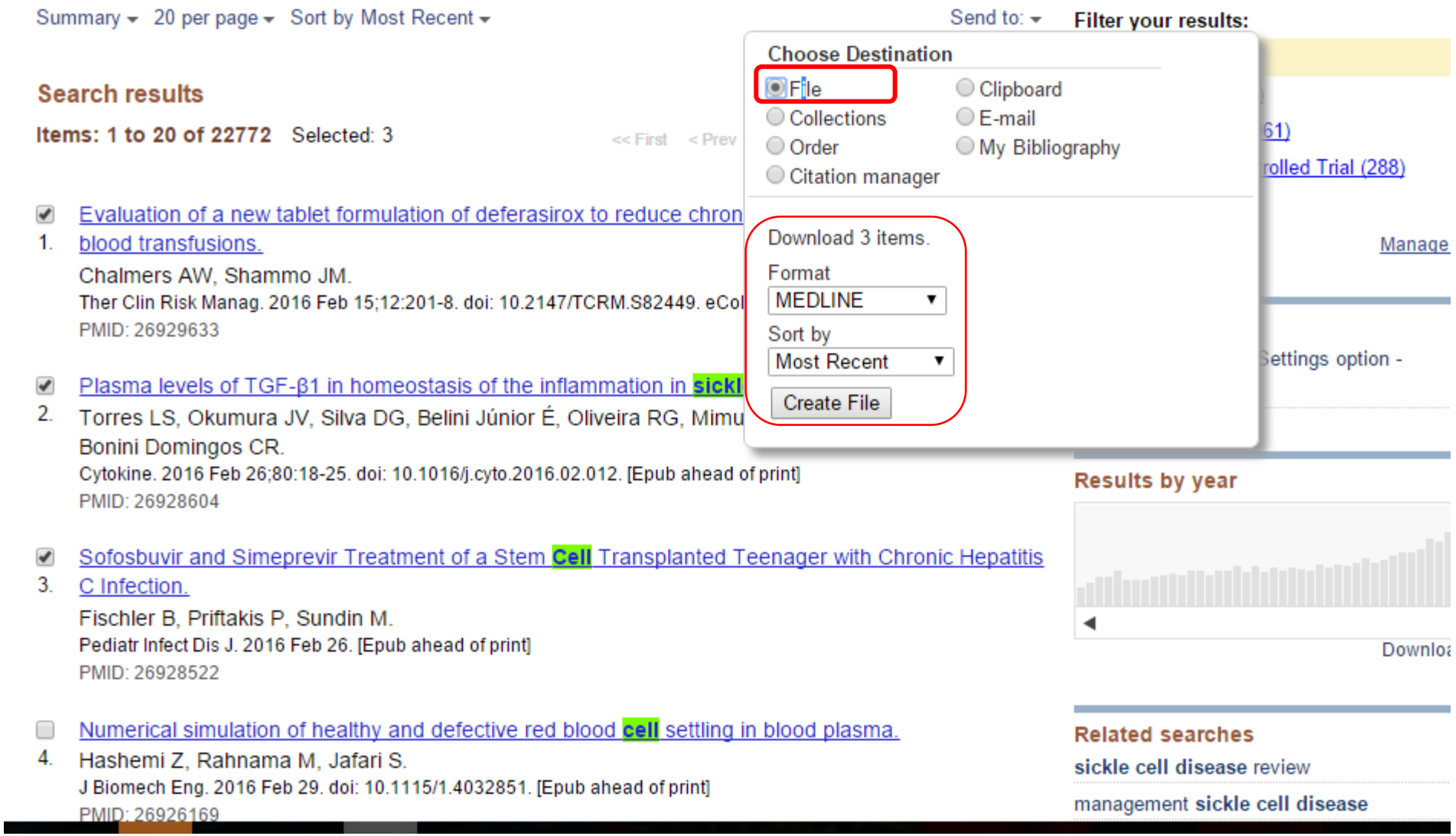
10.30-10.45	Presentazione ed obiettivi del Corso Stefania GORI - Fabrizio NICOLIS Giovanni L. PAPPAGALLO
10.45-11.30	Tipologia delle Revisioni della Letteratura Scientifica Obiettivi di una Revisione Sistematica Michela CINQUINI
11.30-12.00	Definizione del quesito clinico e degli outcome di interesse; misure di associazione Giovanni L. PAPPAGALLO
12.00-13.00	Lavoro di gruppo *Summing-Up* (metodo: *What? So What? Now What?*) (valido come prova ECM)
13.000-14.00	Colazione di lavoro
14.00-14.45	Come trovare informazioni - I database bibliografici, i siti di linee guida e studi clinici... Veronica Andrea FITTIPALDO
14.45-15.30	Definizione della strategia di ricerca e di selezione degli studi; *study flow* Michela CINQUINI
15.30-16.00	Metodi di valutazione di autori e riviste scientifiche: indici bibliometrici classici e innovativi Giulio ZUANETTI
16.00-16.30	Coffee Break
16.30-17.30	Valutazione del rischio di *bias* negli studi selezionati Ivan MOSCHETTI
17.30-18.30	Lavoro di gruppo *Summing-Up* (metodo: *What? So What? Now What?*) (valido come prova ECM)

Output della strategia di ricerca

RISULTATO

Lista di studi potenzialmente includibili

List of records



pubmed_result (1) - Blocco note

File Modifica Formato Visualizza ?

```
PMID- 26929633
OWN - NLM
STAT- PubMed-not-MEDLINE
DA  - 20160301
DCOM- 20160301
IS  - 1176-6336 (Print)
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
```

pubmed_result (1) - Blocco note

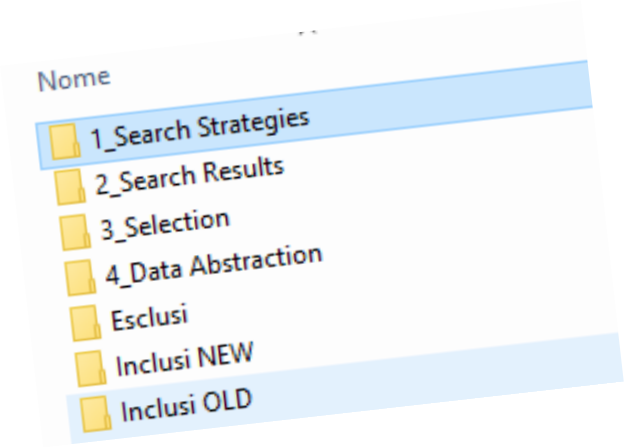
File Modifica Formato Visualizza ?

```
PMID- 26929633
OWN - NLM
STAT- PubMed-not-MEDLINE
DA  - 20160301
DCOM- 20160301
IS  - 1176-6336 (Print)
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
```

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..

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)

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

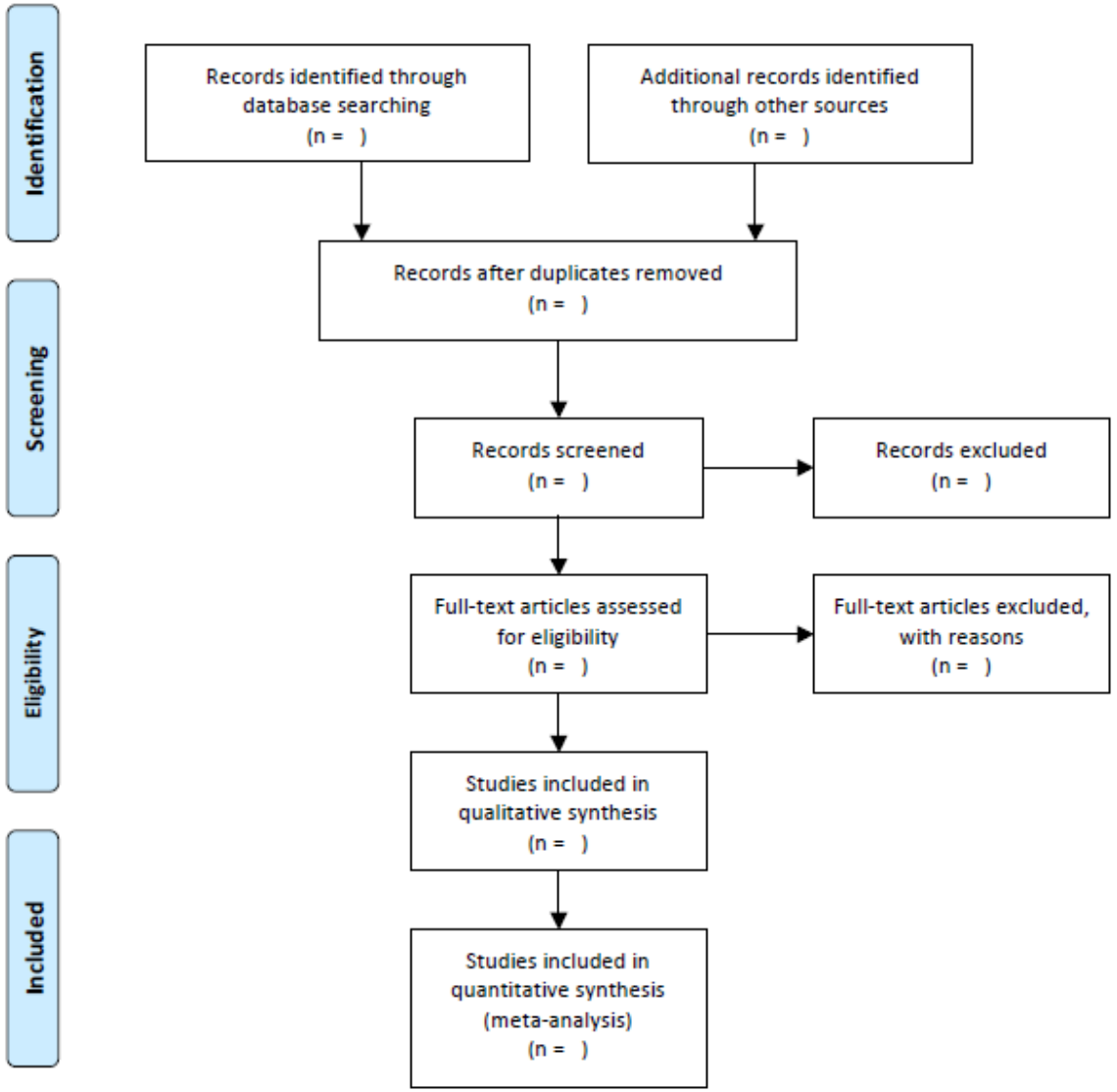
- Indicare ragione dell'esclusione sempre in base al PICOS
- Es: studi esclusi perché partecipanti non nei criteri di inclusione, intervento non nei criteri di inclusione, disegno di studio non nei criteri di inclusione
- Questo lavoro va fatto solo sui full text, non per gli studi esclusi sulla base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

7. Fare lista finali di studi inclusi

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

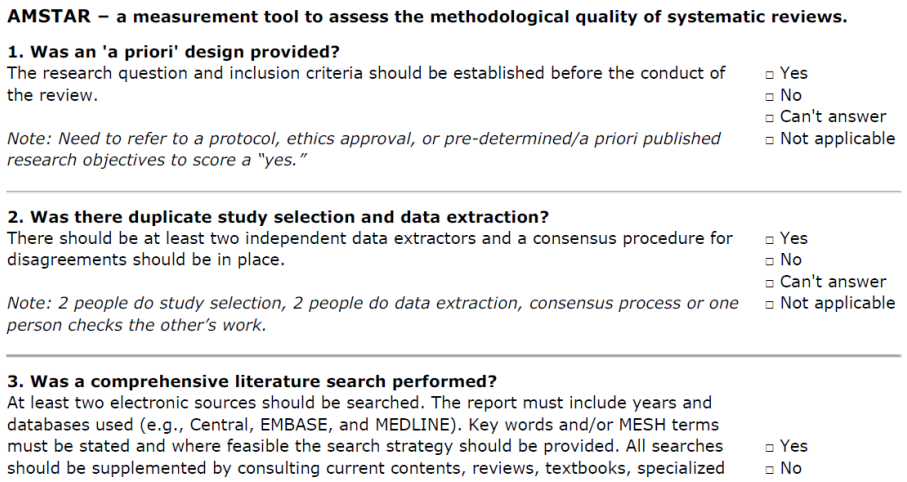
  Es: diversi periodi di follow up, analisi di sottogruppi; doppie pubblicazioni (stesso studio pubblicato più volte su riviste diverse con titolo diverso e/o diverso ordine degli autori)

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):	For Yes, should also have (all the following):	
☐ searched at least 2 databases (relevant to research question) ☐ provided key word and/or search strategy ☐ justified publication restrictions (eg, language)	☐ 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-analysis 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

[a]School of Social and Community Medicine, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol BS8 2PS, UK
[b]The National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care West at University Hospitals Bristol NHS Foundation Trust, 9th Floor, Whitefriars, Lewins Mead, Bristol BS1 2NT
[c]Kleijnen Systematic Reviews Ltd, Unit 6, Escrick Busi
[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; Publ

Abstract

Objective: To develop ROBIS, a new tool for assessing the risk
Study Design and Setting: We used four-stage approach to develo 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

PRISMA Statement

QUALITY OF REPORTING

OPEN ACCESS Freely available online

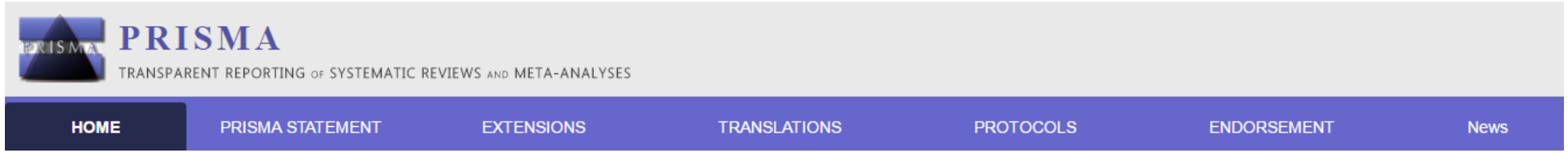
PLoS MEDICINE

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/

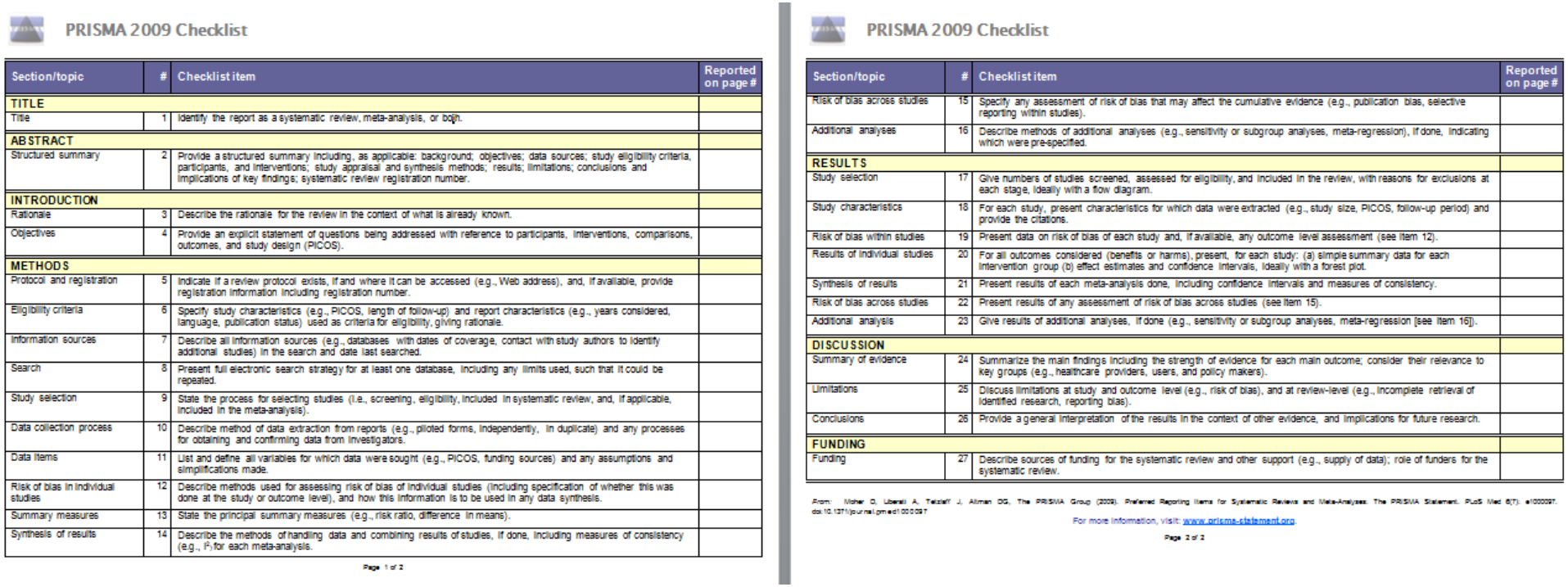
PRISMA

- 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.	

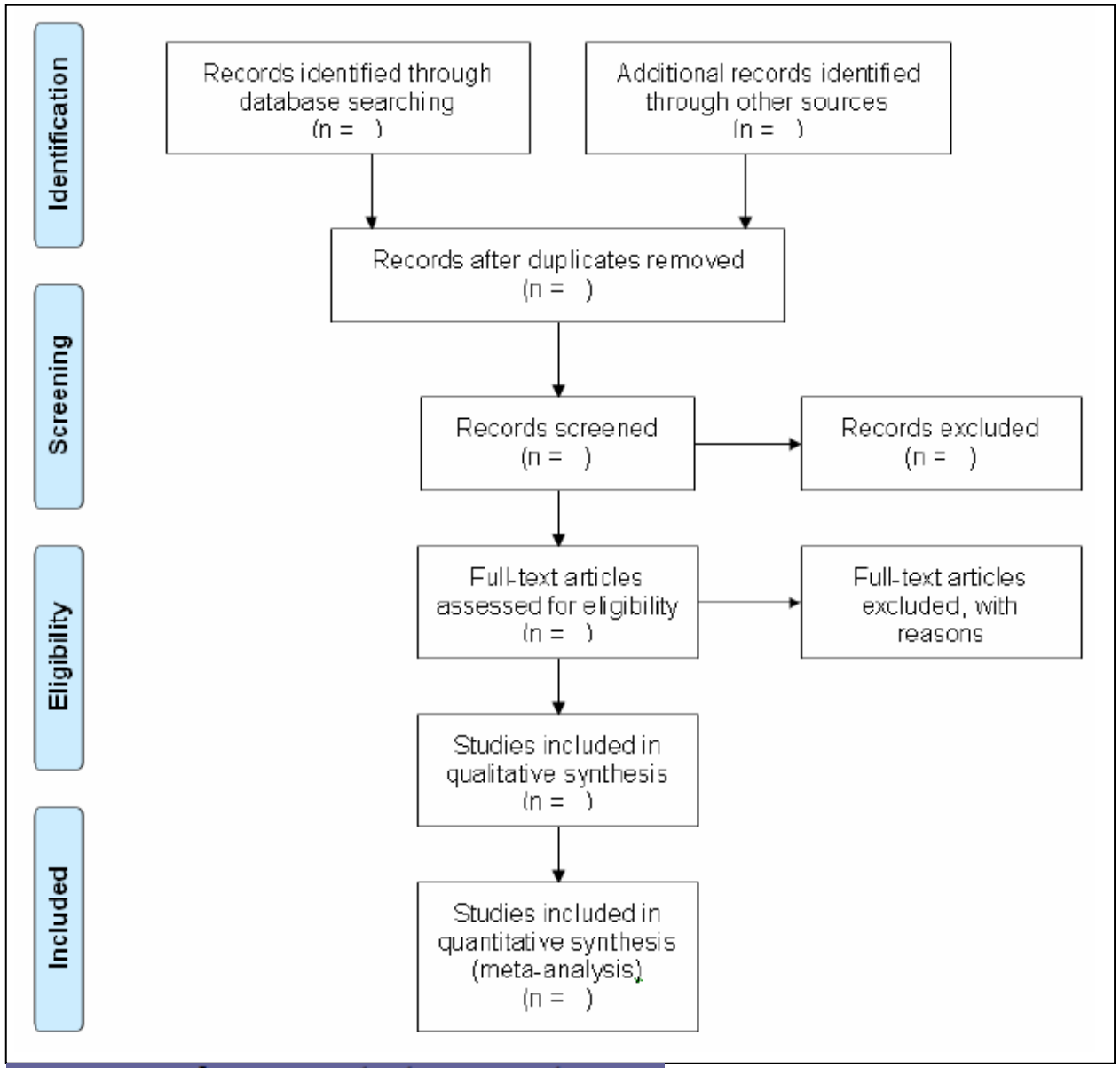
PRISMA 2009 Checklist

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
effect

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

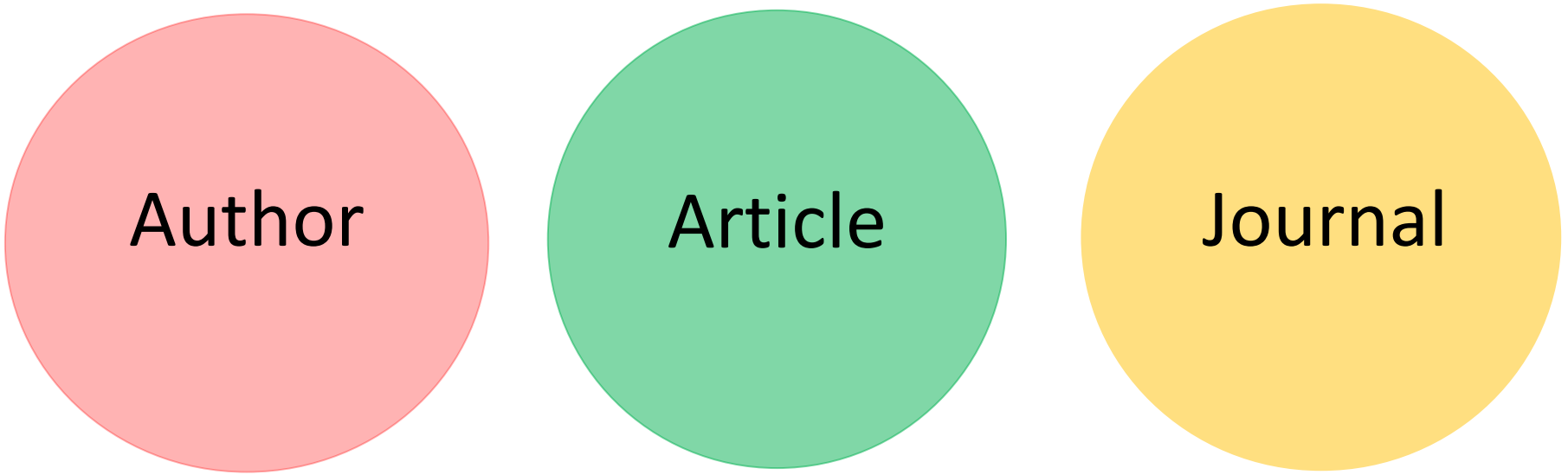
NEGRAR DI VALPOLICELLA
11-12 FEBBRAIO 2022

Centro Formazione IRCCS "Sacro Cuore-Don Calabria"

11 Febbraio 2022

10.30-10.45	Presentazione ed obiettivi del Corso Stefania GORI - Fabrizio NICOLIS Giovanni L. PAPPAGALLO
10.45-11.30	Tipologia delle Revisioni della Letteratura Scientifica Obiettivi di una Revisione Sistematica Michela CINQUINI
11.30-12.00	Definizione del quesito clinico e degli outcome di interesse; misure di associazione Giovanni L. PAPPAGALLO
12.00-13.00	Lavoro di gruppo *Summing-Up* (metodo: *What? So What? Now What?*) (valido come prova ECM)
13.000-14.00	Colazione di lavoro
14.00-14.45	Come trovare informazioni - I database bibliografici, i siti di linee guida e studi clinici... Veronica Andrea FITTIPALDO
14.45-15.30	Definizione della strategia di ricerca e di selezione degli studi; *study flow* Michela CINQUINI
15.30-16.00	Metodi di valutazione di autori e riviste scientifiche: indici bibliometrici classici e innovativi Giulio ZUANETTI
16.00-16.30	Coffee Break
16.30-17.30	Valutazione del rischio di *bias* negli studi selezionati Ivan MOSCHETTI
17.30-18.30	Lavoro di gruppo *Summing-Up* (metodo: *What? So What? Now What?*) (valido come prova ECM)

Ci sono tre ”elementi” fondamentali su cui si basa la letteratura scientifica



Gli indici di valutazione sono stati sviluppati e vengono utilizzati per ciascuno di questi elementi

Journal

Ci sono quattro - cinque database fondamentali dove le riviste sono indicizzate, una di gestione «statale», le altre invece di società private:

Web of Science, ESCI

Clarivate Analytics

Medline/ Pubmed

Embase, Scopus

ELSEVIER

Ci sono quattro - cinque database fondamentali dove le riviste sono indicizzate, una di gestione «statale», le altre invece di società private

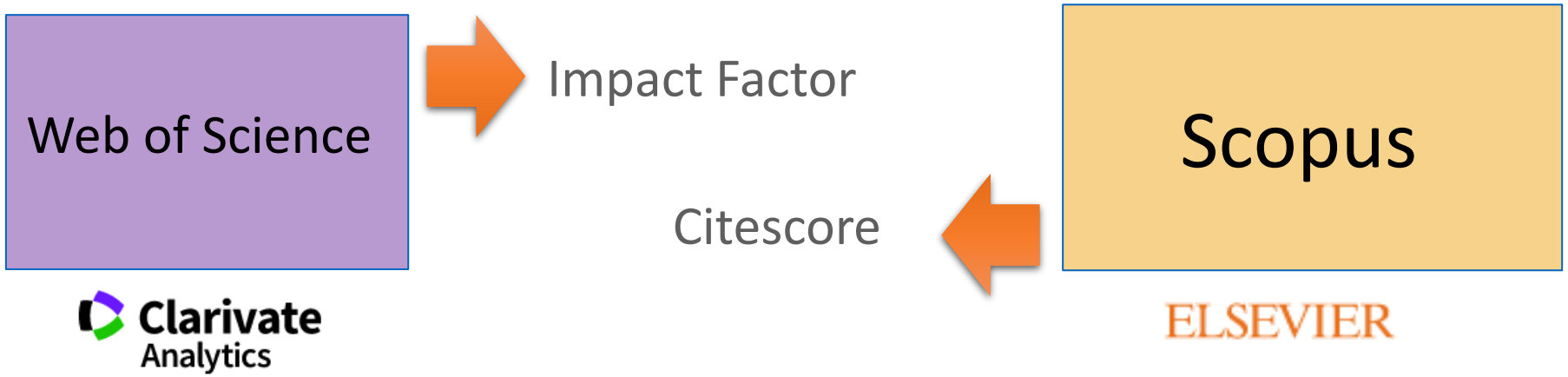
Web of Science, ESCI

Medline/ Pubmed

Embase, Scopus

La presenza di un articolo in uno o più di questi database è stata ed è tuttora un elemento di garanzia sulla qualità del lavoro, tuttavia i confini sono diventati meno definiti di un tempo.

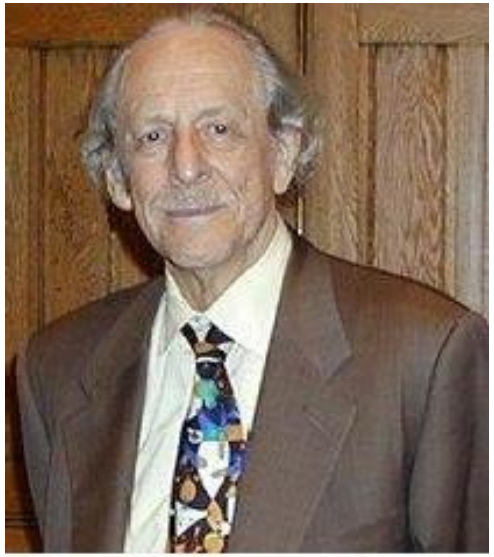
Le società private hanno sviluppato degli indicatori di performance delle riviste: sono indici **bibliometrici** (quindi basati sul numero di citazioni) che vengono ottenuti analizzando i dati da due dei loro databases.



L’IF non è un indice molto recente….

Eugene Garfield è il creatore dell’Impact Factor.

Il lavoro su cui si basa l’indice è stato pubblicato nel **1955**……..



Citation Indexes for Science

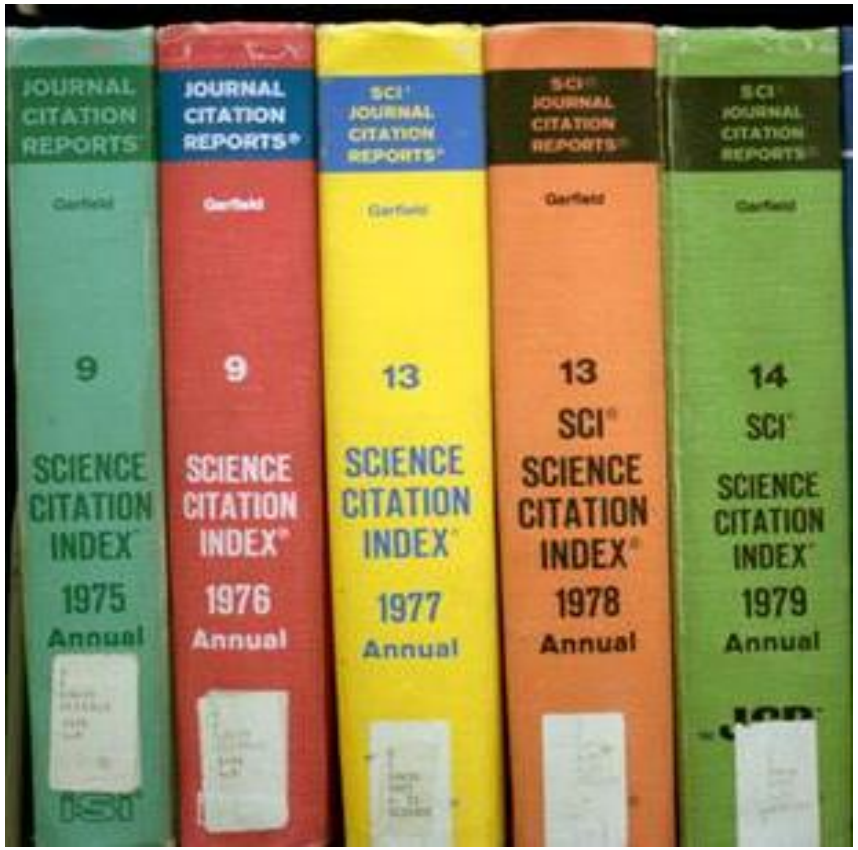
A New Dimension in Documentation through Association of Ideas

Eugene Garfield

Mr. Garfield is a documentation consultant with offices at 1530 Spring Garden St., Philadelphia 1, Pa.

1955 SCIENCE, VOL. 122

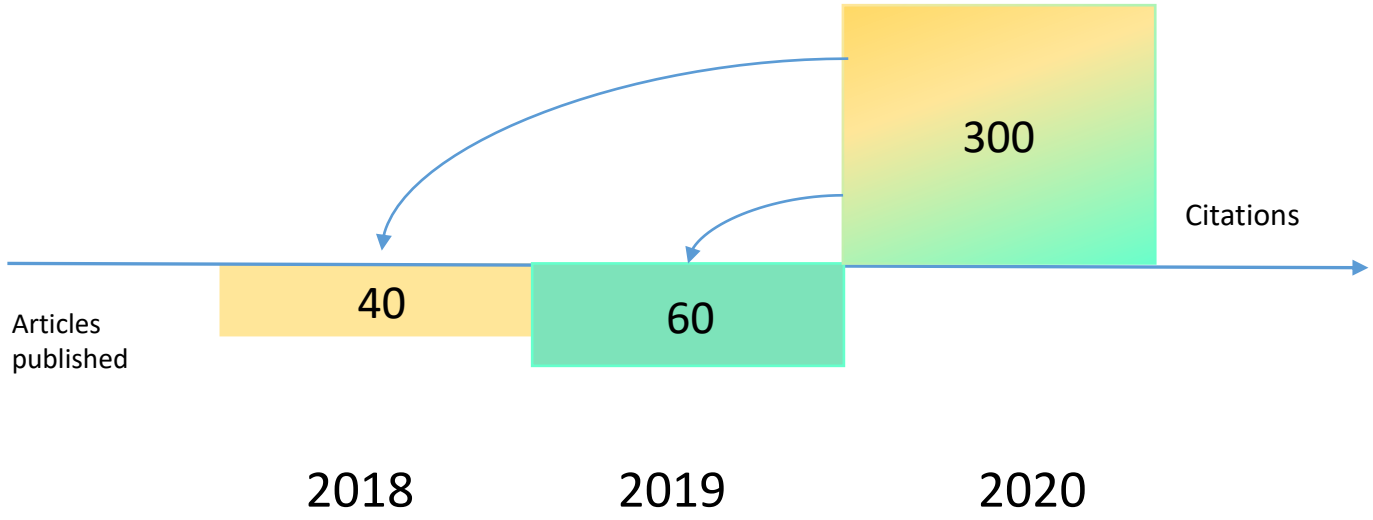
…anche se ufficialmente l’anno in cui si è iniziato a calcolare l’Impact Factor è il **1975**….



L'Impact Factor comunemente utilizzato è il **2-Year IF**

Alla data del corso (Febbraio 2022), l'ultimo IF è quello pubblicato nel Giugno 2021 che si basa sulle citazioni totali dell'anno 2020

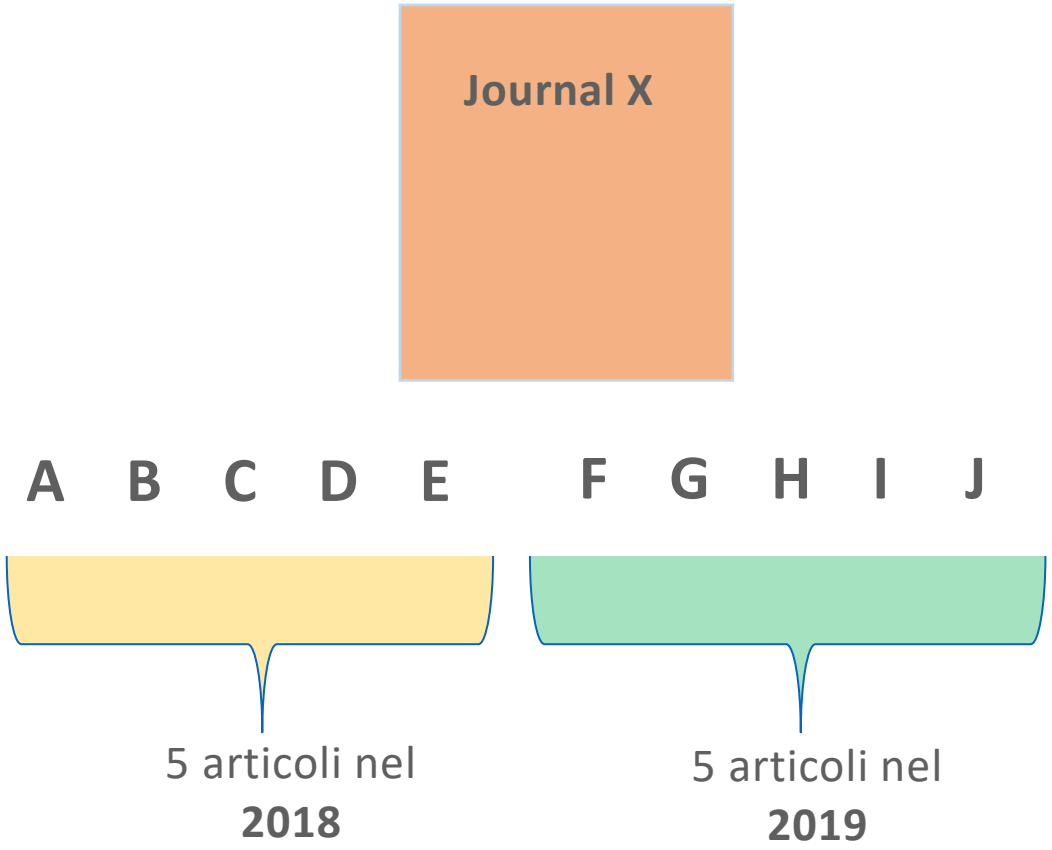
È definito come il **rapporto** tra numero complessivo di citazioni presenti durante l'anno per il quale l'IF viene calcolato da parte di qualsiasi rivista presente nel database Web of Science e pertinenti ad articoli della rivista in esame pubblicati nei due anni precedenti, **diviso** il numero totale degli articoli della rivista in esame pubblicati nei due anni precedenti.



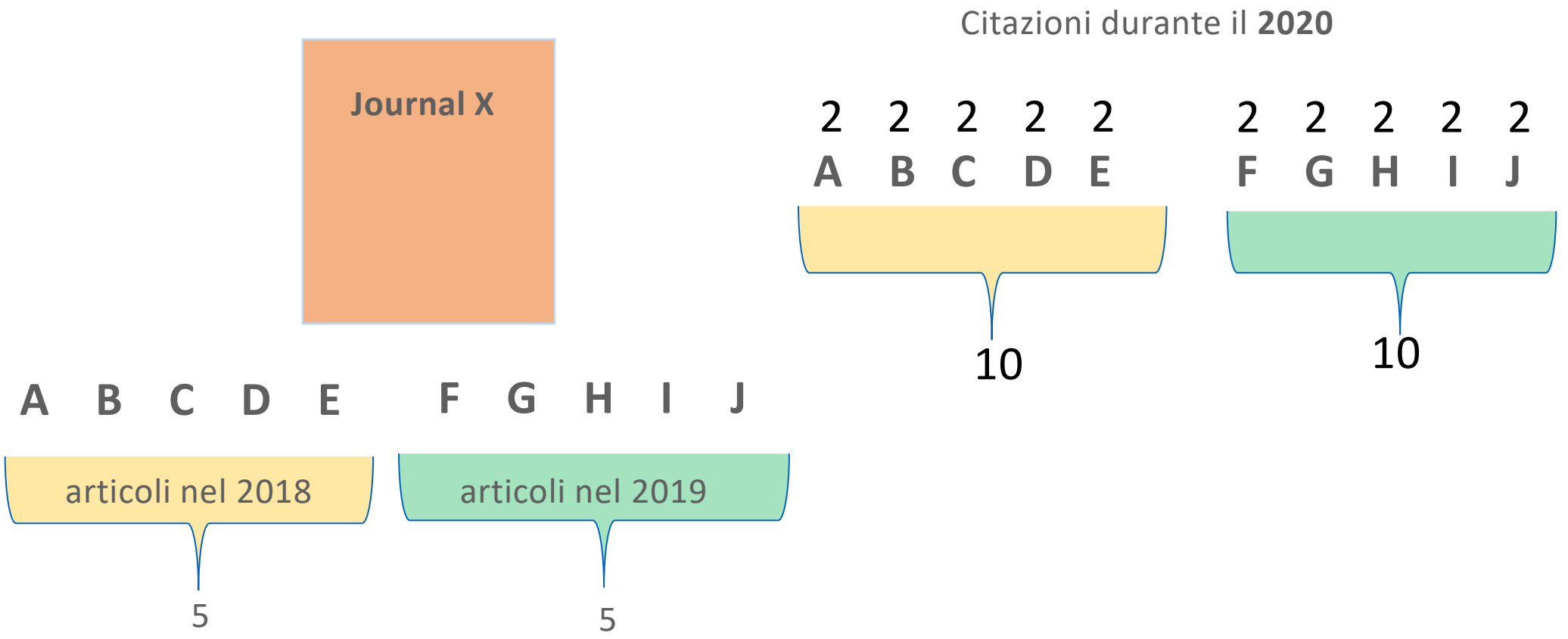
$$\textbf{2020 IF} = \frac{300}{40 + 60} = 3$$

L’IF non deve essere utilizzato per la valutazione degli autori

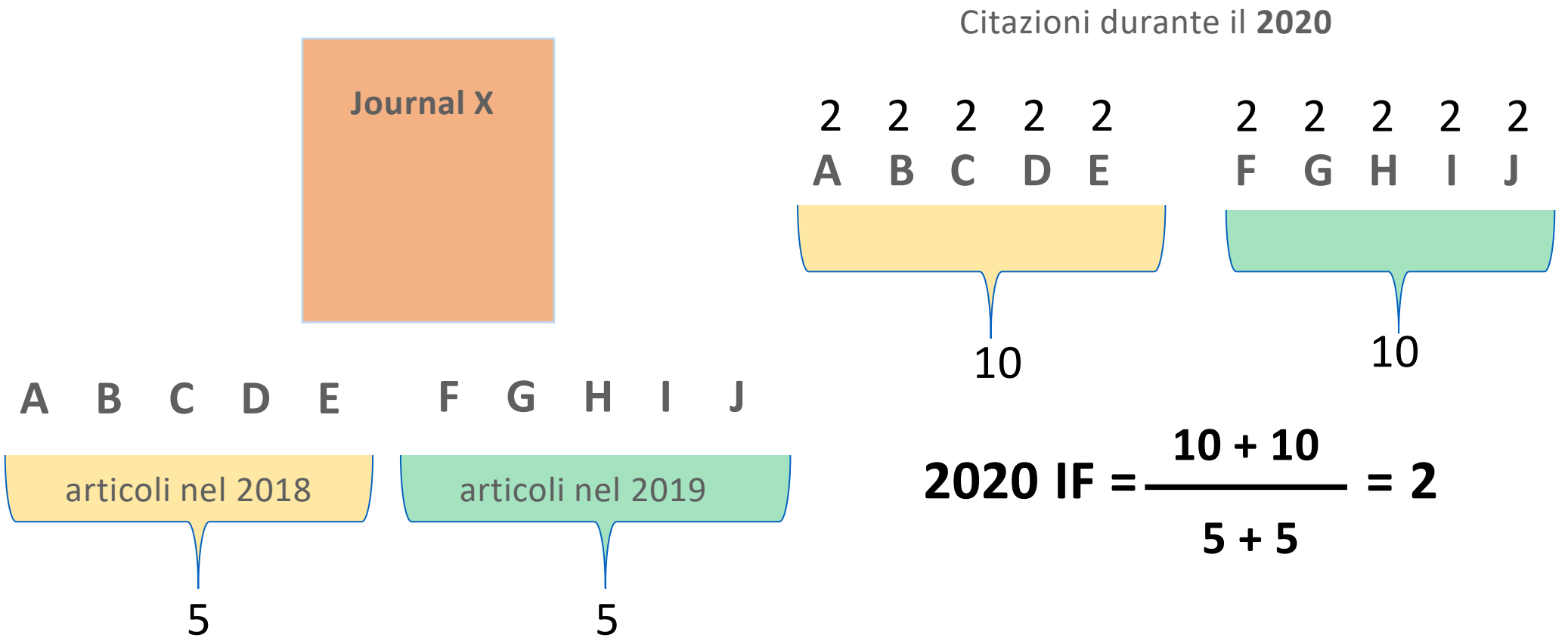
Immaginiamo che la rivista X abbia pubblicato gli articoli A,B,C,D,E nel corso del **2018** e F,G,H,I,J nel corso del **2019**



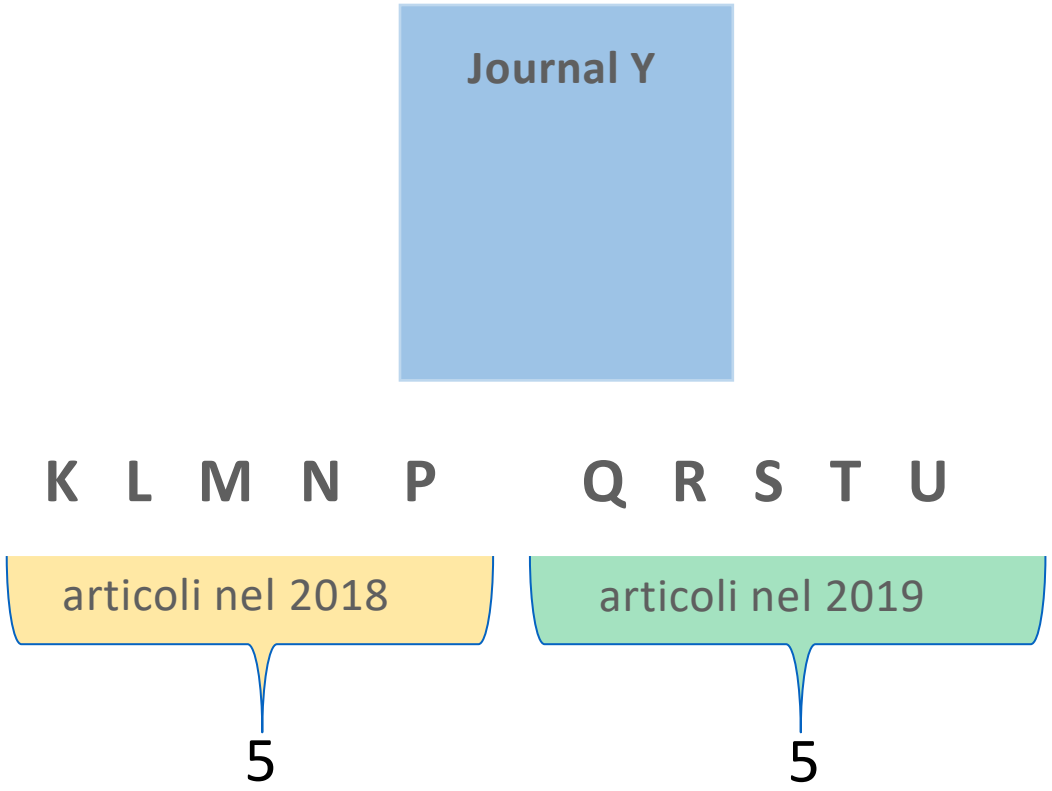
Immaginiamo ora che tutti questi articoli abbiano avuto due citazioni nel corso del 2020.
Quale sarà l'IF?



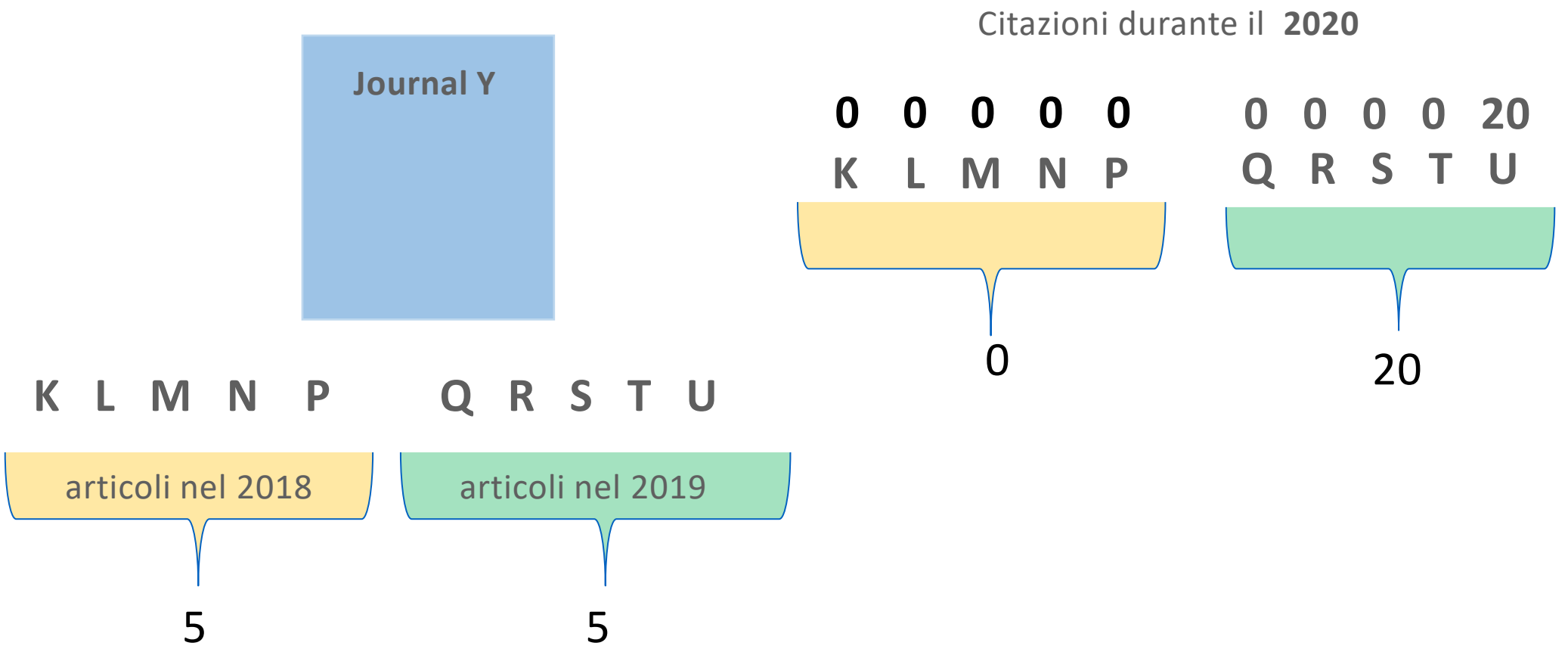
Immaginiamo ora che tutti questi articoli abbiano avuto due citazioni nel corso del 2020.
Quale sarà l'IF?



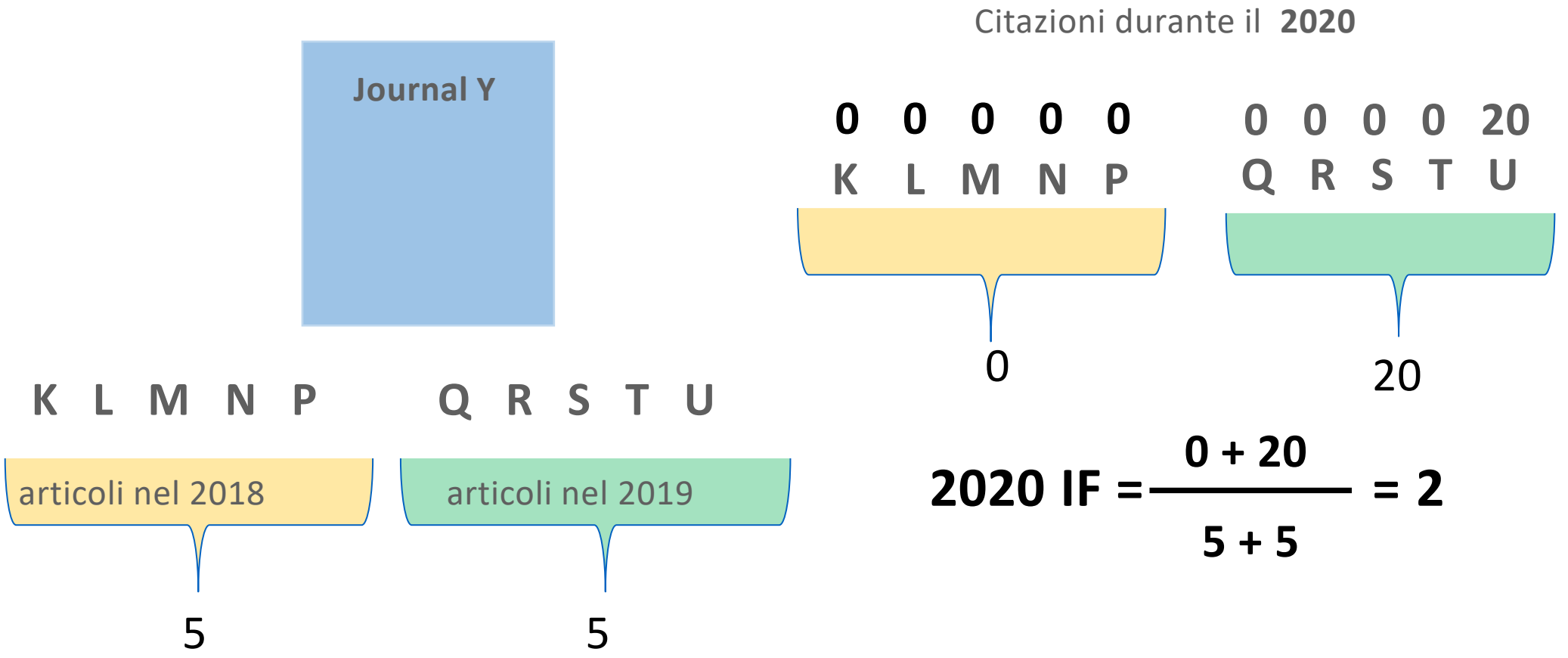
Immaginiamo ora che la rivista Y abbia pubblicato lo stesso numero di articoli della rivista X



Immaginiamo ora che tutti questi articoli abbiano avuto zero citazioni nel corso del 2020, tranne uno che ne ha avute venti. Quale sarà l'IF?



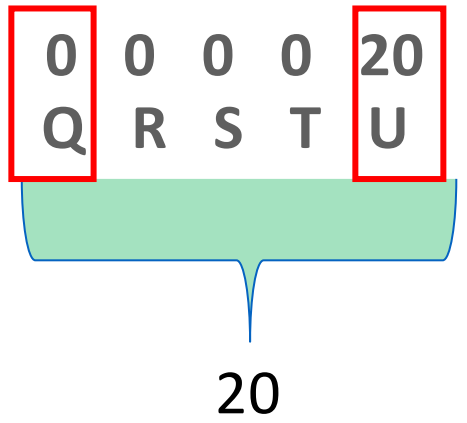
Immaginiamo ora che tutti questi articoli abbiano avuto zero citazioni nel corso del 2020, tranne uno che ne ha avute venti. Quale sarà l'IF?



Cosa significa per gli autori?

Gli autori dell'articolo Q, con zero citazioni….

…possono fare il claim di aver pubblicato su una rivista "impattata" o di essere **"autori impattati"** senza aver avuto neanche una citazione del loro articolo, esattamente come gli autori dell'articolo U che di citazioni ne hanno venti e hanno contribuito in modo sostanziale all'IF della rivista.



L'IF è un indicatore (con diversi limiti) della "bontà" di una rivista ma sicuramente NON degli autori che pubblicano sulla stessa.

L’ IF ha quindi diversi limiti

- ✓ Il fatto che l’IF si riferisca sempre ad articoli pubblicati da 2 a 3 anni prima della valutazione la rende poco “attuale”
- ✓ Una problematica che recentemente è diventata importante è quella dalla Advance Online Publication: spesso l’articolo è pubblicato online molto prima di essere “ufficialmente” pubblicato.

Clarivate sta cercando di superare questi limiti lanciando nuovi indicatori

Clarivate™

Introducing the Journal Citation Indicator

A new approach to measure the citation impact of journals in the Web of Science Core Collection

→ Il problema è che non abbiamo comunque niente di veramente meglio dell’IF….

Il Competitor dell'IF: CiteScore di Elsevier

- ✓ Inizialmente c'erano tre differenze fondamentali con l'Impact Factor:

1. I dati erano (e sono ancora) disponibili a tutti, non soltanto agli abbonati al JCR come nel caso dell'IF

2. Il CiteScore includeva tutti i tipi di articolo: non solo articles e reviews ma anche letters, notes, editorials, conference papers etc

3. Venivano conteggiati 3 anni invece di 2

Il Competitor dell'IF: CiteScore di Elsevier

Nel 2020 la metodologia è cambiata:

1. Solo gli articoli peer-reviewed sono inclusi nel numeratore e nel denominatore
2. Si contano tutti gli articoli e tutte le citazioni presenti andando indietro fino a 4 anni.
3. Il CiteScore può essere calcolato anche dopo un solo anno di pubblicazione
4. Questo cambio ha determinato una variazione improvvisa dei CiteScore precedenti per tutte le riviste e quindi i "vecchi" valori non sono più validi

Oggi è veramente complicato usare il CiteScore come indice di riferimento

I Competitor dell'IF: Le bufale

- Cosmos Impact Factor
- Directory of Indexing and Impact Factor
- General Impact Factor
- Global Impact Factor
- Global Science Citation Impact Factor
- Impact Factor Services for International Journals
- International Journal Impact Factor
- Journal Impact Factor
- Journals Impact Factor
- Research Journal Impact Factor
- Science Impact Factor
- Scientific Journal Impact Factor
- Systematic Impact Factor
- Technical Impact Factor
- Universal Impact Factor

Journal of Medical – Clinical Research & Reviews

Open Access

ISSN: 2639-944X

Journal of Medical - Clinical Research & Reviews (ISSN 2639-944X) is an international, open-access with **0.34** Impact Factor, journal give special importance to publish research and reviews in the fields of general & scientific medical research and clinical practice. It also publishes valuable studies in Cardiology, Neurology, Obstetrics and Gynecology, Surgery, Internal medicine, Orthopaedics, Infectious diseases, and HIV/AIDs, Oncology and all related areas which come under the journal scope.

Journal of Medical - Clinical Research & Reviews requests and encourages researchers to submit their brilliantly orchestrated topics or recent developments in the field of Clinical and Medical areas in the form of Research and Reviews.

Our journal strongly supports the Open Access initiative. All published articles will be assigned DOI provided by Cross Ref. Journal of Medical - Clinical Research & Reviews will keep up-to- date with the latest advancements in the field of medical research. Abstracts and Pdfs of all articles published are freely available to everyone immediately after publication.

Authors are requested to submit manuscripts as an e-mail attachment to the Editorial Office at editor.mcrr@scivisionjournals.com.

I predatory publishers

The definition (Nature, dicembre 2019)

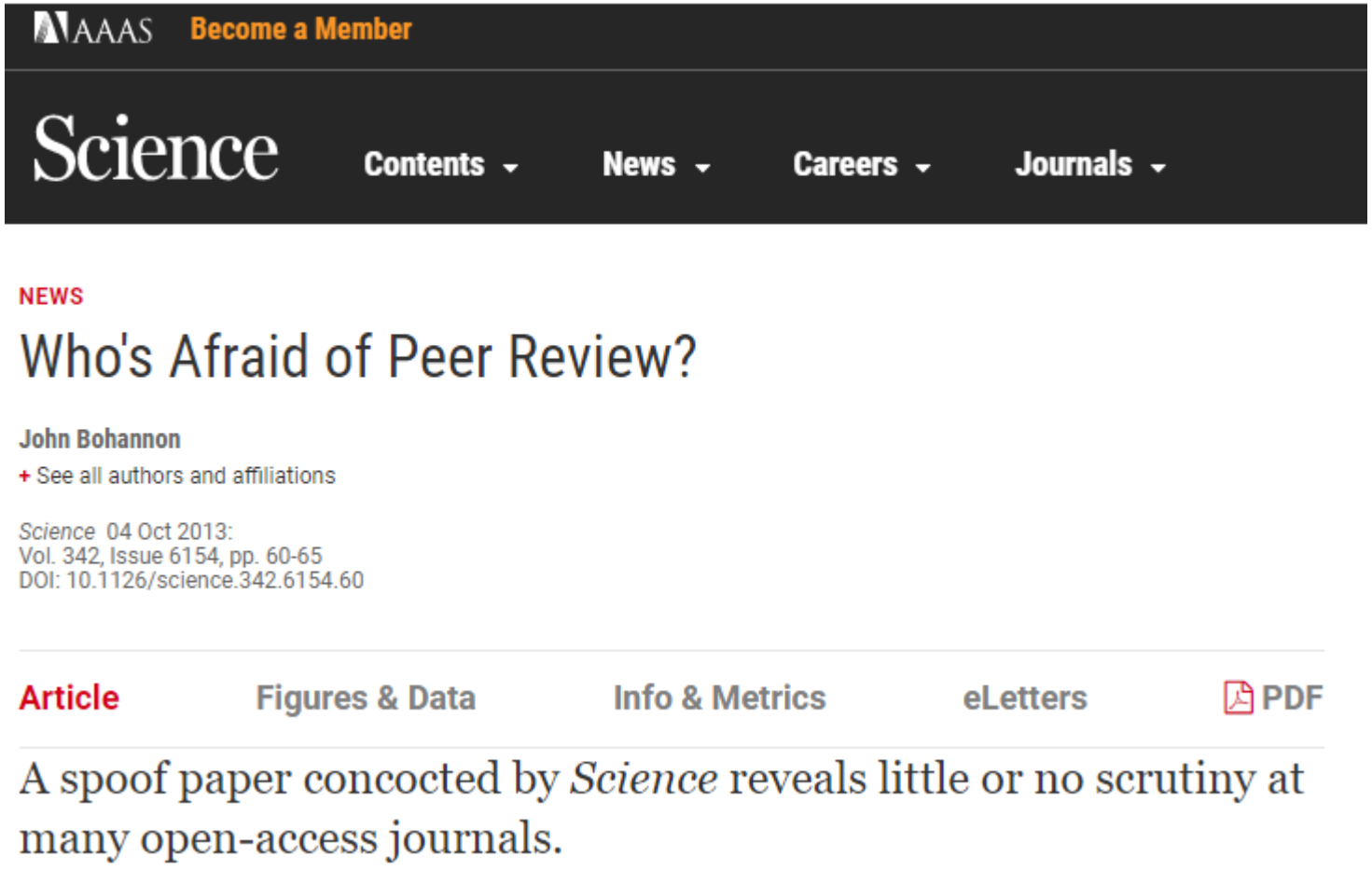
"Predatory journals and publishers are entities that prioritize self-interest at the expense of scholarship and are characterized by **false or misleading information**, **deviation from best editorial and publication practices**, a lack of transparency, and/or the **use of aggressive and indiscriminate solicitation practices."**

Agnes Grudniewicz, David Moher, Kelly D. Cobey and 32 co-authors

Esiste un elenco "indicativo" di predatory publishers che purtroppo non è aggiornato

Stop Predatory Journals

La prima clamorosa evidenza sui predatory publishers risale a più di otto anni fa



Nonostante tutto, i predatory publisher sono più attivi che mai…

Da: Journal of Medical - Clinical Research & Reviews <medclinres@gmail.com>
Inviato: giovedì 22 aprile 2021 09:21
Oggetto: Accepting Reviews and Reports in Medical Research

Dear Dr., Greets from Journal of Medical - Clinical Research & Reviews…

Journal of Medical - Clinical Research & Reviews (ISSN 2639-944X) is an open access journal designed for the widespread dissemination of research findings in the field of Clinical & Medical Research. For this upcoming issue, you are welcome to submit original research articles, reviews, brief reports, case studies, rapid communications, and letters to the editor which may advance our current knowledge about Clinical & Medical Research. There is no restriction on the length of your manuscript.

All manuscripts will be subjected to the double-blinded peer-review process. Manuscripts that are considered within the scope and meet quality expectations will be reviewed by experts. For more details please go through the link http://www.scivisionpub.com/journals/journal-of-medical-clinical-research-reviews-home.
Our journal is indexed in **Google Scholar, CrossRef, CiteFactor, ROAD, Scilit (Scientific Literature), Academic Resource Index (ResearchBib), (SIS) Scientific Indexing Services, ResearchGate, WorldCat, DRJI (Directory of Research Journals Indexing), Semantic Scholar.**

Impact Factor: 0.34

If possible, we would appreciate receiving your submission by **May 05, 2021.** Kindly send the article as an attachment to this email.
Looking forward to your kind response.

With Regards,
Naina K
Editorial Assistant, Journal of Medical - Clinical Research & Reviews, ISSN 2639-944X
Delaware, US

Il rischio dei predatory publishers nella diffusione di fake news non deve essere sottovalutata

Journal of Medical - Clinical Research & Reviews

Review of COVID-19 Vaccines and the Risk of Chronic Adverse Events Including Neurological Degeneration

J. Bart Classen, MD*

Classen Immunotherapies, Inc, 3637 Rockdale Road, Manchester, MD 21102, USA.

***Correspondence:**
J. Bart Classen, Classen Immunotherapies, Inc, 3637 Rockdale Road, Manchester, MD 21102, USA, Tel: 410-377-8526; E-mail: classen@vaccines.net.

Received: 20 March 2021; **Accepted:** 10 April 2021

Citation: J. Bart Classen. Review of COVID-19 Vaccines and the Risk of Chronic Adverse Events Including Neurological Degeneration. J Med - Clin Res & Rev. 2021; 5(4): 1-7.

ABSTRACT

Many have argued that the outbreak of COVID-19 is the result of the release of a viral based bioweapon. Vaccines to COVID-19 have been developed and a policy of universal immunization has been initiated with total disregard to the fact that the virus may be a bioweapon. The potential risk of a catastrophe exists in part because all the vaccines contain the spike protein and or the mRNA/DNA encoding for the COVID-19 associated spike protein. These vaccines were designed and placed on the market with little knowledge of how the spike protein or its nucleic acid causes disease and without knowledge of long-term adverse effects of the vaccines. This paper reviews many of the potential long-term risks that could result from receiving one of the COVID-19 vaccines. The potential for the spike protein and its mRNA to cause prion disease is reviewed as well as reasons why the vaccine could be much more dangerous than the natural infection. Adenoviral derived COVID-19 vaccines are particularly risky because of their potential to recombine with human DNA or viruses already in the human recipient. The result could be new infectious adenoviral species containing spike proteins that could infect humans and farm animals used for food. Some of the COVID-19 vaccines utilize novel technology including nanotechnology and novel adjuvants that increase intracellular penetration of cells and can potentially exacerbate chronic toxicity from the spike protein. Governments should consider suspending sale of the COVID-19 vaccines until they have a better understanding of their risks.

Le conseguenze di “scegliere” un predatory journal:

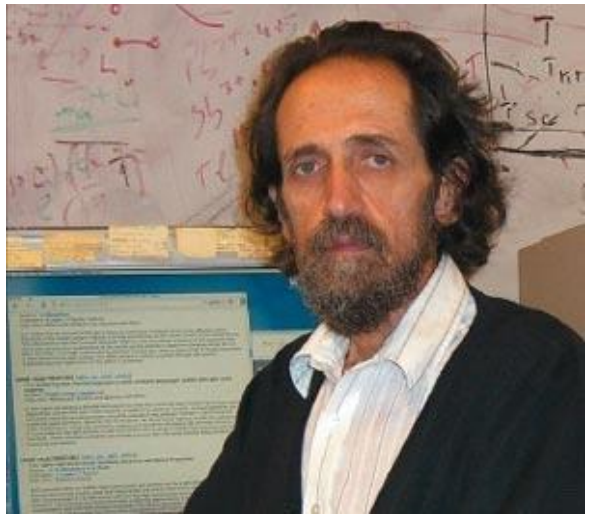
- Fa perdere tempo
- Determina un eventuale danno economico
- Rende impossibile o comunque molto difficile ripubblicare i dati del lavoro su una rivista “seria”
- Aiuta un dark system che contribuisce alla disseminazione di fake-news credibili


Author

Indice bibliometrico che misura gli autori: l'H-Index

Indice molto più "giovane" dell'Impact Factor, creato 14 anni fa

a scientist has an index h if h of their papers have at least h citations each, and their other papers have no more than h citations each



Hirsch, Jorge (2005) PNAS 46: 16569
arXiv:physics/0508025

Un h-index di 10 significa che un ricercatore ha pubblicato almeno 10 lavori che hanno avuto almeno 10 citazioni.

H-index

Si guarda il numero di citazioni di ogni singolo articolo dell'autore

Article	Citations
A	18
B	25
C	9
D	35
E	2
F	6
G	3
H	50
I	15
L	40
M	7
N	2
O	1
P	33
Q	8
R	27
S	21
T	10
U	5
V	2

H-index

Si guarda il numero di citazioni di ogni singolo articolo dell'autore

Si mettono gli articoli in ordine decrescente

Article	Citations
A	18
B	25
C	9
D	35
E	2
F	6
G	3
H	50
I	15
L	40
M	7
N	2
O	1
P	33
Q	8
R	27
S	21
T	10
U	5
V	2

Article	Rank	Citations
H	1	50
L	2	40
D	3	35
P	4	33
R	5	27
B	6	25
S	7	21
A	8	18
I	9	15
T	10	10
C	11	9
Q	12	8
M	13	7
F	14	6
U	15	5
G	16	3
E	17	2
N	18	2
V	19	2
O	20	1

H-index

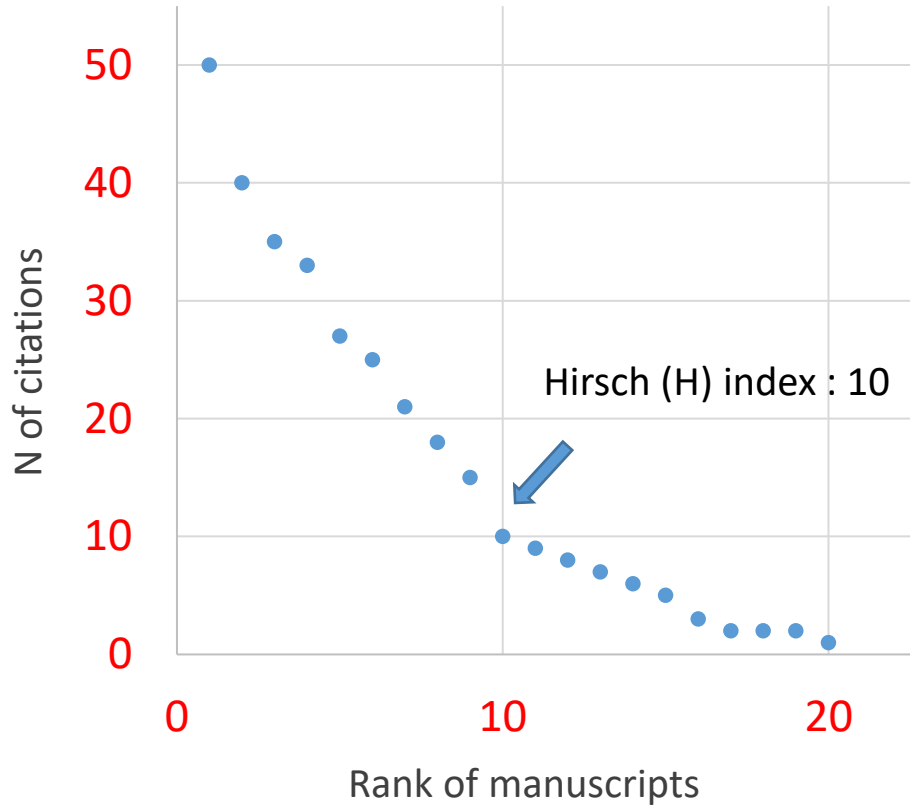
Si guarda il numero di citazioni di ogni singolo articolo dell'autore

Article	Citations
A	18
B	25
C	9
D	35
E	2
F	6
G	3
H	50
I	15
L	40
M	7
N	2
O	1
P	33
Q	8
R	27
S	21
T	10
U	5
V	2

Si mettono gli articoli in ordine decrescente

Article	Rank	Citations
H	1	50
L	2	40
D	3	35
P	4	33
R	5	27
B	6	25
S	7	21
A	8	18
I	9	15
T	10	10
C	11	9
Q	12	8
M	13	7
F	14	6
U	15	5
G	16	3
E	17	2
N	18	2
V	19	2
O	20	1

Si guarda il valore per cui ascissa e ordinata sono uguali



H-index

- ✓ Diversi databases, tra cui Web of Science, Scopus e altri, calcolano automaticamente l'h-index

- ✓ L'h-index è un indicatore sia della quantità che della qualità dei lavori, inteso sempre come numero delle citazioni

- ✓ **Non è un indice per giovani** (è evidente che se un autore ha pubblicato pochi articoli non potrà avere un h-index alto)

Author Beamplots

Sono il nuovo indice alternativo all'h-index, disponibile dal Marzo 2021 e basato sui dati presenti in Web of Science.

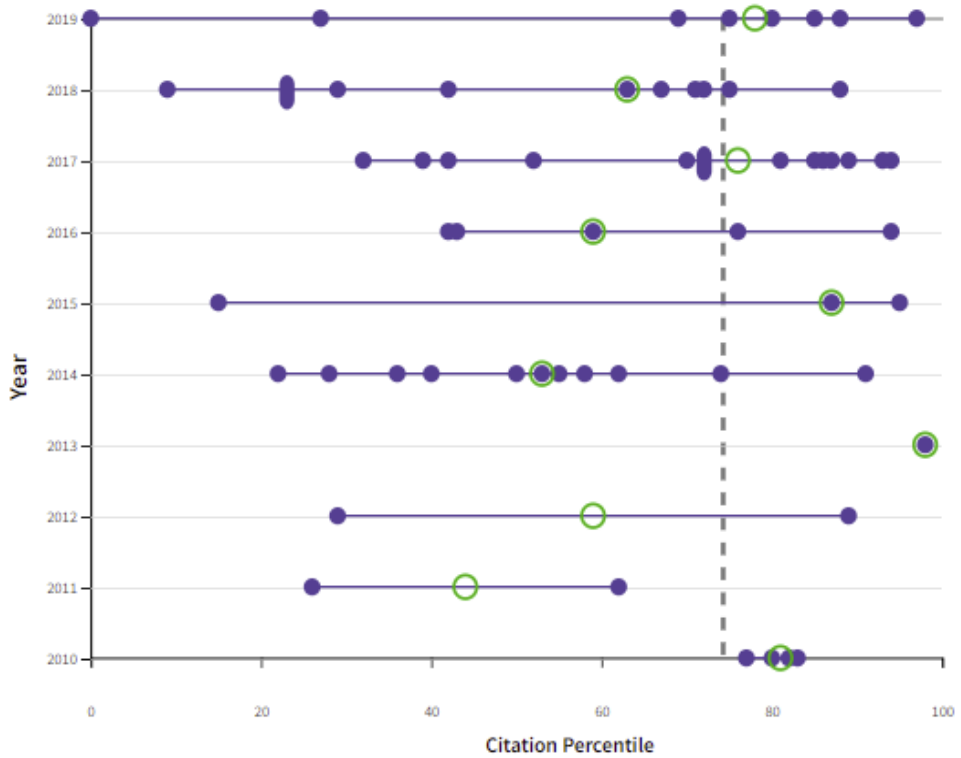
Esprimono i dati in termine di percentile rispetto alle altre pubblicazioni dello stesso anno, dello stesso argomento e dello stesso tipo di documento (articolo di ricerca originale oppure review)

Questo consente di ottenere dei dati normalizzati, quindi più confrontabili tra diverse discipline e che non dipendono dall'età accademica.

Author Beamplots

PUBLICATIONS | AUTHOR IMPACT BEAMPLOT

Range: Recent 10 Years | EXPORT



Citation percentile | Annual citation percentile | Overall citation percentile median

Citation counts are from Web of Science Core Collection; citation percentile data are from InCites.

Citation Network

29 H-Index	173 Total Publications
2,622 Sum of Times Cited	2,048 Citing Articles

VIEW CITATION REPORT

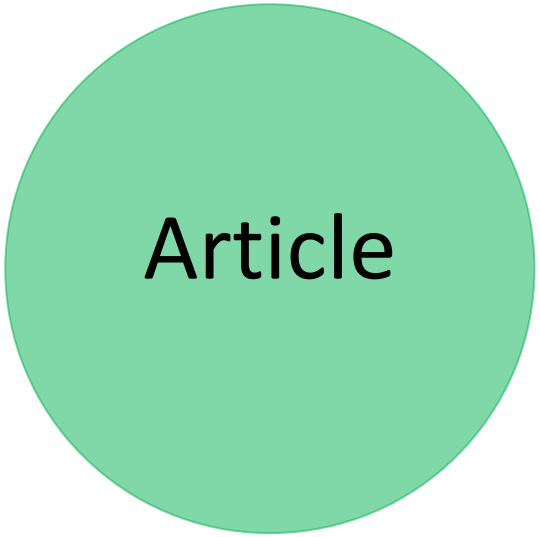
Author Position

First	38%
Last	13%
Corresponding	29%

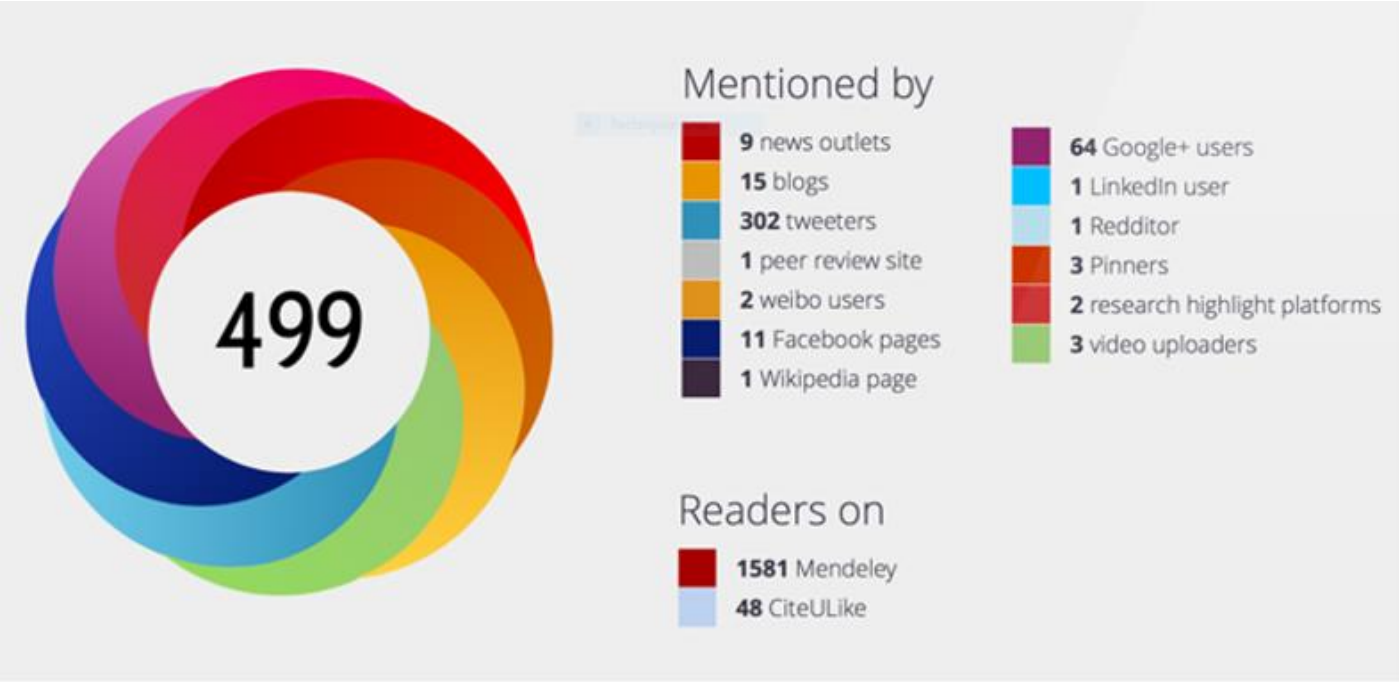
Author Network

Top co-authors

AC	60
DC	45
HG	42
FD	42
XY	42


Article

Alcuni anni orsono sono stati sviluppati indici chiamati Altmetric che utilizzano i Social e altri Media come indice di “impatto” dell’articolo (ma non dell’autore o della rivista)



I colori che formano i “donuts” riflettono il mix delle fonti che determinano lo score, azzurro per Twitter, giallo per i blog etc etc

Rappresenta forse l’elemento più *disruptive* nella misurazione dell’impatto degli articoli scientifici su una audience fatta di addetti ai lavori ma non solo, grazie anche all’adozione sempre più larga dell’open access.

Altmetric: l'Attention Score

Più un articolo è menzionato sul web, più aumenta lo score.

Più la fonte è "importante" più lo score si alza → una menzione sul blog di Science o su un articolo del WSJ vale di più di una menzione su altri fonti meno prestigiose.

L’impatto “mediatico” di alcuni articoli può far crescere in maniera vertiginosa l’indice Altmetric in poco tempo e questo rappresenta una “dissociazione” fondamentale tra indici bibliometrici classici e innovativi.

Questo è molto evidente guardando per esempio gli articoli che trattano il tema COVID-19

Dati al 30 Novembre 2020

Unexpected detection of SARS-CoV-2 antibodies in the prepandemic period in Italy.

Apolone G[1], Montomoli E[2], Manenti A[3], Boeri M[1], Sabia F[1], Hyseni I[4], Mazzini L[2], Martinuzzi D[4], Cantone L[5], Milanese G[6], Sestini S[1], Suatoni P[1], Marchianò A[1], Bollati V[5], Sozzi G[1], Pastorino U[1]

Author information

Tumori, 11 Nov 2020, :300891620974755
DOI: 10.1177/0300891620974755 PMID: 33176598

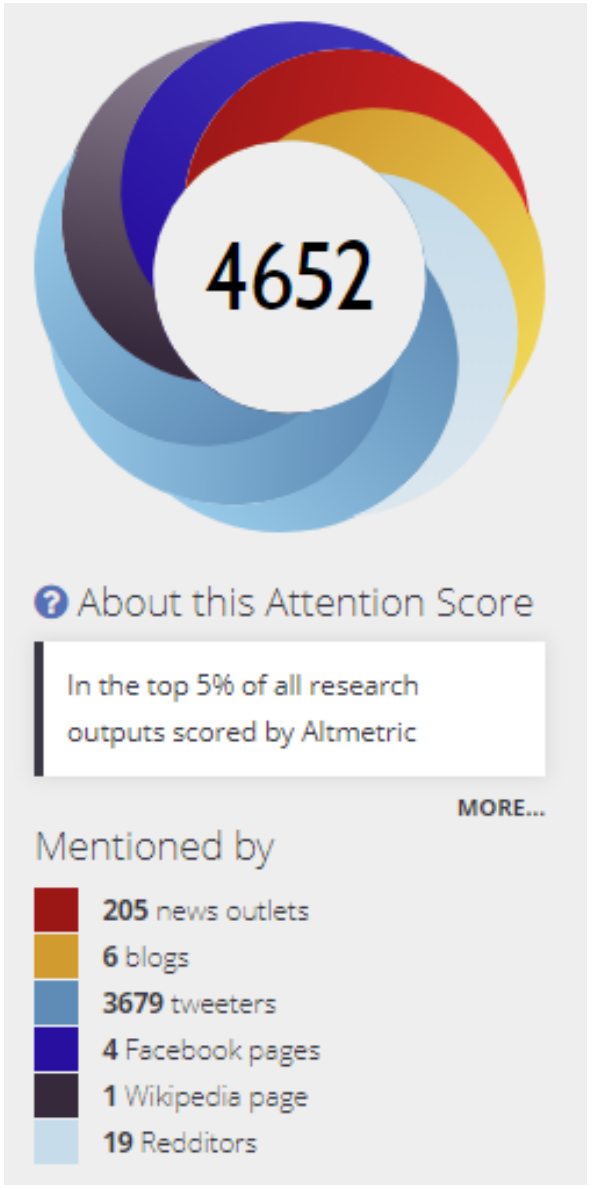
Citations & impact

This article has not been cited yet.

Impact metrics

Alternative metrics

Altmetric
Discover the attention surrounding your research
https://www.altmetric.com/details/94264046



Unexpected detection of SARS-CoV-2 antibodies in the prepandemic period in Italy

Overview of attention for article published in Tumori, November 2020

About this Attention Score

In the top 5% of all research outputs scored by Altmetric

MORE...

Mentioned by

- **205** news outlets
- **6** blogs
- **3679** tweeters
- **4** Facebook pages
- **1** Wikipedia page
- **19** Redditors

Geographical breakdown

Country	Count	As %
United States	353	10%
United Kingdom	211	6%
Germany	137	4%
Poland	99	3%
Canada	75	2%
Italy	74	2%
France	61	2%
Netherlands	46	1%
Japan	44	1%
Other	440	12%
Unknown	2139	58%

Demographic breakdown

	Count	As %
Members of the public	3399	92%
Scientists	139	4%
Practitioners (doctors, other healthcare professionals)	101	3%
Science communicators (journalists, bloggers, editors)	40	1%

Più del 90% dell'interesse viene da persone che NON sono addetti ai lavori

Il successo dell’Altmetric ha stimolato la competizione a creare degli indici che combinassero in qualche modo i dati bibliometrici con i dati di impatto mediatico

The Five Categories:

Citations – This is a category that contains both traditional citation indexes such as Scopus, as well as citations that help indicate societal impact such as Clinical or Policy Citations.

Examples: citation indexes, patent citations, clinical citations, policy citations Learn more

Usage – A way to signal if anyone is reading the articles or otherwise using the research. Usage is the number one statistic researchers want to know after citations.

Examples: clicks, downloads, views, library holdings, video plays Learn more

Captures – Indicates that someone wants to come back to the work. Captures can be an leading indicator of future citations.

Examples: bookmarks, code forks, favorites, readers, watchers Learn more

Mentions – Measurement of activities such as news articles or blog posts about research. Mentions is a way to tell that people are truly engaging with the research.

Examples: blog posts, comments, reviews, Wikipedia references, news media Learn more

Social media -This category includes the tweets, Facebook likes, etc. that reference the research. Social Media can help measure "buzz" and attention. Social media can also be a good measure of how well a particular piece of research has been promoted.

PLUM ANALYTICS

Visualizing Impact: Plum Print

- Includes the 5 categories of metrics
- Circles dynamically change size based on metrics in each category

PLUMX

Usage
Clicks: **12**
Abstract Views: **16349**
Downloads: **4579**

Captures
Bookmarks: **1**
Readers: **19**

Mentions
Comments: **5**

Social Media
Likes: **160**
Shares: **72**
+1s: **91**

Citations
RePEc: **1**

see details

- Citations
- Usage
- Captures
- Mentions
- Social Media

ALLmetrics

Indici bibliometrici classici

Journals

Impact factor

Authors

H-index

Articles

Number of citations

Indici innovativi (bibliometrici e non)

Journals	Journal Citation Indicator
Authors	Author Beamplots
Articles	Altmetric e PlumX metric

NEGRAR DI VALPOLICELLA
11-12 FEBBRAIO 2022

Centro Formazione IRCCS "Sacro Cuore-Don Calabria"

11 Febbraio 2022

10.30-10.45	Presentazione ed obiettivi del Corso Stefania GORI - Fabrizio NICOLIS Giovanni L. PAPPAGALLO
10.45-11.30	Tipologia delle Revisioni della Letteratura Scientifica Obiettivi di una Revisione Sistematica Michela CINQUINI
11.30-12.00	Definizione del quesito clinico e degli outcome di interesse; misure di associazione Giovanni L. PAPPAGALLO
12.00-13.00	Lavoro di gruppo *Summing-Up* (metodo: *What? So What? Now What?*) (valido come prova ECM)
13.000-14.00	Colazione di lavoro
14.00-14.45	Come trovare informazioni - I database bibliografici, i siti di linee guida e studi clinici... Veronica Andrea FITTIPALDO
14.45-15.30	Definizione della strategia di ricerca e di selezione degli studi; *study flow* Michela CINQUINI
15.30-16.00	Metodi di valutazione di autori e riviste scientifiche: indici bibliometrici classici e innovativi Giulio ZUANETTI
16.00-16.30	Coffee Break
16.30-17.30	Valutazione del rischio di *bias* negli studi selezionati Ivan MOSCHETTI
17.30-18.30	Lavoro di gruppo *Summing-Up* (metodo: *What? So What? Now What?*) (valido come prova ECM)

VALIDITA' INTERNA

La misura in cui uno studio riesce a cogliere la relazione «**vera»** fra due variabili

ERRORE CASUALE

ERRORE SISTEMATICO (BIAS)

ERRORE CASUALE

Errore che si verifica per effetto del caso

Replicazioni multiple della stessa misurazione producono differenti risultati in tutte le direzioni per variazioni casuali ma la media dà il risultato corretto

ERRORE SISTEMATICO

Errore che si verifica per la presenza di un fattore che distorce sistematicamente le osservazioni nella stessa direzione

Es: mancanza di cecità e dati self report; pazienti diversi per fattori prognostici nei due gruppi a confronto

Replicazioni multiple della stessa misurazione producono risultati sempre nella stessa direzione e “sbagliati”

Bias

Systematic distortion of the estimated intervention effect away from the truth, caused by **inadequacies** in the **design**, **conduct**, or **analysis** of a trial , or in the **publication of its results**. In other words, in a biased trial, the results observed reflect other factors in addition to (or, in extreme cases, instead of) the effect of the tested therapeutic procedure alone.

Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 2001;134:663–94

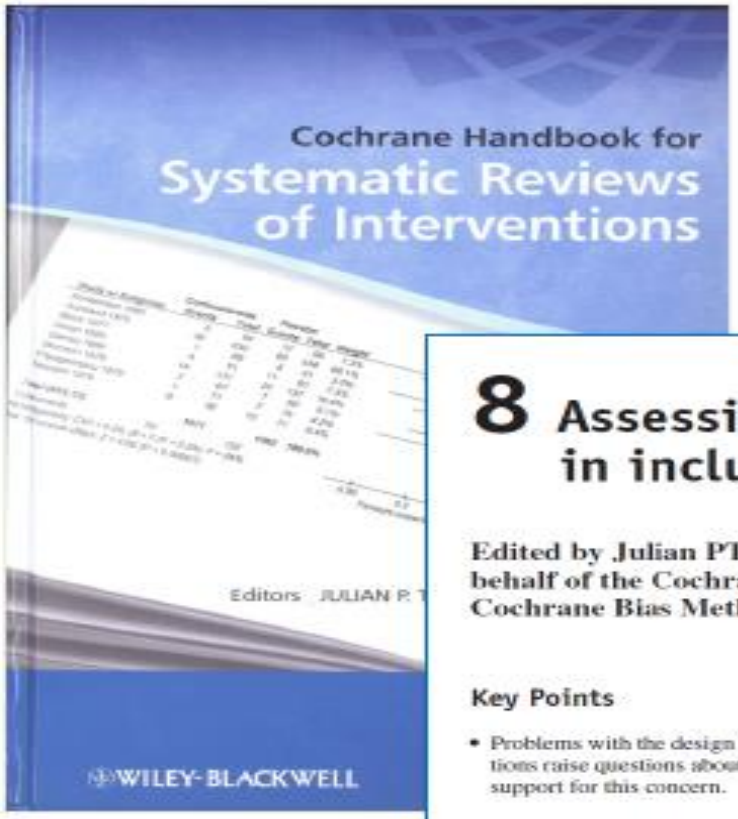
Errore sistematico e validità interna di uno studio

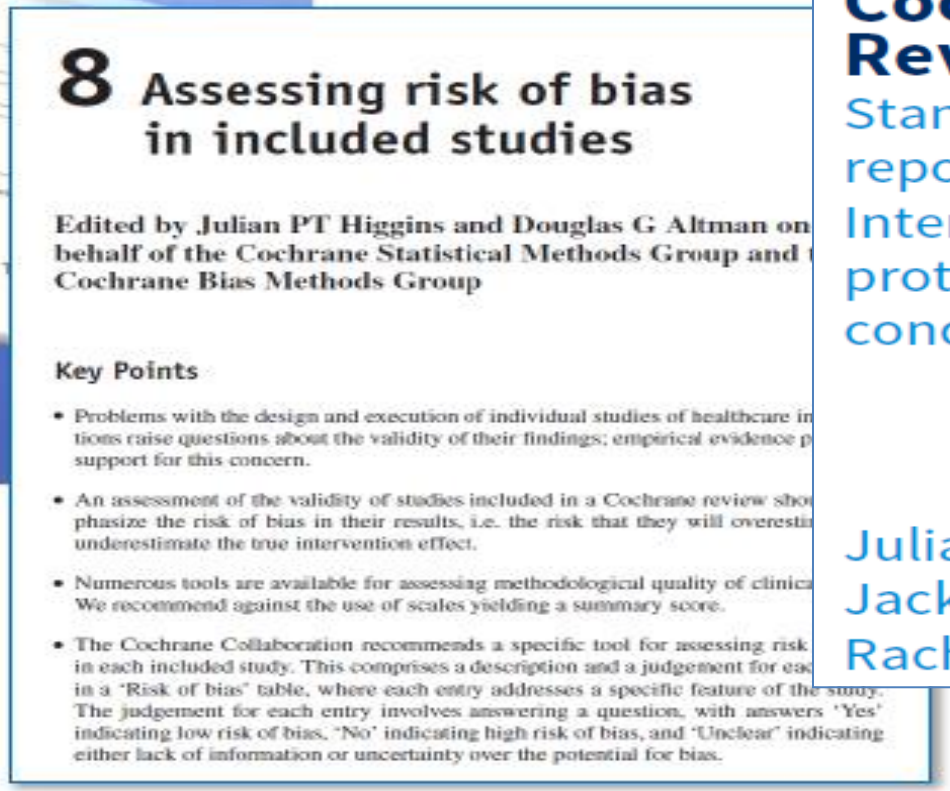
- I risultati di uno studio sono tanto più validi (probabilmente veri) quanto meno esso è affetto da errori sistematici
- Gli errori sistematici vanno previsti ed evitati o ridotti in fase di disegno dello studio

Checklists - le più note

Jadad 1996; ogni area
Pedro; 2000 per valutare i trials inclusi nel database di fisioterapia PEDro
Chalmers: 1981; terapia farmacologica; 32 items
Reisch ; 1989; ogni area; 34 items
DELPHI list; 1998; 9 items; ogni area
Maastricht Amsterdam List (MAL): 1997; back pain
CONSORT (quality of reporting); 1996; aggiornato nel 2010; 25 items
Cochrane Collaboration risk of bias table 2008

Dove approfondire



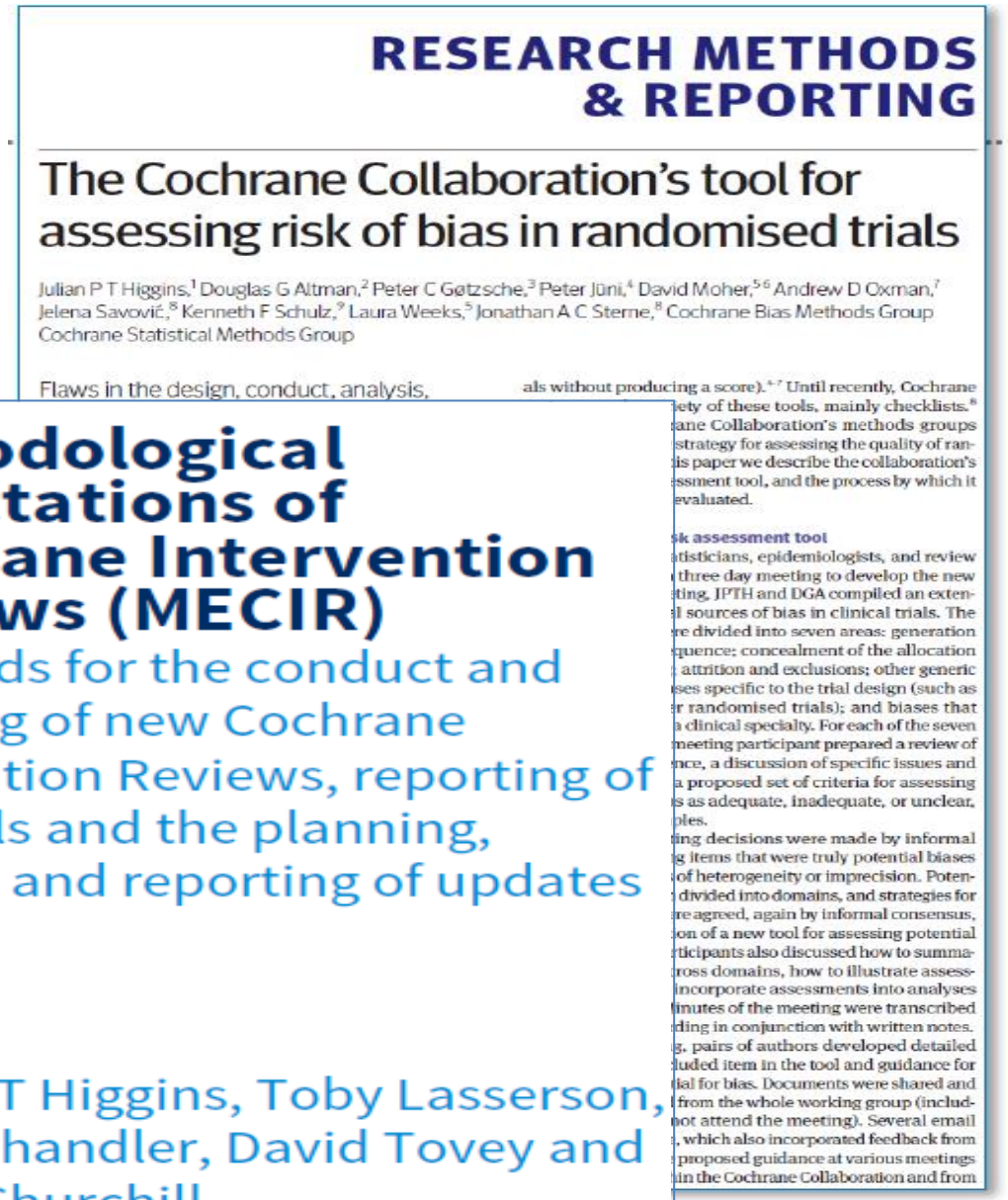


8 Assessing risk of bias in included studies

Edited by Julian PT Higgins and Douglas G Altman on behalf of the Cochrane Statistical Methods Group and t Cochrane Bias Methods Group

Key Points

- Problems with the design and execution of individual studies of healthcare in tions raise questions about the validity of their findings; empirical evidence p support for this concern.
- An assessment of the validity of studies included in a Cochrane review sho phasize the risk of bias in their results, i.e. the risk that they will overesti underestimate the true intervention effect.
- Numerous tools are available for assessing methodological quality of clinica We recommend against the use of scales yielding a summary score.
- The Cochrane Collaboration recommends a specific tool for assessing risk in each included study. This comprises a description and a judgement for eac in a 'Risk of bias' table, where each entry addresses a specific feature of the study. The judgement for each entry involves answering a question, with answers 'Yes' indicating low risk of bias, 'No' indicating high risk of bias, and 'Unclear' indicating either lack of information or uncertainty over the potential for bias.



RESEARCH METHODS & REPORTING

The Cochrane Collaboration's tool for assessing risk of bias in randomised trials

Julian P T Higgins,[1] Douglas G Altman,[2] Peter C Gøtzsche,[3] Peter Jüni,[4] David Moher,[5 6] Andrew D Oxman,[7] Jelena Savović,[8] Kenneth F Schulz,[9] Laura Weeks,[5] Jonathan A C Sterne,[8] Cochrane Bias Methods Group Cochrane Statistical Methods Group

Flaws in the design, conduct, analysis,

als without producing a score).[1-7] Until recently, Cochrane ety of these tools, mainly checklists.[8] ane Collaboration's methods groups strategy for assessing the quality of ran- is paper we describe the collaboration's ssment tool, and the process by which it evaluated.

sk assessment tool

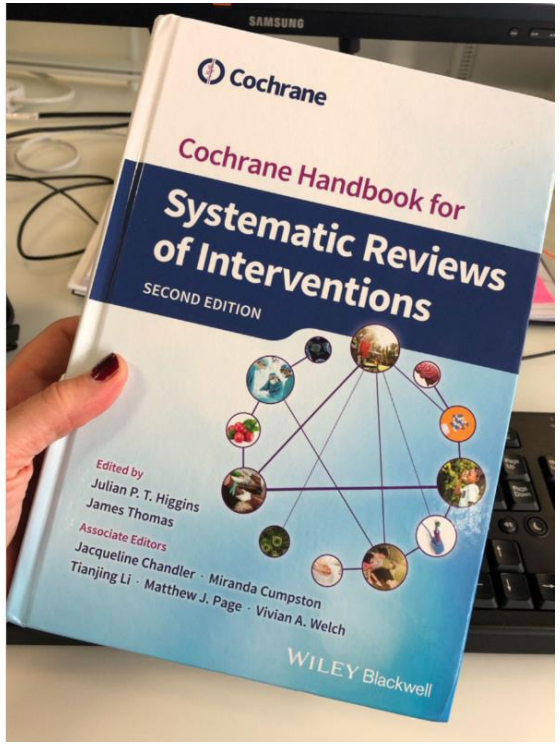
atisticians, epidemiologists, and review three day meeting to develop the new ting. JPTH and DGA compiled an exten- l sources of bias in clinical trials. The re divided into seven areas: generation quence; concealment of the allocation attrition and exclusions; other generic ses specific to the trial design (such as r randomised trials); and biases that a clinical specialty. For each of the seven meeting participant prepared a review of nce, a discussion of specific issues and a proposed set of criteria for assessing s as adequate, inadequate, or unclear, ples. ing decisions were made by informal g items that were truly potential biases of heterogeneity or imprecision. Poten- divided into domains, and strategies for re agreed, again by informal consensus, on of a new tool for assessing potential rticipants also discussed how to summa- ross domains, how to illustrate assess- incorporate assessments into analyses inutes of the meeting were transcribed ding in conjunction with written notes. g, pairs of authors developed detailed luded item in the tool and guidance for ial for bias. Documents were shared and from the whole working group (includ- ot attend the meeting). Several email , which also incorporated feedback from proposed guidance at various meetings in the Cochrane Collaboration and from

Methodological Expectations of Cochrane Intervention Reviews (MECIR)

Standards for the conduct and reporting of new Cochrane Intervention Reviews, reporting of protocols and the planning, conduct and reporting of updates

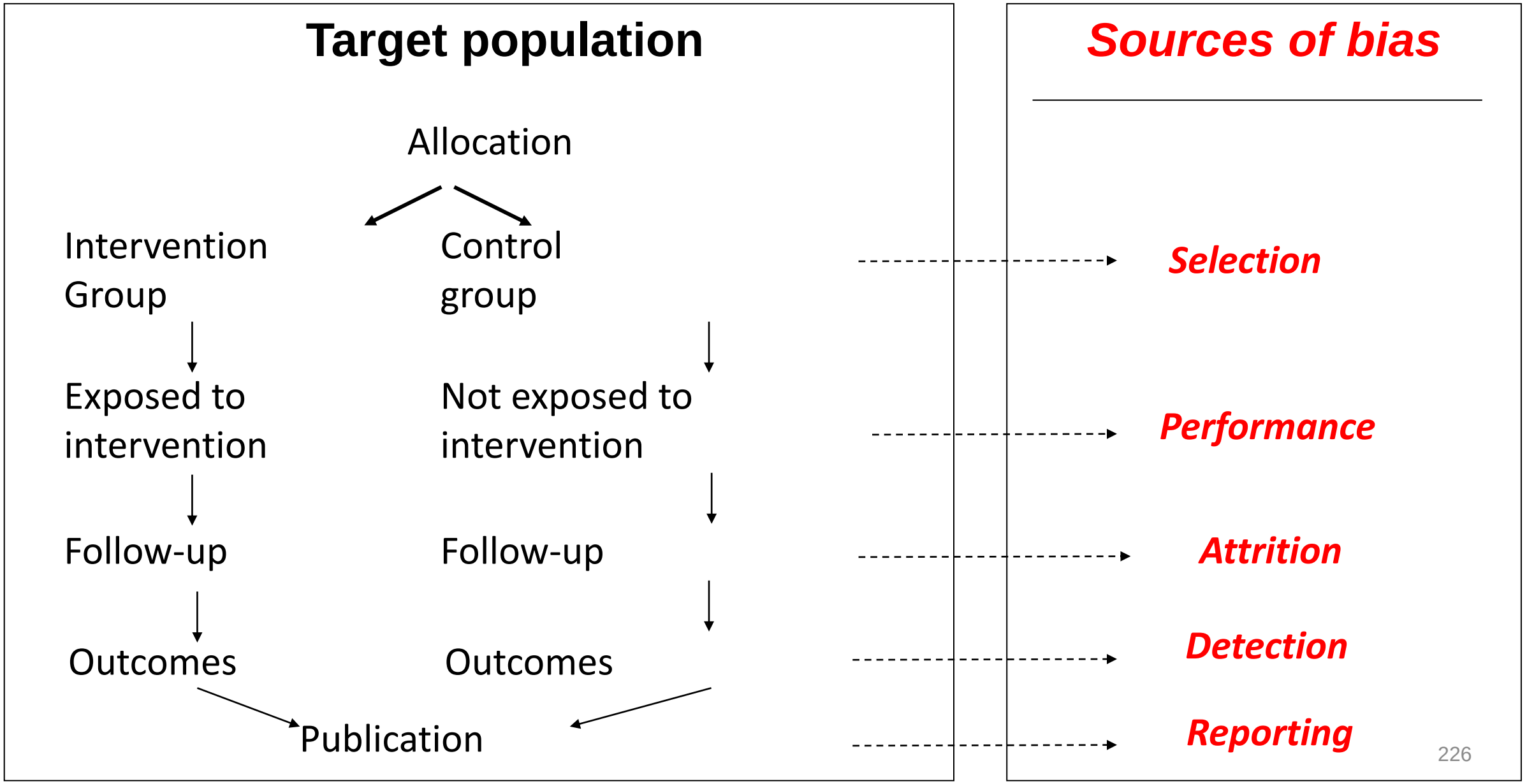
Julian PT Higgins, Toby Lasserson, Jackie Chandler, David Tovey and Rachel Churchill

New Cochrane Handbook for Systematic Reviews of Interventions



Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y / PY / PN / N / NI	[Description]
	1.2 Was the allocation sequence concealed until participants were recruited and assigned to interventions?	Y / PY / PN / N / NI	[Description]
	1.3 Were there baseline imbalances that suggest a problem with the randomization process?	Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias arising from the randomization process?		[Rationale]
Bias due to deviations from intended interventions	2.1. Were participants aware of their assigned intervention during the trial?	Y / PY / PN / N / NI	[Description]
	2.2. Were carers and trial personnel aware of participants' assigned intervention during the trial?	Y / PY / PN / N / NI	[Description]
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention beyond what would be expected in usual practice?	NA / Y / PY / PN / N / NI	[Description]
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?	NA / Y / PY / PN / N / NI	[Description]
	2.5 Were any participants analysed in a group different from the one to which they were assigned?	Y / PY / PN / N / NI	[Description]
	2.6 If Y/PY/NI to 2.5: Was there potential for a substantial impact (on the estimated effect of intervention) of analysing participants in the wrong group?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias due to deviations from intended interventions?		[Rationale]
Bias due to missing outcome data	3.1 Were outcome data available for all, or nearly all, participants randomized?	Y / PY / PN / N / NI	[Description]
	3.2 If N/PN/NI to 3.1: Are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?	NA / Y / PY / PN / N / NI	[Description]
	3.3 If N/PN/NI to 3.1: Is there evidence that results were robust to the presence of missing outcome data?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias due to missing outcome data?		[Rationale]
Bias in measurement of the outcome	4.1 Were outcome assessors aware of the intervention received by study participants?	Y / PY / PN / N / NI	[Description]
	4.2 If Y/PY/NI to 4.1: Was the assessment of the outcome likely to be influenced by knowledge of intervention received?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias due to measurement of the outcome?		[Rationale]
Bias in selection of the reported result	Are the reported outcome data likely to have been selected, on the basis of the results, from...		
	5.1. ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Y / PY / PN / N / NI	[Description]
	5.2 ... multiple analyses of the data?	Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias due to selection of the reported result?		[Rationale]
Overall bias	**Risk of bias judgement**	Low / High / Some concerns	[Support]
	Optional: What is the overall predicted direction of bias for this outcome?		[Rationale]

Trial as a flow



randomizzazione

- attribuzione casuale di ogni paziente al gruppo in trattamento sperimentale oppure al gruppo di controllo
- Se è affettutata correttamente, ogni soggetto ha la stessa probabilità di essere assegnato al gruppo sperimentale o al gruppo di controllo
- assicura che tutti i fattori prognostici - **sia noti che sconosciuti** - si distribuiscano omogeneamente nel gruppo sperimentale e in quello di controllo.

Se la randomizzazione non è eseguita in maniera corretta è possibile introdurre un bias di selezione anche negli studi randomizzati

Selection bias: due componenti

Generazione lista di randomizzazione

- **Basso rischio di bias**. Uso di metodi realmente casuali come ad esempio: tavole di numeri random, sistemi computerizzati, lancio di una moneta o di un dado, sorteggio.
- **Alto rischio di bias.** Uso di metodi **NON** realmente casuali come ad esempio: giorno di nascita o di ammissione in ospedale, giudizio del medico, preferenze del paziente, risultati di test di laboratorio, disponibilità del trattamento, alternanza
- **Rischio incerto**. Quando non sono disponibili sufficienti informazioni per definire il rischio (bassa qualità del reporting)

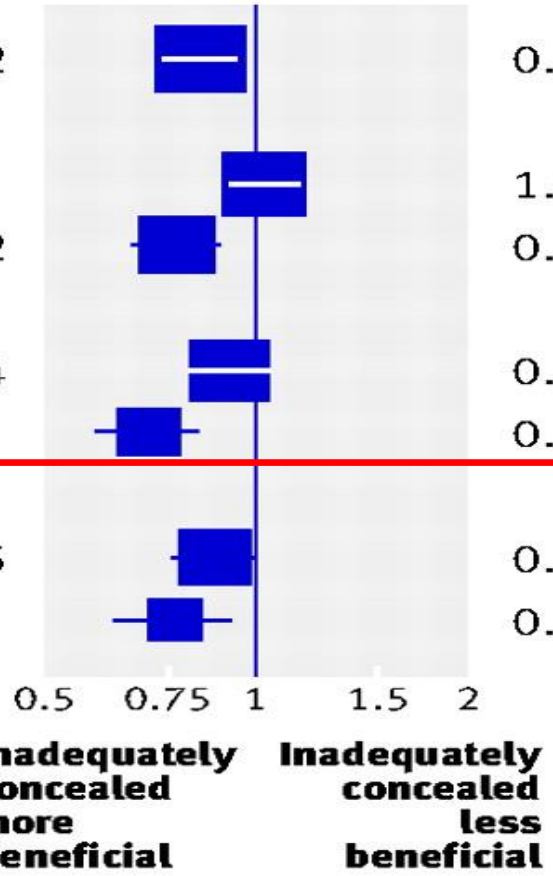
Nascondimento della sequenza di randomizzazione*

- **Basso rischio di bias**. Sperimentatori che arruolano i pazienti non possono prevedere in quale gruppo verrà inserito il paziente perché si usa uno dei seguenti metodi: randomizzazione centralizzata (telefonica, via web, o gestita da personale esterno alla sperimentazione - farmacista, statistico); buste chiuse e opache.
- **Alto rischio di bias.** Sperimentatori che arruolano i pazienti possono prevedere in quale gruppo verrà inserito il paziente perché si usa uno dei seguenti metodi: liste di randomizzazione, buste aperte o non opache, alternanza, data di nascita, numero di cartella, ect.
- **Rischio incerto**. Non sono disponibili sufficienti informazioni per definire il rischio (bassa qualità del reporting)

*allocation concealment

Ratios of odds ratios comparing estimates of intervention effects
532 trials with inadequate or unclear allocation concealment versus 272 trials with adequate concealment

Comparison (No of meta-analyses)	No of trials*	Ratio of odds ratios	Ratio of odds ratios (95% CI)	P value of test of interaction	Variability in bias† (P value)
Overall (102)	532 *v* 272		0.83 (0.74 to 0.93)	–	0.11 (<0.001)
All cause mortality (23)	119 *v* 90		1.01 (0.90 to 1.15)	0.002	0.02 (0.24)
Other outcomes (79)	415 *v* 182		0.76 (0.66 to 0.87)		0.14 (<0.001)
Objective outcomes (62)	310 *v* 174		0.91 (0.80 to 1.03)	0.009	0.11 (<0.001)
Subjective outcomes (40)	222 *v* 98		0.69 (0.59 to 0.82)		0.07 (0.011)
Drug intervention (65)	411 *v* 205		0.87 (0.76 to 1.00)	0.27	0.09 (<0.001)
Other intervention (37)	121 *v* 67		0.77 (0.64 to 0.93)		0.16 (<0.001)



* Inadequately or unclearly concealed *v* adequately concealed

† Between-meta-analysis heterogeneity variance

Wood, L. et al. BMJ 2008;336:601-605

Blinding

- Sperimentatori e partecipanti non conoscono gruppo di allocazione (*performance bias*)

- Valutatori degli esiti non conoscono gruppo di allocazione (*detection bias*)

Singolo cieco
i pazienti inclusi nello studio non conoscono il gruppo al quale sono stati assegnati

Doppio cieco
i pazienti e gli sperimentatori non conoscono il gruppo al quale (i pazienti) sono stati assegnati

Triplo cieco
i pazienti, gli sperimentatori e i valutatori degli esiti non conoscono il gruppo di allocazione

…

Non sempre il significato è questo … è sempre bene valutare chi è davvero in cieco!

Performance bias

Si verifica quando i partecipanti allo studio (sperimentatori o pazienti) modificano i loro comportamenti perché sanno a quale gruppo è assegnato un dato paziente

Esempi:

Lo sperimentatore controlla la presenza di effetti avversi più frequentemente nei pazienti assegnati al gruppo di trattamento.

Un paziente nel gruppo placebo assume altri farmaci, fa più (o meno) visite di controllo.

Detection bias

Si verifica quando la valutazione degli esiti dello studio viene influenzata dalla conoscenza del gruppo al quale è assegnato un dato paziente

Esempi:

Interpretazione di esiti radiologici, risoluzione dei sintomi, valutazione delle ricadute di malattia diversa nei pazienti assegnati al trattamento e al controllo

Performance&Detection bias

- Derivano da comportamenti consci o non consci
- Sovrastimano/sottostimano l'effetto dell'intervento
- La distorsione potenziale è tanto maggiore quanto più soggettivo è l'esito misurato
- Si limitano se pazienti, sperimentatori, valutatori degli esiti dello studio non sono a conoscenza del trattamento che il paziente sta effettivamente ricevendo

Performance bias

Cecità di pazienti e sperimentatori

- **Basso rischio di bias.** Pazienti e sperimentatori non conoscono l'assegnazione dei pazienti al gruppo di controllo o di trattamento oppure è poco probabile che la mancanza di cecità influenzi la performance di pazienti e sperimentatori
- **Alto rischio di bias.** Pazienti e sperimentatori conoscono l'assegnazione dei pazienti o, durante lo studio, diventa chiaro a quale gruppo di trattamento sono allocati (rottura del cieco). Studi definiti come "open label"
- **Rischio incerto**. Quando non sono disponibili sufficienti informazioni per definire il rischio (bassa qualità del reporting)

Conduzione dello studio in cieco

Trattamento sperimentale = controllo (ad esempio, capsule identiche nell'aspetto, forma, colore, sapore).

Non sempre si può fare (ad esempio confronto tra farmaci con profili di tossicità specifici, interventi fisioterapici, educativi, chirurgici, ecc).

Non basta pianificarlo. E' importante garantire che, durante lo studio, sperimentatori e pazienti non "scoprano" il gruppo di allocazione (ad esempio perché un trattamento ha effetti collaterali particolari).

Detection bias

Cecità del valutatore degli esiti dello studio (outcome)

- **Basso rischio di bias.** L'esito dello studio è valutato senza conoscere l'assegnazione dei pazienti al gruppo di controllo o di intervento; oppure è poco probabile che la mancanza di cecità influenzi la valutazione
- **Alto rischio di bias.** L'esito dello studio è valutato conoscendo l'assegnazione dei pazienti al gruppo di controllo o di intervento ed è probabile che la mancanza di cecità influenzi la valutazione
- **Rischio incerto**. Quando non sono disponibili sufficienti informazioni per definire il rischio (bassa qualità del reporting)

Valutazione esiti in cieco

- Gli esiti di uno studio possono essere valutati dai pazienti stessi (diari, questionari), dagli sperimentatori, oppure da valutatori indipendenti
- Visite di follow up effettuate da uno sperimentatore diverso
- Non sempre si può fare (ad esempio esiti riferiti dal paziente in uno studio in aperto)
- Tanto più l'esito è soggettivo (dolore, qualità della vita, ecc.) tanto più il rischio di detection bias è alto se la valutazione non avviene in cieco.
- Anche esiti apparentemente oggettivi, non sempre lo sono (imaging, morte/causa)

Performance and detection bias

- Impatto diverso su outcome **soggettivi** e **oggettivi** (quindi la valutazione va fatta separatamente)
- Se studio su **farmaco in doppio cieco** e dice che tutti gli operatori erano all'oscuro dell'assegnazione è probabile che sia in cieco anche l'outcome assessor, anche se non espressamente detto
- Se studio su **interventi che non possono essere in doppio cieco** (psicosociali, educativi, chirurgici, riabilitativi) importante che sia in cieco l'outcome assessor e deve essere specificato
  - Performance: high risk per outcomes soggettivi sempre
  - Detection: low risk se c'è blinding of outcome assessor anche per outcomes soggettivi

Allocation concealment

≠

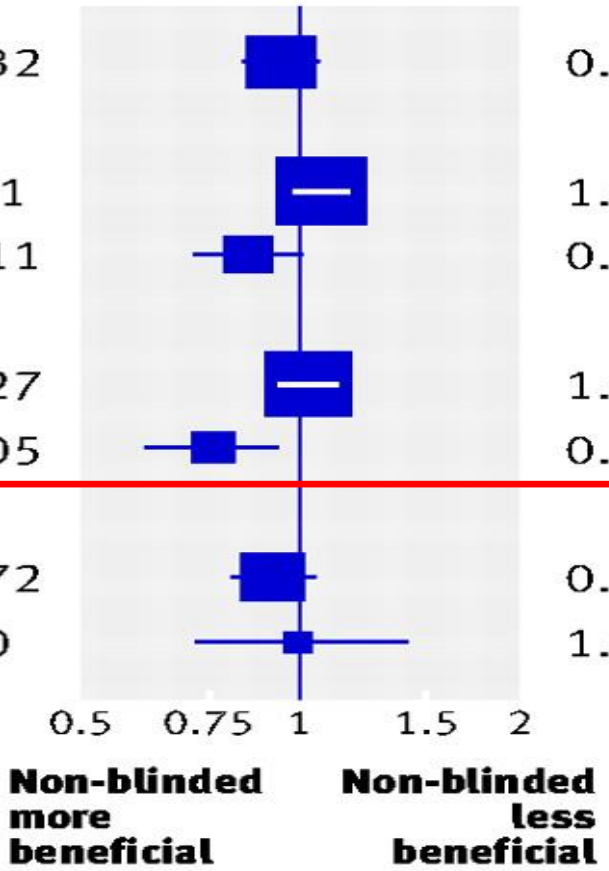
Blinding

- It prevents **selection bias** in intervention assignment by protecting the allocation sequence **before and until** assignment
- It can always be successfully implemented regardless of the study topic

- It seeks to prevent **performance and detection bias** by protecting the sequence **after** assignment
- Not always feasible – for example, in trials comparing surgical with medical interventions

Ratios of odds ratios comparing intervention effect estimates in 314 non-blinded trials versus 432 blinded trials.

Comparison (No of meta-analyses)	No of trials*	Ratio of odds ratios	Ratio of odds ratios (95% CI)	P value of test of interaction	Variability in bias† (P value)
Overall (76)	314 *v* 432		0.93 (0.83 to 1.04)	–	0.11 (<0.001)
All cause mortality (18)	79 *v* 121		1.04 (0.95 to 1.14)	0.011	0.01 (0.27)
Other outcomes (58)	235 *v* 311		0.83 (0.70 to 0.98)		0.18 (<0.001)
Objective outcomes (44)	210 *v* 227		1.01 (0.92 to 1.10)	0.01	0.08 (<0.001)
Subjective outcomes (32)	104 *v* 205		0.75 (0.61 to 0.82)		0.14 (0.001)
Drug intervention (57)	250 *v* 372		0.92 (0.81 to 1.05)	0.66	0.10 (<0.001)
Other intervention (19)	64 *v* 60		1.00 (0.71 to 1.39)		0.22 (0.003)



* Non-blinded *v* blinded

† Between-meta-analysis heterogeneity variance

Wood, L. et al. BMJ 2008;336:601-605

Attrition bias

- Quando non tutti i soggetti randomizzati completano lo studio
- i soggetti non escono a caso dallo studio: è possibile che quelli che escono siano sistematicamente diversi da quelli che non escono: i gruppi non sono più randomizzati
- **Validità esterna** : es: escono tutti i più giovani, o i meno gravi, o i maschi: posso trarre conclusioni solo su quelli che rimangono
- **Validità interna (Bias):** se la probabilità di uscire dallo studio è legata all'intervento o all'outcome, cioè se quelli che escono hanno sistematicamente probabilità più alte o più basse di avere l'outcome di quelli che restano

Attrition bias

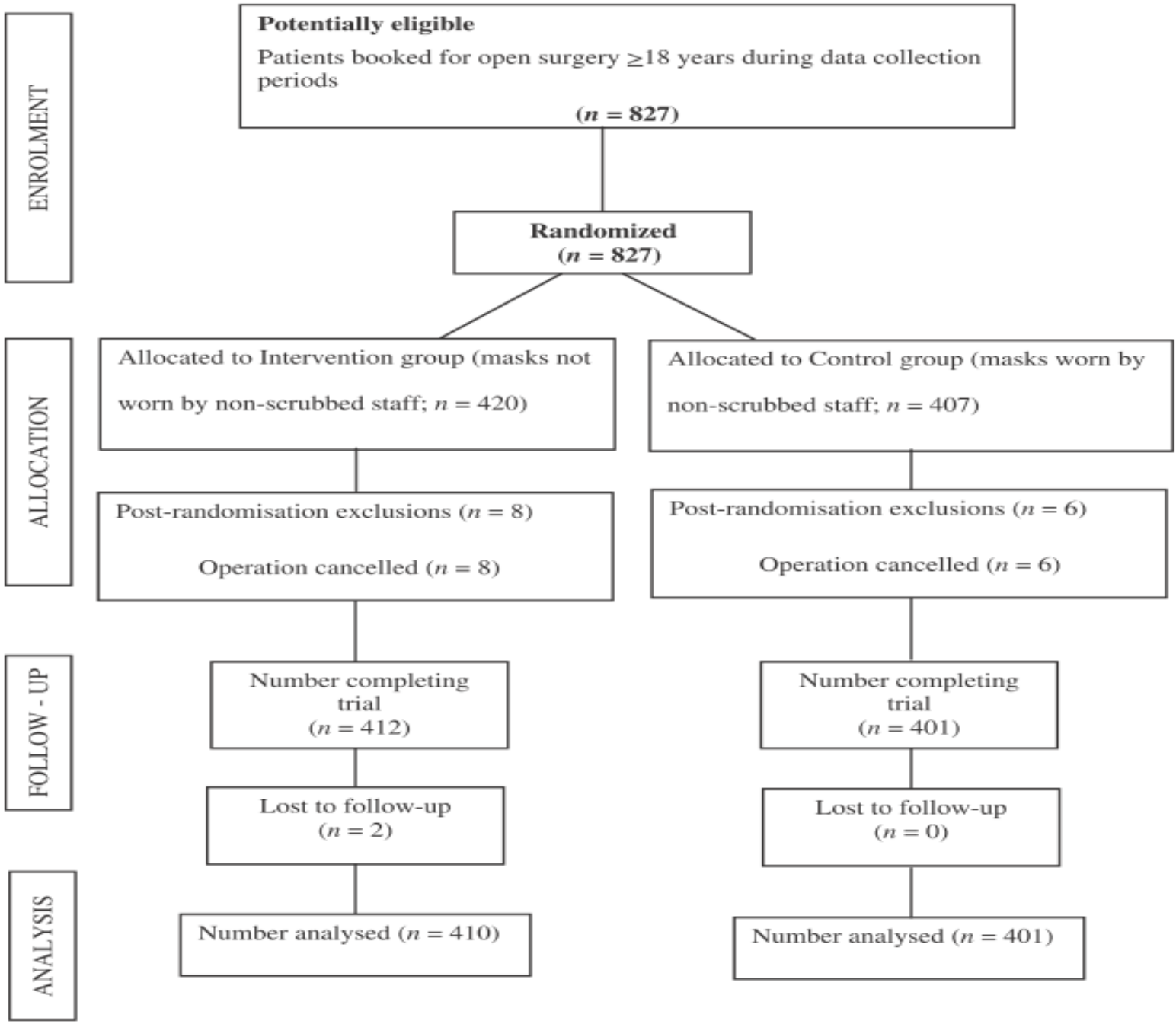
Low risk of bias

- No missing outcome data;
- the proportion of missing outcomes compared with observed event risk not enough to have a relevant impact on the intervention effect;
- Missing outcome data balanced in numbers across intervention groups, with similar reasons across groups;
- Missing data imputed using appropriate methods
- All patients analysed in the group they were allocated to by randomisation irrespective of non-compliance and co-interventions (intention to treat)

High risk of bias:

- the proportion of missing outcomes compared with observed event risk enough to induce relevant bias in intervention effect estimate
- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;

A tota
enrolled and 811 (98.1%) patients complete
group and 410 No Mask group (Fig. 1).



What is publication bias (1)?

- Definition

"Publication bias refers to the greater likelihood that studies with positive results will be published"

JAMA 2002;287:2825-2828

What is publication bias (2)?

- An alternative definition:

Publication bias is the selective or *multiple* publication *or suppression* of trial results so that the scientific record is distorted

Extension: applied to trial parts - outcomes, subgroups, adverse events REPORTING BIAS

The likelihood of finding studies is related to the results of those studies (positive vs negative/detrimental)

Why does it matter?

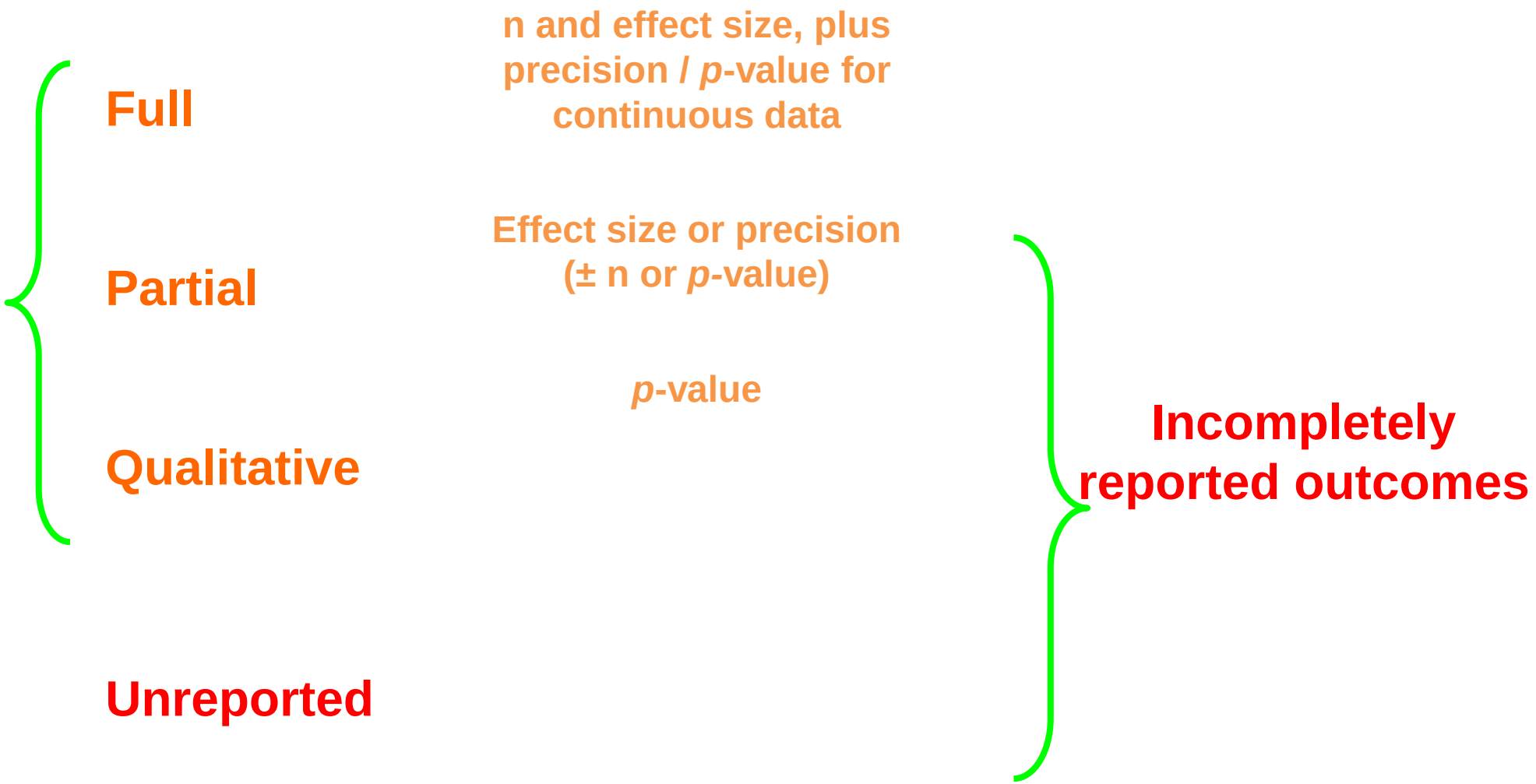
- Distorts the scientific record
- Hides the “truth”
- Influences doctors’ decision making
- Misleads policy makers
- Causes harm to patients
- Costly for the health service
- A form of scientific and research misconduct

- TO U: It will matter if the studies you don’t find differ systematically from the ones you have found
- You might arrive at different answers, or even THE WRONG ANSWER

Outcome reporting bias

Reporting bias is selection bias

- Reporting bias is perhaps the greatest source of selection bias
- Originally defined as the publication or non-publication of studies depending on the direction and statistical significance of the results
- Is a complex phenomenon


Full
n and effect size, plus precision / p-value for continuous data
Partial
Effect size or precision (± n or p-value)
Qualitative
p-value
Unreported
Incompletely reported outcomes

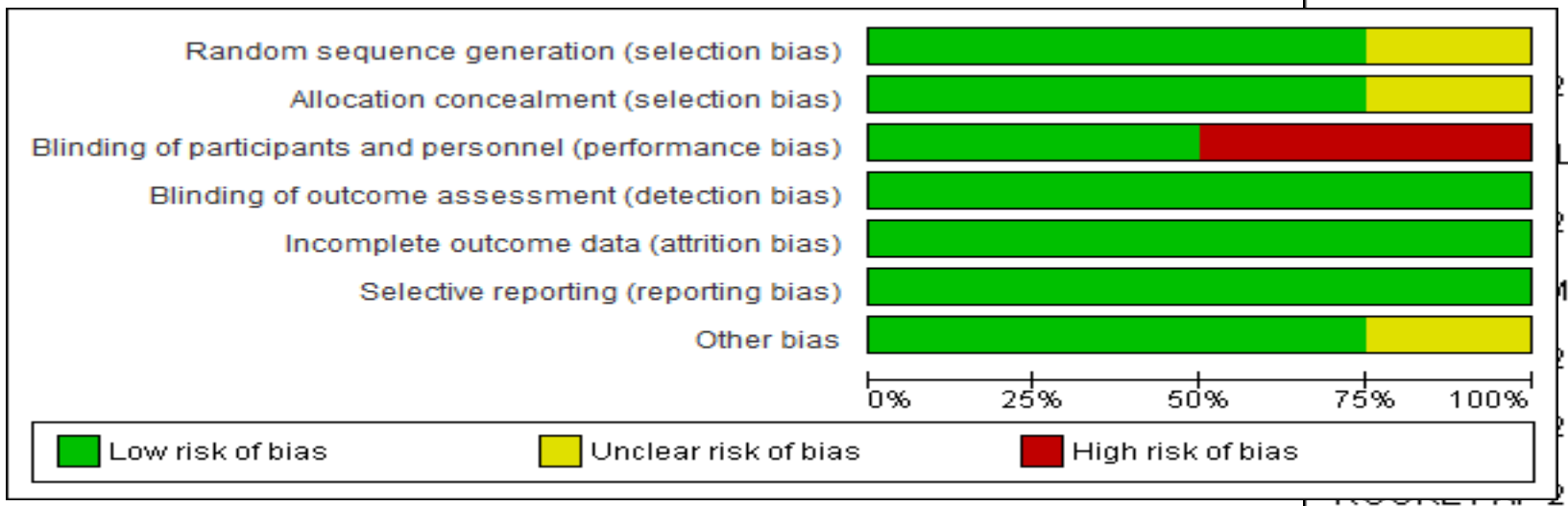
(Chan, 2004)

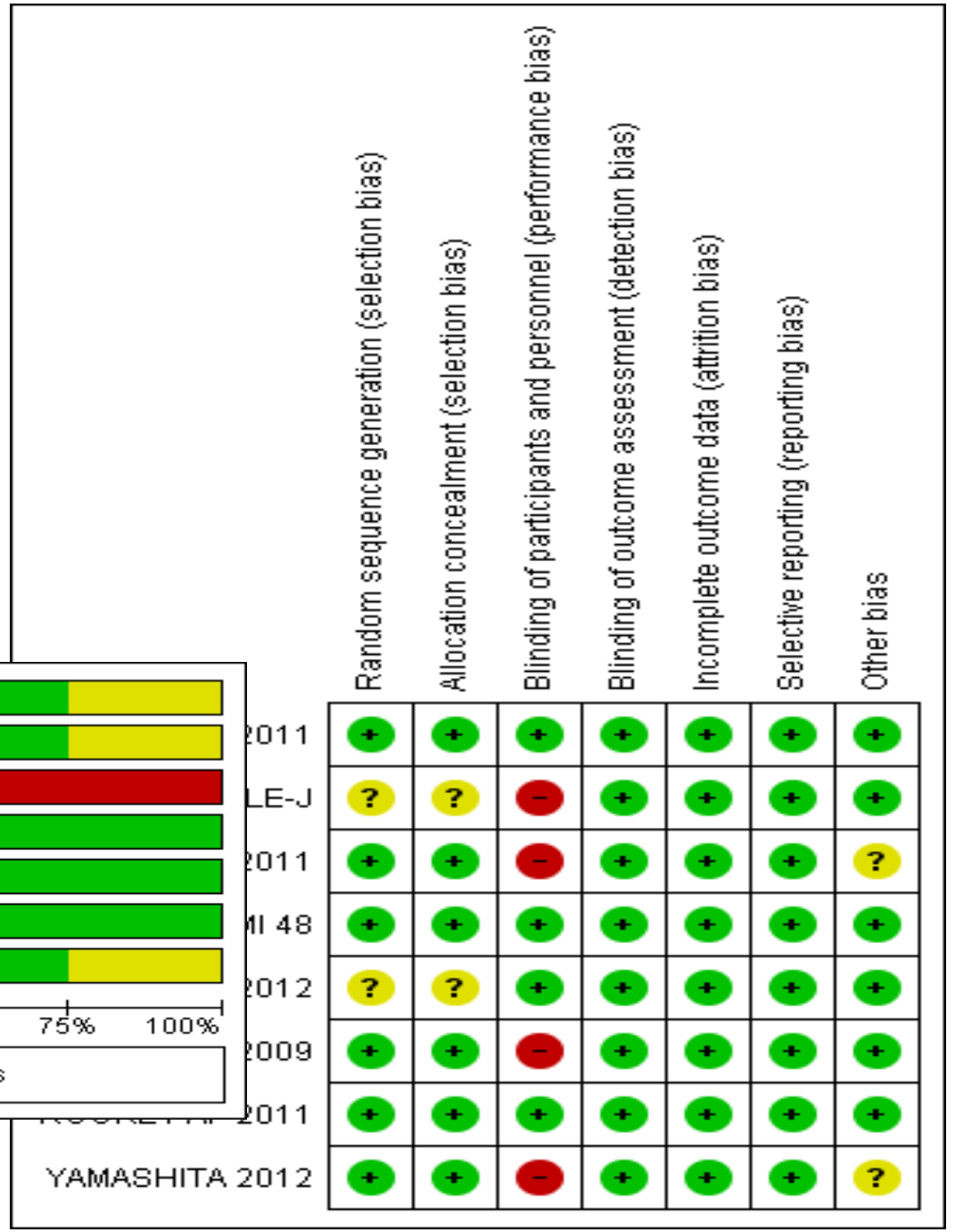
Risk of bias in one study

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias)	High risk	open label
Blinding of outcome assessment (detection bias)	Low risk	An independent blinded endpoint committee adjudicated all reported bleeding and efficacy events
Incomplete outcome data (attrition bias)	Low risk	ITT. all patients followed up
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Risk of bias across studies/domains





NEGRAR DI VALPOLICELLA
11-12 FEBBRAIO 2022

Centro Formazione IRCCS "Sacro Cuore-Don Calabria"

11 Febbraio 2022

10.30-10.45	Presentazione ed obiettivi del Corso Stefania GORI - Fabrizio NICOLIS Giovanni L. PAPPAGALLO
10.45-11.30	Tipologia delle Revisioni della Letteratura Scientifica Obiettivi di una Revisione Sistematica Michela CINQUINI
11.30-12.00	Definizione del quesito clinico e degli outcome di interesse; misure di associazione Giovanni L. PAPPAGALLO
12.00-13.00	Lavoro di gruppo *Summing-Up* (metodo: *What? So What? Now What?*) (valido come prova ECM)
13.000-14.00	Colazione di lavoro
14.00-14.45	Come trovare informazioni - I database bibliografici, i siti di linee guida e studi clinici... Veronica Andrea FITTIPALDO
14.45-15.30	Definizione della strategia di ricerca e di selezione degli studi; *study flow* Michela CINQUINI
15.30-16.00	Metodi di valutazione di autori e riviste scientifiche: indici bibliometrici classici e innovativi Giulio ZUANETTI
16.00-16.30	Coffee Break
16.30-17.30	Valutazione del rischio di *bias* negli studi selezionati Ivan MOSCHETTI
17.30-18.30	Lavoro di gruppo *Summing-Up* (metodo: *What? So What? Now What?*) (valido come prova ECM)

NEGRAR DI VALPOLICELLA
11-12 FEBBRAIO 2022

Centro Formazione IRCCS "Sacro Cuore-Don Calabria"

12 Febbraio 2022

09.00-10.00	Eterogeneità Michela CINQUINI
10.00-11.00	Summary of Findings Tables (1ª parte) Ivan MOSCHETTI
11.00-11.30	Coffee Break
11.30-12.00	Summary of Findings Tables (2ª parte) Ivan MOSCHETTI
12.00-13.00	Lavoro di gruppo *Summing-Up* (metodo: *What? So What? Now What?*) (valido come prova ECM)
13.00-13.15	Conclusione del Corso Stefania GORI - Giovanni L. PAPPAGALLO

Principi di una meta-analisi

Una **meta-analisi** può:

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

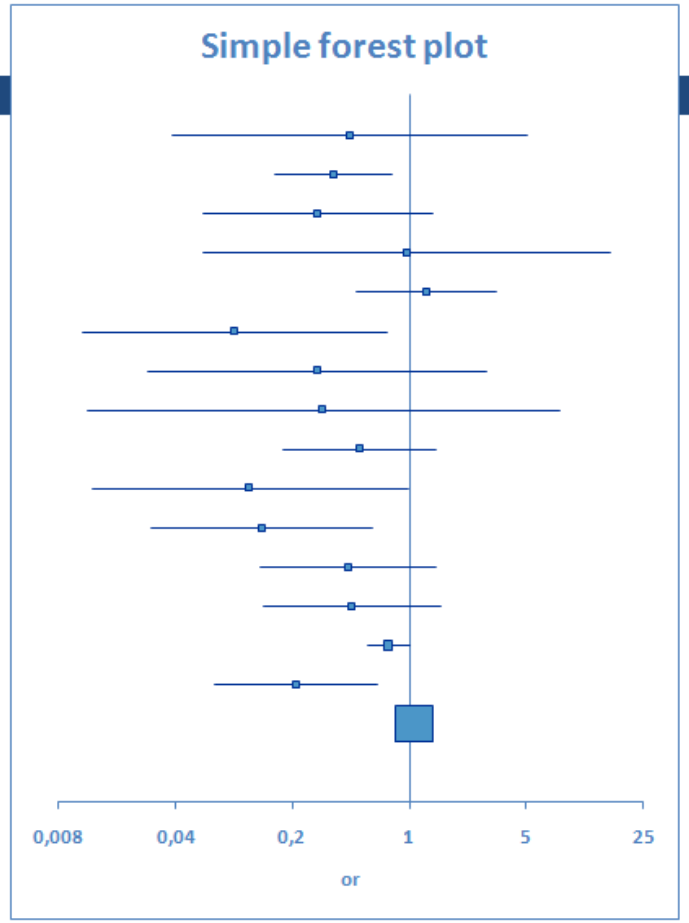
•Esplorare l'eterogeneità tra gli studi (e le relative fonti di eterogeneità).

E' efficace?

Author(s)		Reference					
Teo et al.		Effects of intravenous magnesium in suspected acute myocardial infarction. BMJ 1991;303:1499–501					
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

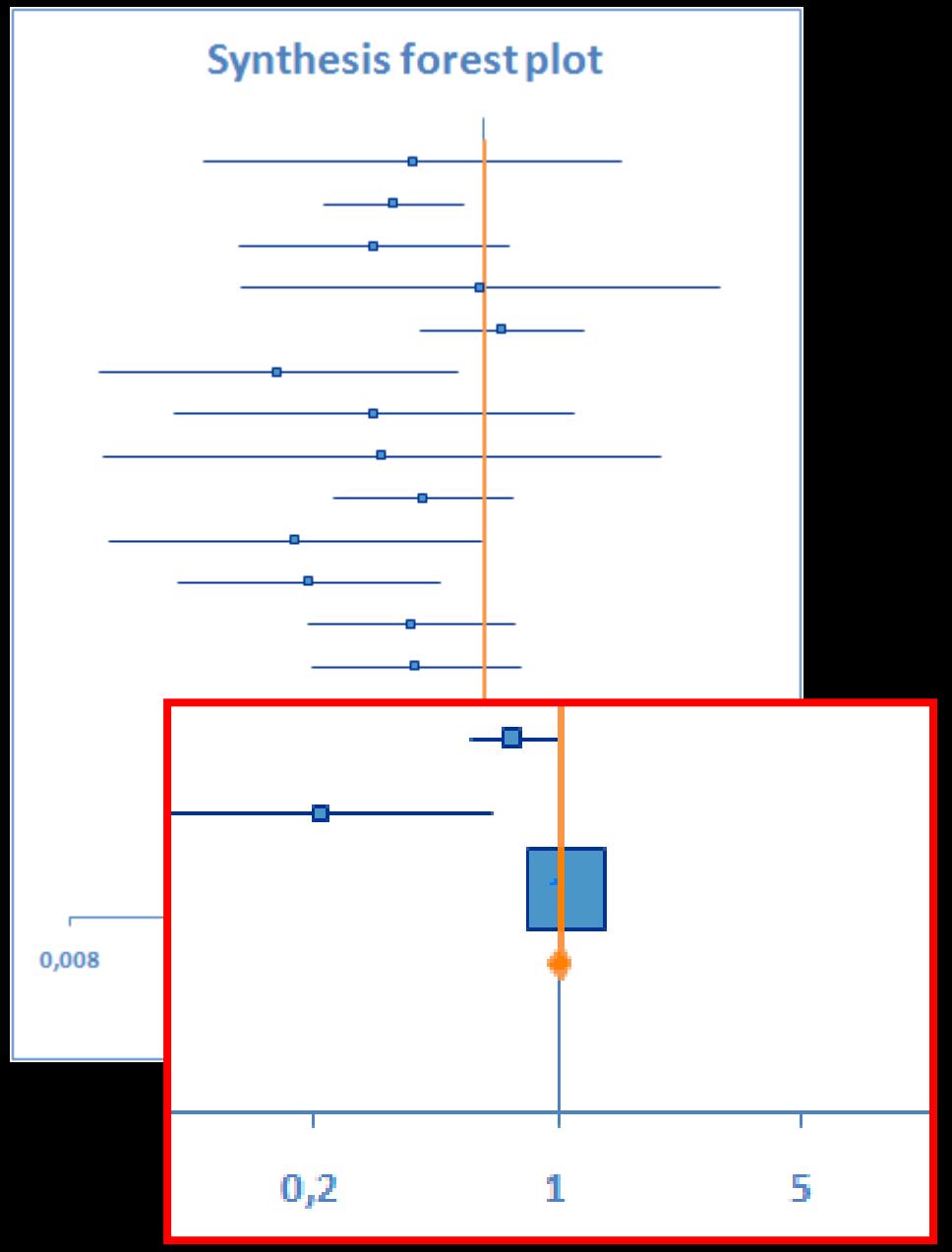
Number of studies	16
Number of participants	62607 (62607)

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

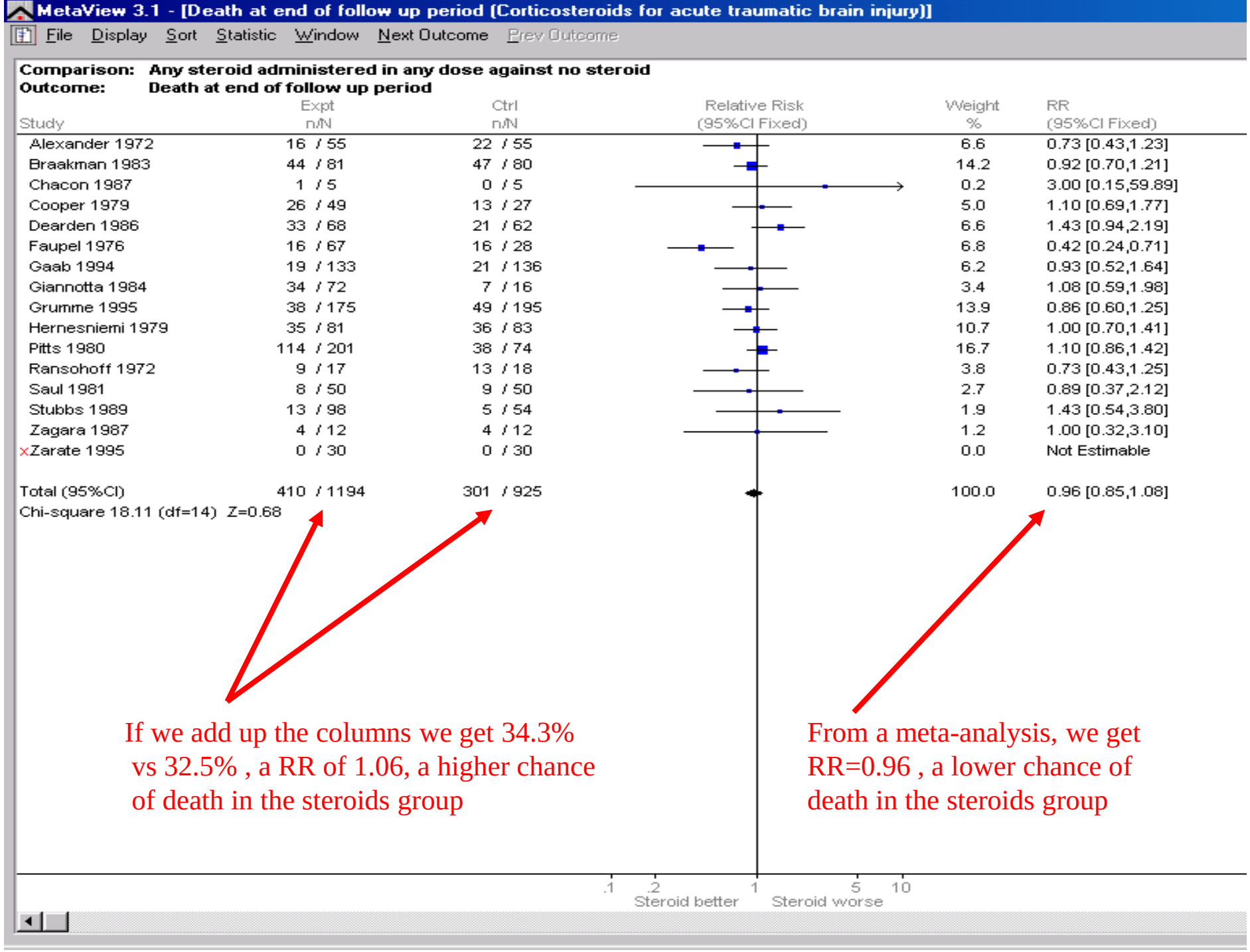
Heterogeneity

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%



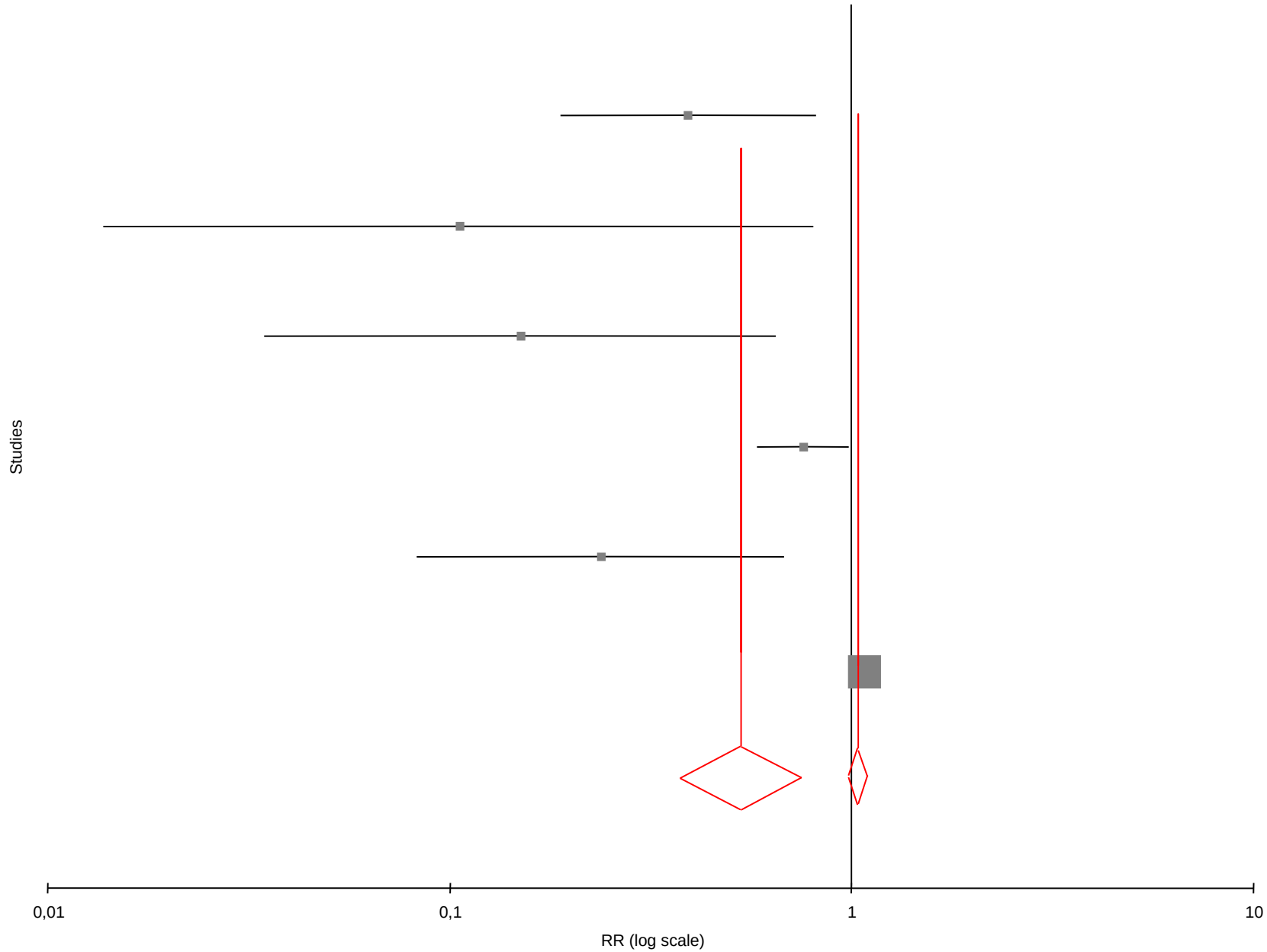
Could we just add the data from all the trials together?

- 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



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


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?


KEEP
CALM
e fà
BALA'
L'OEUCC!

- 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)

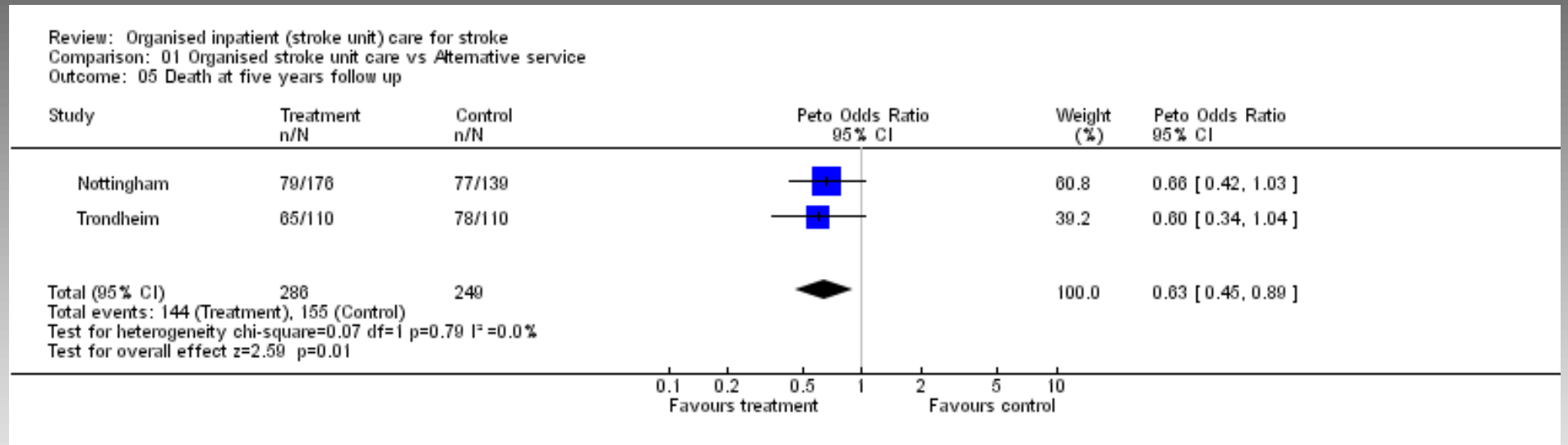
p=<0.10 (heterogeneity)

- 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….

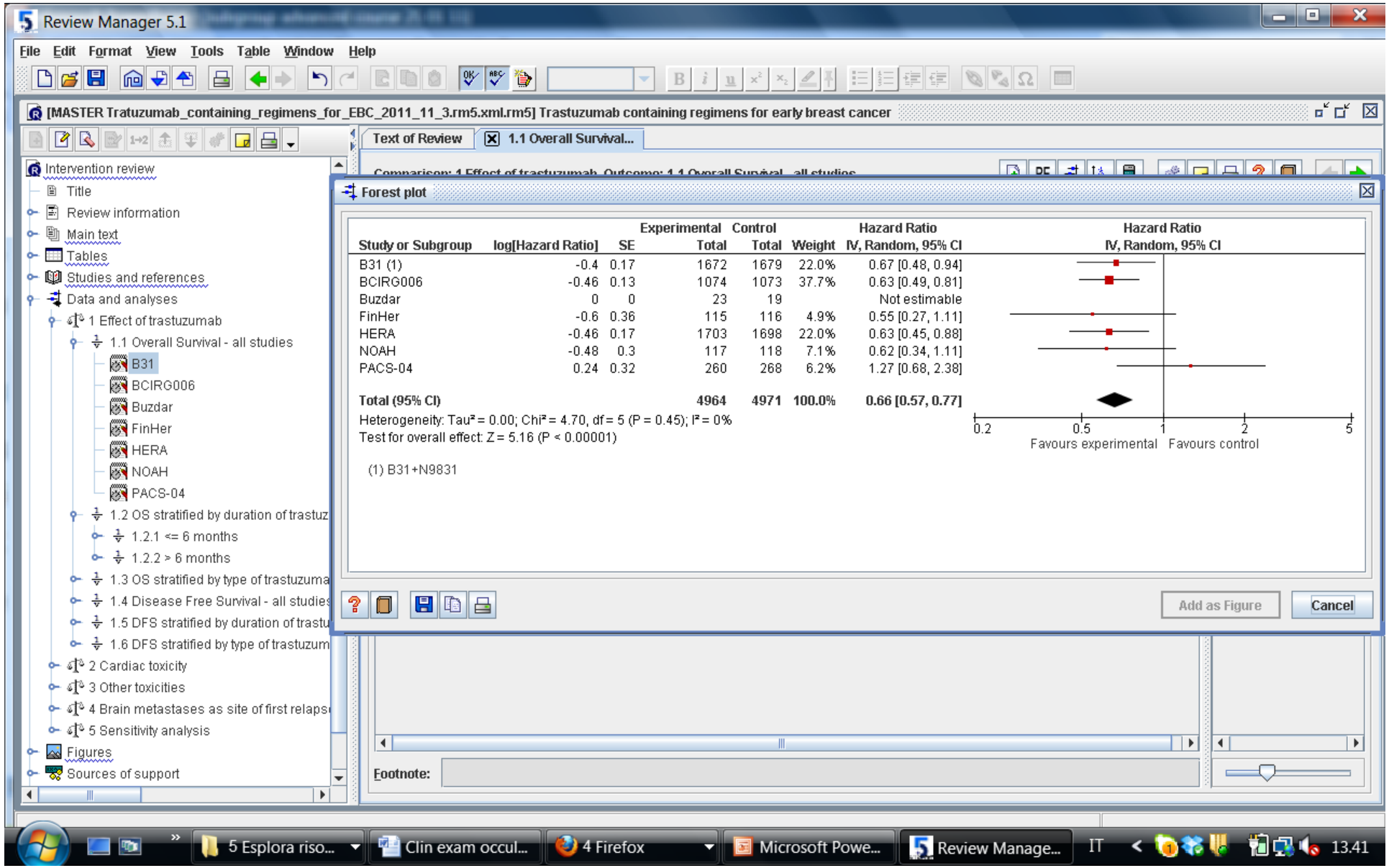
Esempio di Metaview

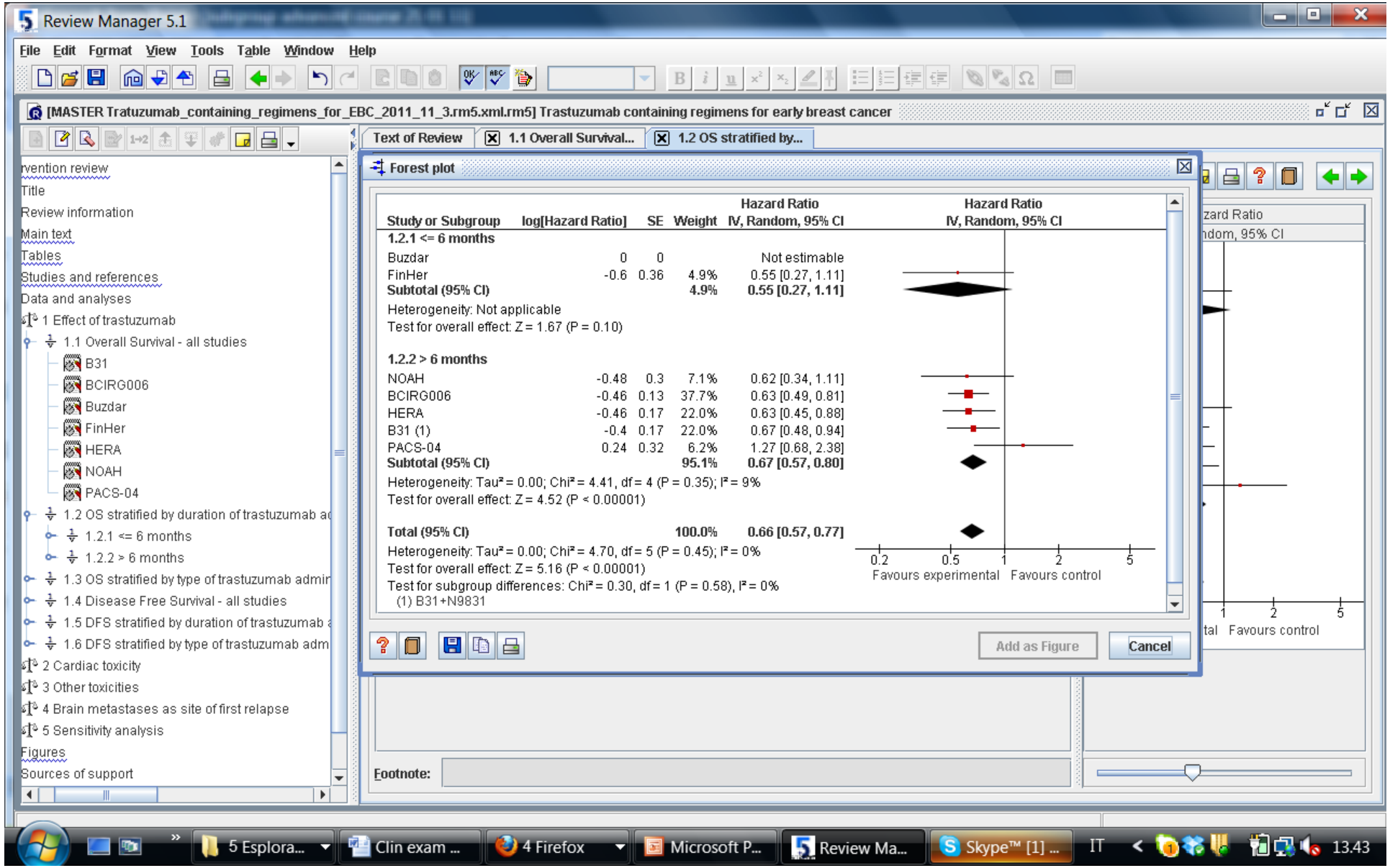


How to deal with heterogeneity

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)

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)
(1) B31+N9831
0.2 0.5 1 2 5
Favours experimental Favours control
Add as Figure
Cancel
Footnote:
5 Esplora riso...
Clin exam occul...
4 Firefox
Microsoft Powe...
Review Manage...
IT
13.41


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
Hazard Ratio IV, Random, 95% CI
0.2 0.5 1 2 5
Favours experimental Favours control
Add as Figure
Cancel
Footnote:
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 trastuzumab
1.2.1 <= 6 months
1.2.2 > 6 months
1.3 OS stratified by type of trastuzumab
1.4 Disease Free Survival - all studies
1.5 DFS stratified by duration of trastuzumab
1.6 DFS stratified by type of trastuzumab
2 Cardiac toxicity
3 Other toxicities
4 Brain metastases as site of first relapse
5 Sensitivity analysis
Figures
Sources of support
Favours control
IT
13.43

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

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

NEGRAR DI VALPOLICELLA
11-12 FEBBRAIO 2022

Centro Formazione IRCCS "Sacro Cuore-Don Calabria"

12 Febbraio 2022

09.00-10.00	Eterogeneità Michela CINQUINI
10.00-11.00	Summary of Findings Tables (1ª parte) **Ivan MOSCHETTI**
11.00-11.30	Coffee Break
11.30-12.00	Summary of Findings Tables (2ª parte) **Ivan MOSCHETTI**
12.00-13.00	Lavoro di gruppo *Summing-Up* (metodo: *What? So What? Now What?*) (valido come prova ECM)
13.00-13.15	Conclusione del Corso Stefania GORI - Giovanni L. PAPPAGALLO

Cos'è la Summary Of Findings

- **Summary of findings**: tabular presentation of key information about relevant outcomes of alternative health care interventions. It presents information about the body of evidence, key numerical results, and **summary judgment about the certainty of underlying evidence** for each outcome. SoF table has been chosen by the Cochrane Collaboration to present main findings of a systematic review.

Evidence profile: summary of evidence for a given question; it rpesentes relevant information about the body of evidence, key numerical results, and with a **detailed quality assessment** and a explicit judgment of each factor that determines the quality. Used by guideline producers

PICO

Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease
Settings: primary care, community, outpatient
Intervention: self management[1]
Comparision: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **usual care**	Corresponding risk **self management**				
Quality of Life St George's Respiratory Questionnaire. Scale from: 0 to 100. (follow-up: 3 to 12 months)	The mean quality of life ranged across control groups from **38 to 60 points**	The mean Quality of Life in the intervention groups was **2.58 lower** (5.14 to 0.02 lower)		698 (7)	⊕⊕⊕◯ **moderate**[2]	Lower score indicates better quality of life. A change of less than 4 points is not shown to be important to patients.
Dyspnoea Borg Scale. Scale from: 0 to 10. (follow-up: 3 to 6 months)	The mean dyspnoea ranged across control groups from **1.2 to 4.1 points**	The mean Dyspnoea in the intervention groups was **0.53 lower** (0.96 to 0.1 lower)		144 (2)	⊕⊕◯◯ **low**[3,4]	Lower score indicates improvement
Number and severity of exacerbations[5]	See comment	See comment	Not estimable[5]	591 (3)	See comment	Effect is uncertain
Respiratory-related hospital admissions (follow-up: 3 to 12 months)	**Low risk population**[6]		**OR 0.64** (0.47 to 0.89)	966 (8)	⊕⊕⊕◯ **moderate**[7]	
	10 per 100	**7 per 100** (5 to 9)				
	High risk population[6]					
	50 per 100	**35 per 100** (27 to 46)				
Emergency department visits for lung diseases (follow-up: 6 to 12 months)	The mean emergency department visits for lung diseases ranged across control groups from **0.2 to 0.7 visits per person per year**	The mean Emergency department visits for lung diseases in the intervention groups was **0.1 higher** (0.2 lower to 0.3 higher)		328 (4)	⊕⊕⊕◯ **moderate**[4]	
Doctor and nurse visits (follow-up: 6 to 12 months)	The mean doctor and nurse visits ranged across control groups from **1 to 5 vists per**	The mean Doctor and nurse visits in the intervention groups was **0.02 higher** (1 lower to 1 higher)		629 (8)	⊕⊕⊕◯ **moderate**[8]	

McMaster University
Inspiring Innovation and Discovery

Primary outcomes – up to 7

Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease
Settings: primary care, community, outpatient
Intervention: self management[1]
Comparision: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **usual care**	Corresponding risk **self management**				
Quality of Life St George's Respiratory Questionnaire. Scale from: 0 to 100. (follow-up: 3 to 12 months)	The mean quality of life ranged across control groups from **38 to 60 points**	The mean Quality of Life in the intervention groups was **2.58 lower** (5.14 to 0.02 lower)		698 (7)	⊕⊕⊕◯ **moderate**[2]	Lower score indicates better quality of life. A change of less than 4 points is not shown to be important to patients.
Dyspnoea Borg Scale. Scale from: 0 to 10. (follow-up: 3 to 6 months)	The mean dyspnoea ranged across control groups from **1.2 to 4.1 points**	The mean Dyspnoea in the intervention groups was **0.53 lower** (0.96 to 0.1 lower)		144 (2)	⊕⊕◯◯ **low**[3,4]	Lower score indicates improvement
Number and severity of exacerbations[5]	See comment	See comment	Not estimable[5]	591 (3)	See comment	Effect is uncertain
Respiratory-related hospital admissions (follow-up: 3 to 12 months)	**Low risk population**[6]		**OR 0.64** (0.47 to 0.89)	966 (8)	⊕⊕⊕◯ **moderate**[7]	
	10 per 100	**7 per 100** (5 to 9)				
	High risk population[6]					
	50 per 100	**35 per 100** (27 to 46)				
Emergency department visits for lung diseases (follow-up: 6 to 12 months)	The mean emergency department visits for lung diseases ranged across control groups from **0.2 to 0.7 visits per person per year**	The mean Emergency department visits for lung diseases in the intervention groups was **0.1 higher** (0.2 lower to 0.3 higher)		328 (4)	⊕⊕⊕◯ **moderate**[4]	
Doctor and nurse visits (follow-up: 6 to 12 months)	The mean doctor and nurse visits ranged across control groups from **1 to 5 vists per**	The mean Doctor and nurse visits in the intervention groups was **0.02 higher** (1 lower to 1 higher)		629 (8)	⊕⊕⊕◯ **moderate**[8]	

- Choose primary outcomes early – avoid reporting bias
- Choose patient important outcomes
- Include primary outcomes – even if no information
- Describe the outcome – scale, follow-up

McMaster University
Inspiring Innovation and Discovery

Results – Baseline risks (Assumed Risk)

Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease
Settings: primary care, community, outpatient
Intervention: self management[1]
Comparision: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **usual care**	Corresponding risk **self management**				
Quality of Life St George's Respiratory Questionnaire. Scale from: 0 to 100. (follow-up: 3 to 12 months)	The mean quality of life ranged across control groups from **38 to 60 points**	The mean Quality of Life in the intervention groups was **2.58 lower** (5.14 to 0.02 lower)		698 (7)	⊕⊕⊕◯ **moderate**[2]	Lower score indicates better quality of life. A change of less than 4 points is not shown to be important to patients.
Dyspnoea Borg Scale. Scale from: 0 to 10. (follow-up: 3 to 6 months)	The mean dyspnoea ranged across control groups from **1.2 to 4.1 points**	The mean Dyspnoea in the intervention groups was **0.53 lower** (0.96 to 0.1 lower)		144 (2)	⊕⊕◯◯ **low**[3,4]	Lower score indicates improvement
Number and severity of exacerbations[5]	See comment	See comment	Not estimable[5]	591 (3)	See comment	Effect is uncertain
Respiratory-related hospital admissions (follow-up: 3 to 12 months)	**Low risk population**[6] **10 per 100**	**7 per 100** (5 to 9)	**OR 0.64** (0.47 to 0.89)	966 (8)	⊕⊕⊕◯ **moderate**[7]	
	High risk population[6] **50 per 100**	**35 per 100** (27 to 46)				
Emergency department visits for lung diseases (follow-up: 6 to 12 months)	The mean emergency department visits for lung diseases ranged across control groups from **0.2 to 0.7 visits per person per year**	The mean Emergency department visits for lung diseases in the intervention groups was **0.1 higher** (0.2 lower to 0.3 higher)		328 (4)	⊕⊕⊕◯ **moderate**[4]	
Doctor and nurse visits (follow-up: 6 to 12 months)	The mean doctor and nurse visits ranged across control groups from **1 to 5 vists per**	The mean Doctor and nurse visits in the intervention groups was **0.02 higher** (1 lower to 1 higher)		629 (8)	⊕⊕⊕◯ **moderate**[8]	

- From meta-analysis
- Needs to be representative of population
- Can present mean, range, low risk, moderate risk, high risk

McMaster University
Inspiring Innovation and Discovery

Results – Risk with intervention (Corresponding Risk)

Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease
Settings: primary care, community, outpatient
Intervention: self management[1]
Comparision: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **usual care**	Corresponding risk **self management**				
Quality of Life St George's Respiratory Questionnaire. Scale from: 0 to 100. (follow-up: 3 to 12 months)	The mean quality of life ranged across control groups from **38 to 60 points**	The mean Quality of Life in the intervention groups was **2.58 lower** (5.14 to 0.02 lower)		698 (7)	⊕⊕⊕◯ **moderate**[2]	Lower score indicates better quality of life. A change of less than 4 points is not shown to be important to patients.
Dyspnoea Borg Scale. Scale from: 0 to 10. (follow-up: 3 to 6 months)	The mean dyspnoea ranged across control groups from **1.2 to 4.1 points**	The mean Dyspnoea in the intervention groups was **0.53 lower** (0.96 to 0.1 lower)		144 (2)	⊕⊕◯◯ **low**[3,4]	Lower score indicates improvement
Number and severity of exacerbations[5]	See comment	See comment	Not estimable[5]	591 (3)	See comment	Effect is uncertain
Respiratory-related hospital admissions (follow-up: 3 to 12 months)	**Low risk population**[6] **10 per 100**	**7 per 100** (5 to 9)	**OR 0.64** (0.47 to 0.89)	966 (8)	⊕⊕⊕◯ **moderate**[7]	
	High risk population[6] **50 per 100**	**35 per 100** (27 to 46)				
Emergency department visits for lung diseases (follow-up: 6 to 12 months)	The mean emergency department visits for lung diseases ranged across control groups from **0.2 to 0.7 visits per person per year**	The mean Emergency department visits for lung diseases in the intervention groups was **0.1 higher** (0.2 lower to 0.3 higher)		328 (4)	⊕⊕⊕◯ **moderate**[4]	
Doctor and nurse visits (follow-up: 6 to 12 months)	The mean doctor and nurse visits ranged across control groups from **1 to 5 vists per**	The mean Doctor and nurse visits in the intervention groups was **0.02 higher** (1 lower to 1 higher)		629 (8)	⊕⊕⊕◯ **moderate**[8]	

- Calculated using the Relative Effect or Mean Differences
- Confidence intervals provided

McMaster University
Inspiring Innovation and Discovery

Results – Relative effects

Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease
Settings: primary care, community, outpatient
Intervention: self management[1]
Comparision: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **usual care**	Corresponding risk **self management**				
Quality of Life St George's Respiratory Questionnaire. Scale from: 0 to 100. (follow-up: 3 to 12 months)	The mean quality of life ranged across control groups from **38 to 60 points**	The mean Quality of Life in the intervention groups was **2.58 lower** (5.14 to 0.02 lower)		698 (7)	⊕⊕⊕◯ **moderate**[2]	Lower score indicates better quality of life. A change of less than 4 points is not shown to be important to patients.
Dyspnoea Borg Scale. Scale from: 0 to 10. (follow-up: 3 to 6 months)	The mean dyspnoea ranged across control groups from **1.2 to 4.1 points**	The mean Dyspnoea in the intervention groups was **0.53 lower** (0.96 to 0.1 lower)		144 (2)	⊕⊕◯◯ **low**[3,4]	Lower score indicates improvement
Number and severity of exacerbations[5]	See comment	See comment	Not estimable[5]	591 (3)	See comment	Effect is uncertain
Respiratory-related hospital admissions (follow-up: 3 to 12 months)	**Low risk population**[6] **10 per 100**	**7 per 100** (5 to 9)	**OR 0.64** (0.47 to 0.89)	966 (8)	⊕⊕⊕◯ **moderate**[7]	
	High risk population[6] **50 per 100**	**35 per 100** (27 to 46)				
Emergency department visits for lung diseases (follow-up: 6 to 12 months)	The mean emergency department visits for lung diseases ranged across control groups from **0.2 to 0.7 visits per person per year**	The mean Emergency department visits for lung diseases in the intervention groups was **0.1 higher** (0.2 lower to 0.3 higher)		328 (4)	⊕⊕⊕◯ **moderate**[4]	
Doctor and nurse visits (follow-up: 6 to 12 months)	The mean doctor and nurse visits ranged across control groups from **1 to 5 vists per**	The mean Doctor and nurse visits in the intervention groups was **0.02 higher** (1 lower to 1 higher)		629 (8)	⊕⊕⊕◯ **moderate**[8]	

- From meta-analysis
- Relative Risks, Odds ratios, Hazard ratios, etc.

McMaster University
Inspiring Innovation and Discovery

Results – Number of Participants/studies

Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease
Settings: primary care, community, outpatient
Intervention: self management[1]
Comparision: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **usual care**	Corresponding risk **self management**				
Quality of Life St George's Respiratory Questionnaire. Scale from: 0 to 100. (follow-up: 3 to 12 months)	The mean quality of life ranged across control groups from **38 to 60 points**	The mean Quality of Life in the intervention groups was **2.58 lower** (5.14 to 0.02 lower)		698 (7)	⊕⊕⊕◯ **moderate**[2]	Lower score indicates better quality of life. A change of less than 4 points is not shown to be important to patients.
Dyspnoea Borg Scale. Scale from: 0 to 10. (follow-up: 3 to 6 months)	The mean dyspnoea ranged across control groups from **1.2 to 4.1 points**	The mean Dyspnoea in the intervention groups was **0.53 lower** (0.96 to 0.1 lower)		144 (2)	⊕⊕◯◯ **low**[3,4]	Lower score indicates improvement
Number and severity of exacerbations[5]	See comment	See comment	Not estimable[5]	591 (3)	See comment	Effect is uncertain
Respiratory-related hospital admissions (follow-up: 3 to 12 months)	**Low risk population**[6] **10 per 100**	**7 per 100** (5 to 9)	**OR 0.64** (0.47 to 0.89)	966 (8)	⊕⊕⊕◯ **moderate**[7]	
	High risk population[6] **50 per 100**	**35 per 100** (27 to 46)				
Emergency department visits for lung diseases (follow-up: 6 to 12 months)	The mean emergency department visits for lung diseases ranged across control groups from **0.2 to 0.7 visits per person per year**	The mean Emergency department visits for lung diseases in the intervention groups was **0.1 higher** (0.2 lower to 0.3 higher)		328 (4)	⊕⊕⊕◯ **moderate**[4]	
Doctor and nurse visits (follow-up: 6 to 12 months)	The mean doctor and nurse visits ranged across control groups from **1 to 5 vists per**	The mean Doctor and nurse visits in the intervention groups was **0.02 higher** (1 lower to 1 higher)		629 (8)	⊕⊕⊕◯ **moderate**[8]	

- From meta-analysis
- Or when no meta-analysis from individual studies

McMaster University
Inspiring Innovation and Discovery

Results

Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease
Settings: primary care, community, outpatient
Intervention: self management[1]
Comparision: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **usual care**	Corresponding risk **self management**				
Quality of Life St George's Respiratory Questionnaire. Scale from: 0 to 100. (follow-up: 3 to 12 months)	The mean quality of life ranged across control groups from **38 to 60 points**	The mean Quality of Life in the intervention groups was **2.58 lower** (5.14 to 0.02 lower)		698 (7)	⊕⊕⊕◯ **moderate**[2]	Lower score indicates better quality of life. A change of less than 4 points is not shown to be important to patients.
Dyspnoea Borg Scale. Scale from: 0 to 10. (follow-up: 3 to 6 months)	The mean dyspnoea ranged across control groups from **1.2 to 4.1 points**	The mean Dyspnoea in the intervention groups was **0.53 lower** (0.96 to 0.1 lower)		144 (2)	⊕⊕◯◯ **low**[3,4]	Lower score indicates improvement
Number and severity of exacerbations[5]	See comment	See comment	Not estimable[5]	591 (3)	See comment	Effect is uncertain
Respiratory-related hospital admissions (follow-up: 3 to 12 months)	**Low risk population**[6] **10 per 100**	**7 per 100** (5 to 9)	**OR 0.64** (0.47 to 0.89)	966 (8)	⊕⊕⊕◯ **moderate**[7]	
	High risk population[6] **50 per 100**	**35 per 100** (27 to 46)				
Emergency department visits for lung diseases (follow-up: 6 to 12 months)	The mean emergency department visits for lung diseases ranged across control groups from **0.2 to 0.7 visits per person per year**	The mean Emergency department visits for lung diseases in the intervention groups was **0.1 higher** (0.2 lower to 0.3 higher)		328 (4)	⊕⊕⊕◯ **moderate**[4]	
Doctor and nurse visits (follow-up: 6 to 12 months)	The mean doctor and nurse visits ranged across control groups from **1 to 5 vists per**	The mean Doctor and nurse visits in the intervention groups was **0.02 higher** (1 lower to 1 higher)		629 (8)	⊕⊕⊕◯ **moderate**[8]	

- Describes the score on a scale (38 to 60 points)
- Describes change on the scale with intervention (2.58 points lower)

McMaster University
Inspiring Innovation and Discovery

Results – Outcomes not reported / not measured / not pooled

Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease
Settings: primary care, community, outpatient
Intervention: self management[1]
Comparision: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **usual care**	Corresponding risk **self management**				
Quality of Life St George's Respiratory Questionnaire. Scale from: 0 to 100. (follow-up: 3 to 12 months)	The mean quality of life ranged across control groups from **38 to 60 points**	The mean Quality of Life in the intervention groups was **2.58 lower** (5.14 to 0.02 lower)		698 (7)	⊕⊕⊕◯ **moderate**[2]	Lower score indicates better quality of life. A change of less than 4 points is not shown to be important to patients.
Dyspnoea Borg Scale. Scale from: 0 to 10. (follow-up: 3 to 6 months)	The mean dyspnoea ranged across control groups from **1.2 to 4.1 points**	The mean Dyspnoea in the intervention groups was **0.53 lower** (0.96 to 0.1 lower)		144 (2)	⊕⊕◯◯ **low**[3,4]	Lower score indicates improvement
Number and severity of exacerbations[5]	See comment	See comment	Not estimable[5]	591 (3)	See comment	Effect is uncertain
Respiratory-related hospital admissions (follow-up: 3 to 12 months)	**Low risk population**[6] **10 per 100**	**7 per 100** (5 to 9)	**OR 0.64** (0.47 to 0.89)	966 (8)	⊕⊕⊕◯ **moderate**[7]	
	High risk population[6] **50 per 100**	**35 per 100** (27 to 46)				
Emergency department visits for lung diseases (follow-up: 6 to 12 months)	The mean emergency department visits for lung diseases ranged across control groups from **0.2 to 0.7 visits per person per year**	The mean Emergency department visits for lung diseases in the intervention groups was **0.1 higher** (0.2 lower to 0.3 higher)		328 (4)	⊕⊕⊕◯ **moderate**[4]	
Doctor and nurse visits (follow-up: 6 to 12 months)	The mean doctor and nurse visits ranged across control groups from **1 to 5 vists per**	The mean Doctor and nurse visits in the intervention groups was **0.02 higher** (1 lower to 1 higher)		629 (8)	⊕⊕⊕◯ **moderate**[8]	

- Outcomes without data are still presented
- Outcomes not pooled are still presented and graded

McMaster University
Inspiring Innovation and Discovery

Comments

Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease
Settings: primary care, community, outpatient
Intervention: self management[1]
Comparision: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **usual care**	Corresponding risk **self management**				
Quality of Life St George's Respiratory Questionnaire. Scale from: 0 to 100. (follow-up: 3 to 12 months)	The mean quality of life ranged across control groups from **38 to 60 points**	The mean Quality of Life in the intervention groups was **2.58 lower** (5.14 to 0.02 lower)		698 (7)	⊕⊕⊕◯ **moderate**[2]	Lower score indicates better quality of life. A change of less than 4 points is not shown to be important to patients.
Dyspnoea Borg Scale. Scale from: 0 to 10. (follow-up: 3 to 6 months)	The mean dyspnoea ranged across control groups from **1.2 to 4.1 points**	The mean Dyspnoea in the intervention groups was **0.53 lower** (0.96 to 0.1 lower)		144 (2)	⊕⊕◯◯ **low**[3,4]	Lower score indicates improvement
Number and severity of exacerbations[5]	See comment	See comment	Not estimable[5]	591 (3)	See comment	Effect is uncertain
Respiratory-related hospital admissions (follow-up: 3 to 12 months)	**Low risk population**[6]		**OR 0.64** (0.47 to 0.89)	966 (8)	⊕⊕⊕◯ **moderate**[7]	
	10 per 100	**7 per 100** (5 to 9)				
	High risk population[6]					
	50 per 100	**35 per 100** (27 to 46)				
Emergency department visits for lung diseases (follow-up: 6 to 12 months)	The mean emergency department visits for lung diseases ranged across control groups from **0.2 to 0.7 visits per person per year**	The mean Emergency department visits for lung diseases in the intervention groups was **0.1 higher** (0.2 lower to 0.3 higher)		328 (4)	⊕⊕⊕◯ **moderate**[4]	
Doctor and nurse visits (follow-up: 6 to 12 months)	The mean doctor and nurse visits ranged across control groups from **1 to 5 vists per**	The mean Doctor and nurse visits in the intervention groups was **0.02 higher** (1 lower to 1 higher)		629 (8)	⊕⊕⊕◯ **moderate**[8]	

- More description
- E.g. relevance of findings, notes when no data, no meta-analysis, or meta-analysis plus studies not in meta-analysis

McMaster University
Inspiring Innovation and Discovery

SoF: Quando e Perché?

- Nelle revisioni Cochrane è obbligatorio (si parla di *Summary of Findings*)
- Per concludere una revisione sistematica per sintetizzare i risultati e la loro qualità (si parla di *Summary of Findings*)
- Come materiale di base per la elaborazione di Linee Guida per la pratica clinica (si parla di *Evidence Profile*)

2. Scegliere quali *outcomes* per la SoF

Di interesse per i pazienti e decisori

Utili per prendere decisioni cliniche

E’ possibile riportarne al massimo 7 (desiderabili e indesiderabili)

In genere solo gli outcomes primari della revisione

Dovrebbero essere definiti nel protocollo

Outcomes

Should be

importance driven

NOT

evidence driven

QUALITY OF EVIDENCE

Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease
Settings: primary care, community, outpatient
Intervention: self management[1]
Comparision: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **usual care**	Corresponding risk **self management**				
Quality of Life St George's Respiratory Questionnaire. Scale from: 0 to 100. (follow-up: 3 to 12 months)	The mean quality of life ranged across control groups from **38 to 60 points**	The mean Quality of Life in the intervention groups was **2.58 lower** (5.14 to 0.02 lower)		698 (7)	⊕⊕⊕◯ **moderate**[2]	Lower score indicates better quality of life. A change of less than **4** points is not shown to be important to patients.
Dyspnoea Borg Scale. Scale from: 0 to 10. (follow-up: 3 to 6 months)	The mean dyspnoea ranged across control groups from **1.2 to 4.1 points**	The mean Dyspnoea in the intervention groups was **0.53 lower** (0.96 to 0.1 lower)		144 (2)	⊕⊕◯◯ **low**[3,4]	Lower score indicates improvement
Number and severity of exacerbations[5]	See comment	See comment	Not estimable[5]	591 (3)	See comment	Effect is uncertain
Respiratory-related hospital admissions (follow-up: 3 to 12 months)	**Low risk population**[6] **10 per 100**	**7 per 100** (5 to 9)	**OR 0.64** (0.47 to 0.89)	966 (8)	⊕⊕⊕◯ **moderate**[7]	
	High risk population[6] **50 per 100**	**35 per 100** (27 to 46)				
Emergency department visits for lung diseases (follow-up: 6 to 12 months)	The mean emergency department visits for lung diseases ranged across control groups from **0.2 to 0.7 visits per person per year**	The mean Emergency department visits for lung diseases in the intervention groups was **0.1 higher** (0.2 lower to 0.3 higher)		328 (4)	⊕⊕⊕◯ **moderate**[4]	
Doctor and nurse visits (follow-up: 6 to 12 months)	The mean doctor and nurse visits ranged across control groups from **1 to 5 vists per**	The mean Doctor and nurse visits in the intervention groups was **0.02 higher** (1 lower to 1 higher)		629 (8)	⊕⊕⊕◯ **moderate**[8]	

Formulate question

P
I
C
O

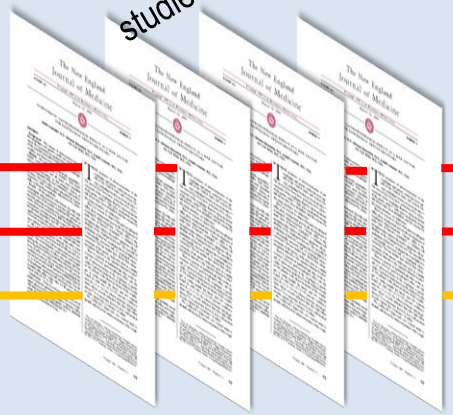
Select outcomes

Outcome
Outcome
Outcome
Outcome

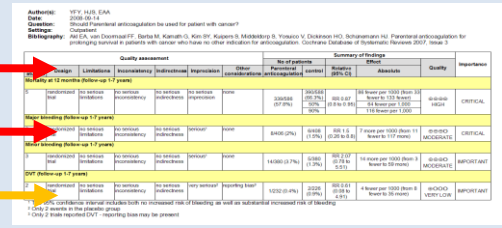
Rate importance

Critical
Critical
Important
Not important

Outcomes across studies



Create evidence profile with GDT



Summary of findings & estimate of effect for each outcome

Rate quality of evidence for each outcome

High
Moderate
Low
Very low

Randomization raises initial quality
RCTs: high
Observational: low

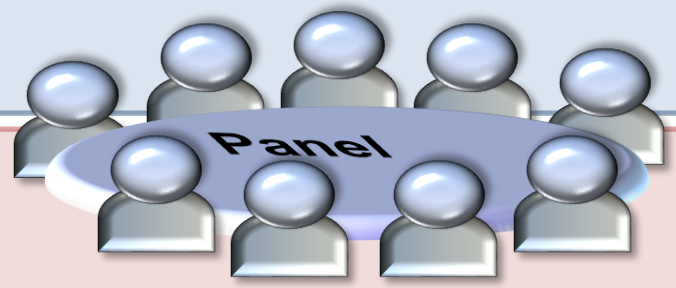
Grade down

1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Grade up

1. Large effect
2. Dose response
3. Opposing bias & Confounders

Evidence synthesis (SR, HTA)



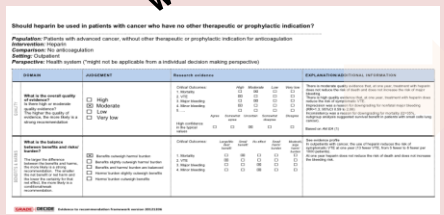
Recommendation/Decision

Grade overall quality of evidence
across outcomes based on lowest quality of ***critical*** outcomes

Grade recommendations (Evidence to Decision)
- For or against (direction) ↓↑
- Strong or conditional/weak (strength)

By considering balance of consequences (evidence to recommendations):
- ❑ Quality of evidence
- ❑ Balance benefits/harms
- ❑ Values and preferences
- ❑ Feasibility, equity and acceptability
- ❑ Resource use (if applicable)

EtD framework with GRADEpro



Guideline/Decision

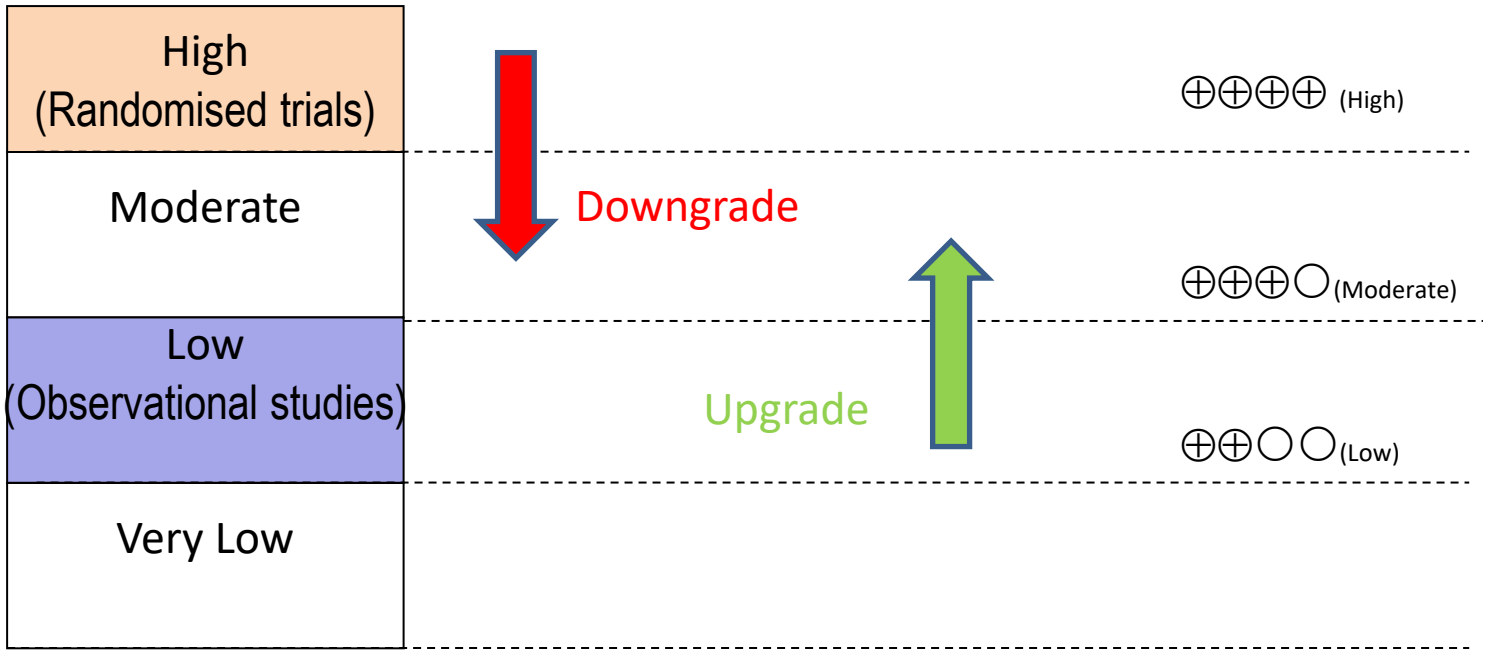
Formulate Recommendations/Decision
"The panel recommends that ….should..."
"The panel suggests that ….should..."
"The panel suggests to **not** ..."
"The panel recommends to **not**..."
Transparency, clear, actionable
Research?

Quality of evidence

- GRADE is "**outcome centric**": rating is made for each outcome, and quality may differ -indeed, is likely to differ - from one outcome to another **within a single study** and **across a body of evidence**
- E.g: subjective outcomes are prone to performance and detection bias, while objective outcomes are not
- E.g. one outcome within a review could have imprecision in the pooled estimate of the effect, while another could have not
- E.g. one outcome could have high attrition bias (use of substance) while another could have not (drop out)

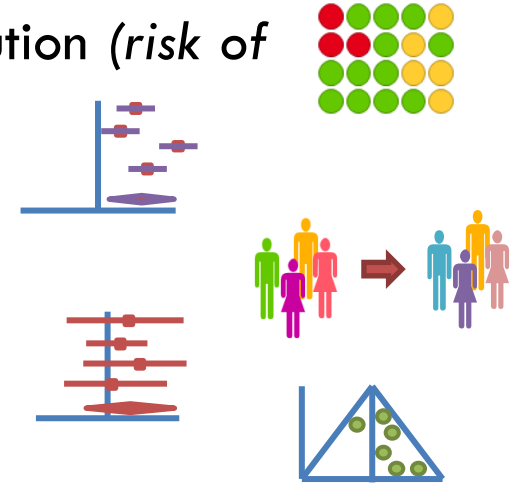
Rating quality of evidence

GRADE's approach begins with the study design. Randomized controlled trials (RCTs) start as high-quality evidence and observational studies as low-quality evidence supporting estimates of intervention effects

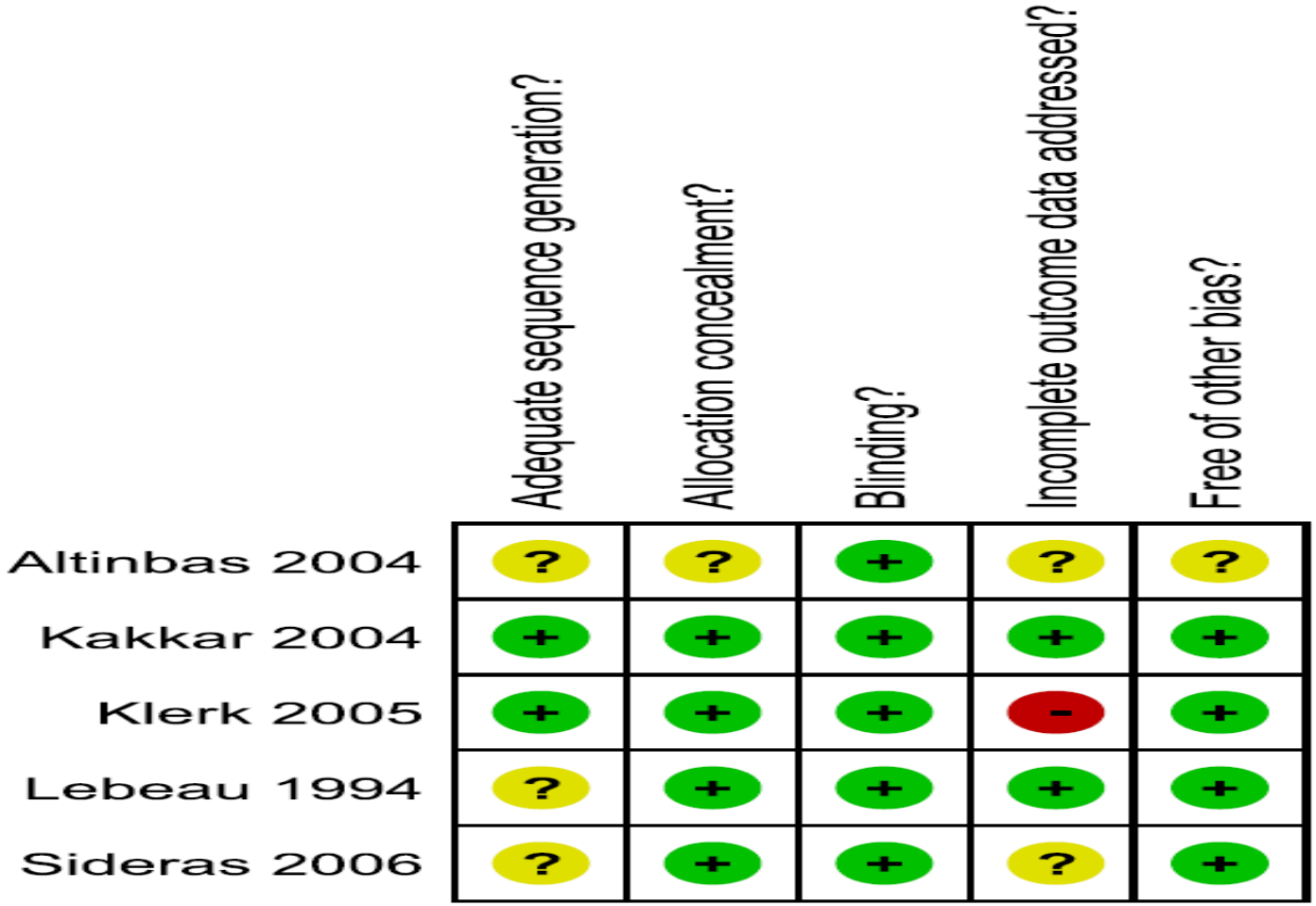


Determinants of quality/certainty of a body of evidence

- **RCTs ⊕⊕⊕⊕**
- **observational studies ⊕⊕◯◯**
- **5 factors that can lower quality**
  1. limitations in detailed study design and execution *(risk of bias criteria)*
  2. Inconsistency *(or heterogeneity)*
  3. Indirectness *(PICO and applicability)*
  4. Imprecision
  5. Publication bias
- **3 factors can increase quality**
  1. large magnitude of effect
  2. opposing plausible residual bias or confounding
  3. dose-response gradient



1. Study limitations (risk of bias)



Akl E, Barba M, Rohilla S, Terrenato I, Sperati F, Schünemann HJ. "*Anticoagulation for the long term treatment of venous thromboembolism in patients with cancer*". Cochrane Database Syst Rev. 2008 Apr 16;(2):CD006650.

Risk of bias

- Outcome specific
- Do not average risk quality across the studies
- Evaluate the extent to which each trial contributes toward the estimate of magnitude of effect. This contribution will usually reflect study sample size and number of outcome events -larger trials with many events will contribute more, much larger trials with many more events will contribute much more (look at the weight of each study in the forest plot)

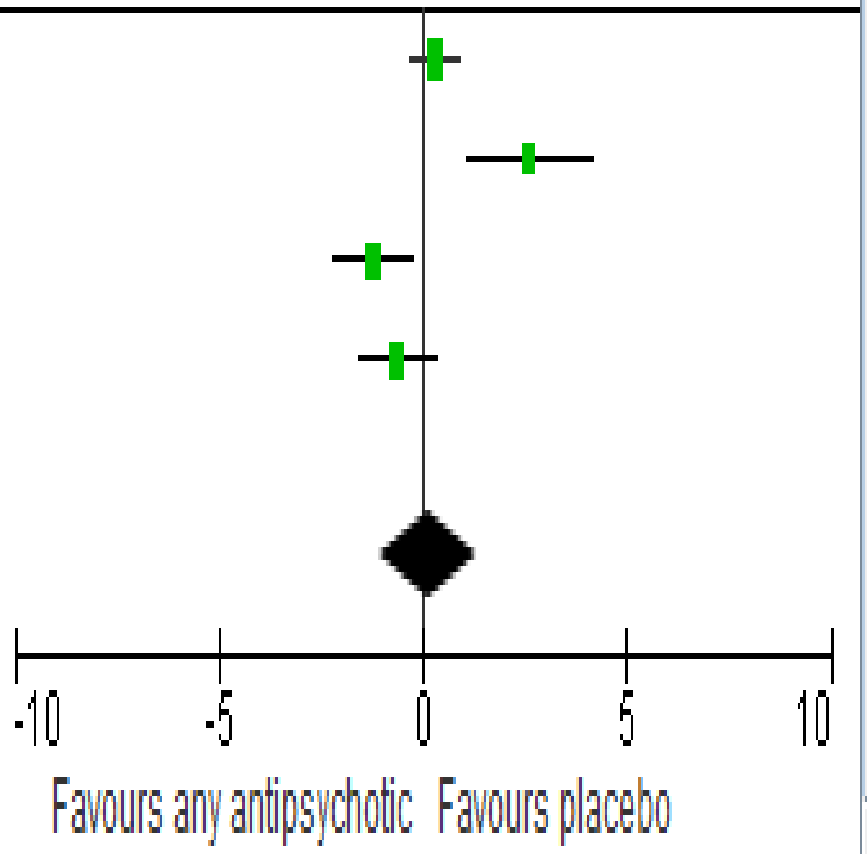
2.Inconsistency (heterogeneity) between studies results

- Variation in size of effect (**Point estimates** vary widely across studies)
- **Confidence intervals** (CIs) show minimal or no overlap
- The statistical test for heterogeneity which tests the null hypothesis that all studies in a meta-analysis have the same underlying magnitude of effect shows a low **P-value** (< 0.05)
- The $\mathbf{I^2}$ which quantifies the proportion of the variation in point estimates due to among-study differences (< 40% : low, 30 e 60% :moderate, 60 e 90% :substantial, 75 e 100% : considerable)
- All statistical approaches have limitations, and their results should be seen in the context of a subjective examination of the variability in point estimates and the overlap in CIs.

Study or Subgroup	Any antispsychotic Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kampman 2003	1.3	0.8	15	1	0.9	15	28.3%	0.30 [-0.31, 0.91]
Reid 2005	6.1	2.1	16	3.5	2.3	15	20.3%	2.60 [1.05, 4.15]
Tapp 2015	0.4	1.26	29	1.63	2.39	31	25.6%	-1.23 [-2.19, -0.27]
Winhusen 2007	2.8	2.45	60	3.44	2.76	59	25.8%	-0.64 [-1.58, 0.30]
Total (95% CI)			120			120	100.0%	0.13 [-1.08, 1.35]

Heterogeneity: $Tau^2 = 1.26$; $Chi^2 = 19.78$, df = 3 ($P = 0.0002$); $I^2 = 85\%$

Test for overall effect: $Z = 0.22$ ($P = 0.83$)



3. Directness of Evidence generalizability, transferability, applicability

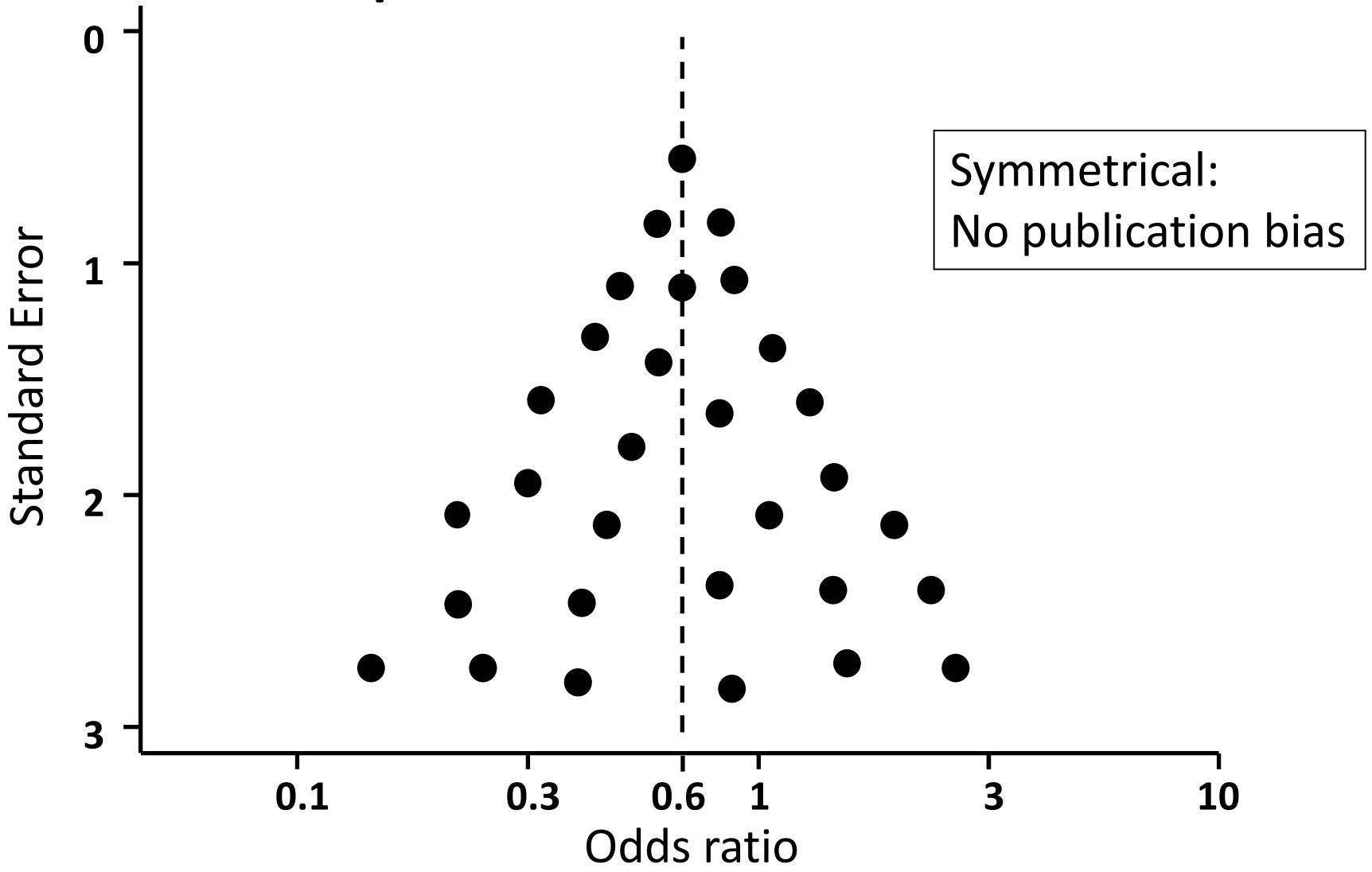
- differences between PICO and available evidence in
  - populations/patients (interested in children but found adults population)
  - interventions (interested in high dosage but found low dosage, interested in long treatment but found short, etc)
  - outcomes (interested in important but we found surrogate; e.g hip fracture vs bone density; interested in long term but found short term results)
- indirect comparisons
  - interested in A versus B
  - found A versus C and B versus C

4. Publication Bias

Consider rating down if:

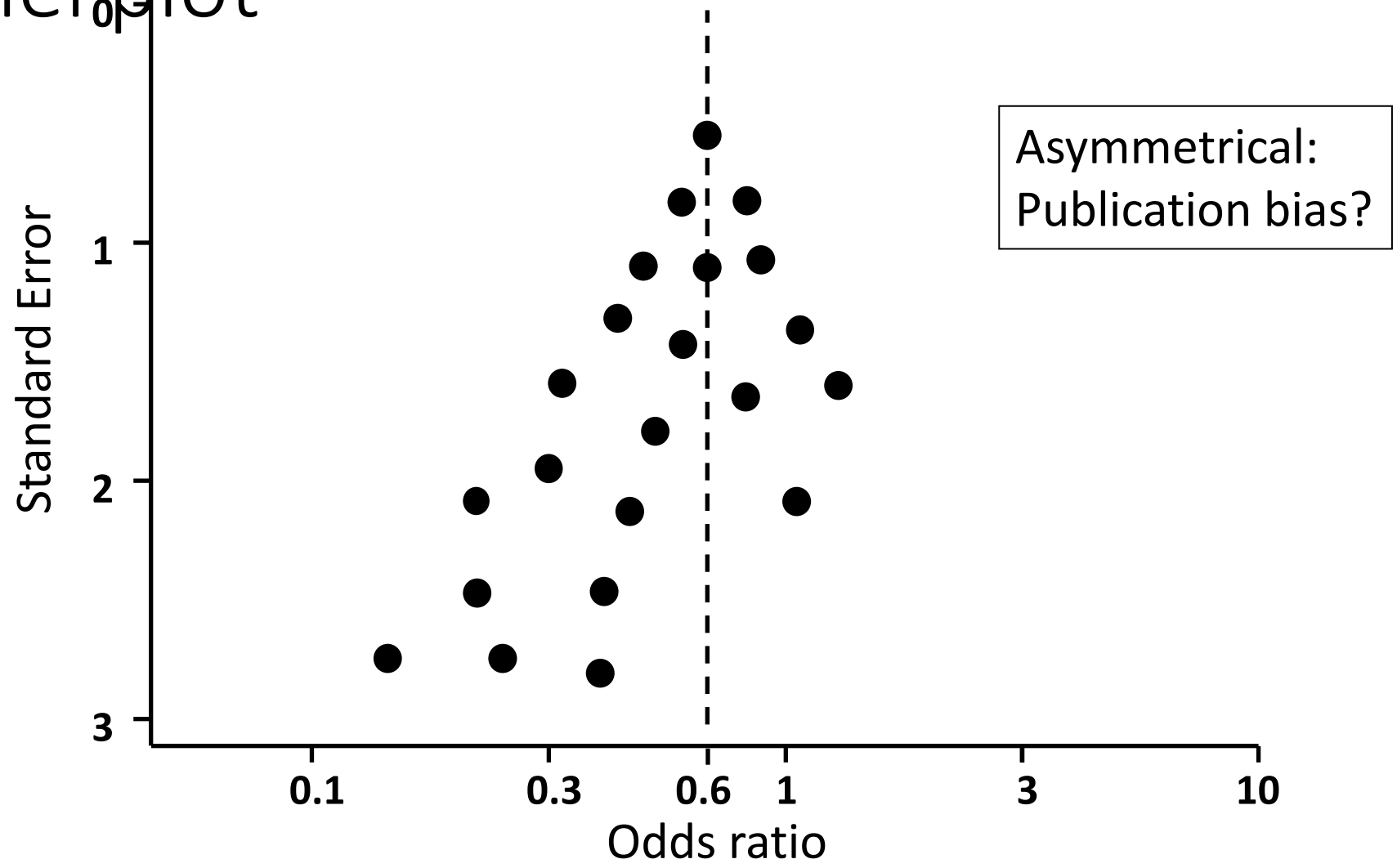
- You find **systematic reviews performed early**, when only few initial studies are available, that will overestimate effects when ‘‘negative’’ studies face delayed publication. Early positive studies, particularly if small in size, are suspect.
- You **find only small “positive” studies, mainly if sponsored by industry**
- **Funnel plot showing asimmetry** but
- Funnel plot should be seen as a generic means of displaying small-study effects – a tendency for the intervention effects estimated in smaller studies to differ from those estimated in larger studies (Sterne 2000). Small-study effects may be due to reasons other than publication bias (low methodological quality, chance, patients characteristics).
- **Funnel plot should be used only when there are at least 10 studies** included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry

Funnel plot



Egger M, Cochrane Colloquium Lyon 2001

Funnel plot



Asymmetrical:
Publication bias?

Egger M, Cochrane Colloquium Lyon 2001

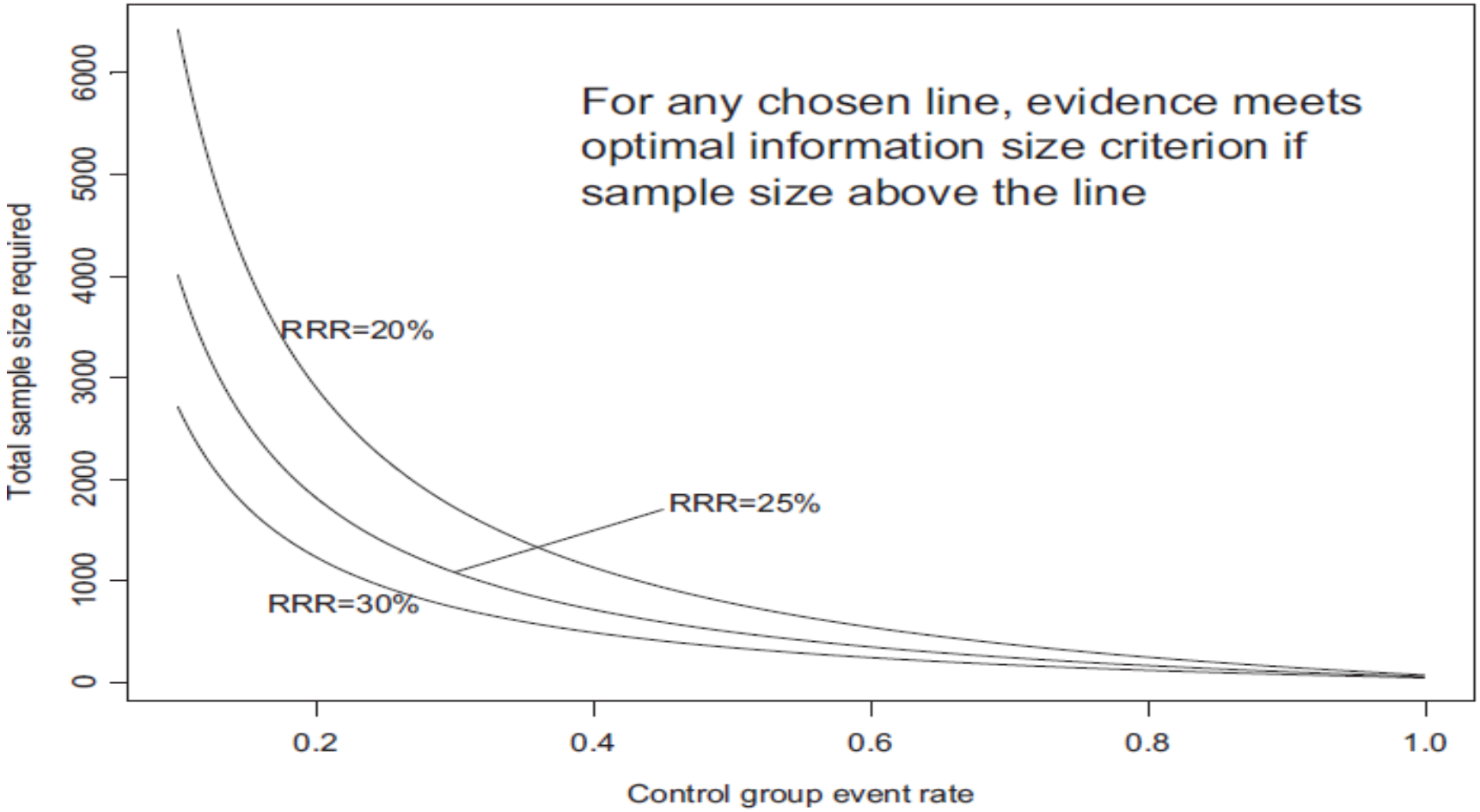
5. Imprecision of the overall estimate

- **Wide confidence intervals** (CIs inform the impact of random error on evidence quality; CI expresses the range in which the truth plausibly lies)
- **Small number of events**
- **Small sample size**
- recommendation or **clinical course of action would differ** if the **upper versus the lower boundary** of the CI represented the truth

Optimal information size

- We suggest the following: if the total number of patients included in a systematic review is less than the number of patients generated by a conventional sample size calculation for a single adequately powered trial, consider rating down for imprecision. Authors have referred to this threshold as the "optimal information size" (OIS)

Required sample size (assuming α of 0.05, and β of 0.2) for RRR of 20%, 25%, and 30% across varying control event rates. For example, if the best estimate of control event rate was 0.2 and one specifies an RRR of 25%, the OIS is approximately 2,000 patients (GRADE guideline n.6 Journal of Clinical Epidemiology 64 (2011) 1283e1293)



ɔtimal information size given α of 0.05 and β of 0.2 for varying control event rates and relative risks.

Power is more closely related to number of events than to sample size

(GRADE guideline n.6 Journal of Clinical Epidemiology 64 (2011) 1283e1293)

Calculating the OIS for **dichotomous outcome** requires specifying:

- probability of detecting a false effect – type I error (α; usually 0.05)
- probability of detecting a true effect – power (usually 80% [power = 1 – type II error; β; usually 0.20])
- realistic relative risk reduction (RRR; we suggest a default of 25%)
- control event rate (we suggest the median of the available trials, or the rate from a dominating trial, if it exists).

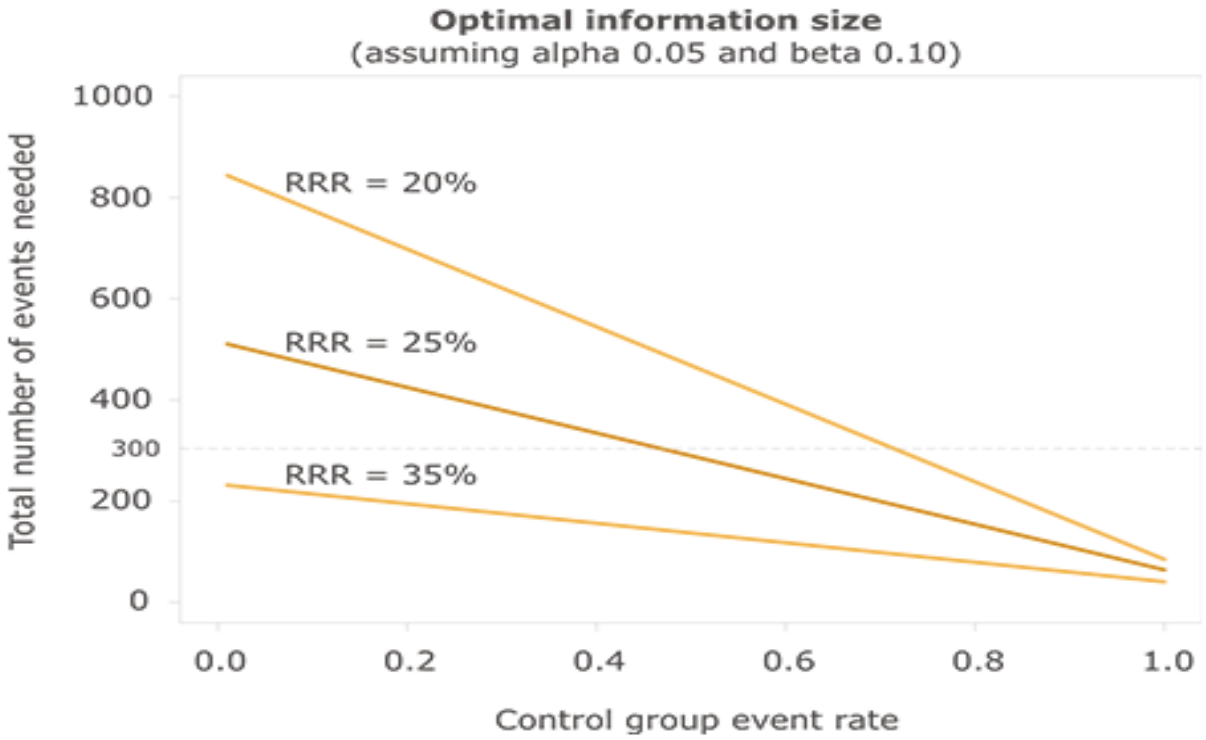


Table 1: Optimal information size implications from Figure above

Total Number of Events	Relative Risk Reduction	Implications for meeting OIS threshold
100 or less	≤ 30%	Will almost never meet threshold whatever control event rate
200	30%	Will meet threshold for control event rates for ~ 25% or greater
200	25%	Will meet threshold for control event rates for ~ 50% or greater
200	20%	Will meet threshold only for control event rates for ~ 80% or greater
300	≥ 30%	Will meet threshold
300	25%	Will meet threshold for control event rates ~ 25% or greater
300	20%	Will meet threshold for control event rates ~ 60% or greater
400 or more	≥ 25%	Will meet threshold for any control event rate
400 or more	20%	Will meet threshold for control event rates of ~ 40% or greater

OIS for continuous outcomes

- Authors can calculate the OIS for continuous variables in exactly the same way they can for binary variables by specifying the α and β errors (we have suggested 0.05 and 0.2) and the Δ (i.e. the difference one wishes to detect as clinically relevant), and choosing an appropriate standard deviation from one of the relevant studies.
- A particular challenge in calculating the OIS for continuous variables arises when studies have used different instruments to measure a construct, and the pooled estimate is calculated using a standardized mean difference.
- we suggest authors choose one of the available instruments (ideally, one in which an estimate of the minimally important difference is available) and calculate an OIS using that instrument

OIS for continuous outcomes

whenever there are **sample sizes** that are less than 400, review authors and guideline developers should certainly consider rating down for imprecision.

Downgrading and OIS

- if OIS not met downgrade for imprecision
- If OIS met and the 95% CI excludes a relative risk (RR) of 1.0 (statistically significant results), precision is adequate.
- if OIS met but the 95% CI includes a RR of 1 (null effect) , authors should consider whether CIs include appreciable benefit or harm (we suggest a RR of under 0.75 or over 1.25 as a rough guide) ; if yes downgrading for imprecision may be appropriate.

What can raise quality?

1. **large magnitude of effect** can upgrade (**RRR 50%/RR 2**)
   - very large two levels **(**RRR 80%/RR 5) ; modeling studies suggests that confounding (from nonrandom allocation) alone is unlikely to explain associations with a relative risk (RR) greater than 2 (or less than 0.5), and very unlikely to explain associations with an RR greater than 5 (or less than 0.2)
   - Es: relationship between infant sleeping position and sudden infant death syndrome (SIDS) found an odds ratio (OR) of 4.1 (95% confidence interval [CI]: 3.1, 5.5) of SIDS occurring with front vs. back sleeping positions

What can raise quality?

2. **dose response relation**
    - higher INR – increased bleeding
    - childhood lymphoblastic leukemia
        - risk for CNS malignancies 15 years after cranial irradiation
        - no radiation: 1% (95% CI 0% to 2.1%)
        - 12 Gy: 1.6% (95% CI 0% to 3.4%)
        - 18 Gy: 3.3% (95% CI 0.9% to 5.6%)

Residual confounding

- 3. all plausible residual confounding may be working to reduce the demonstrated effect or increase the effect if no effect was observed (underestimate of the treatment effect)

- Es: effect of condom use on HIV infection among men who have sex with men RR: 0.34 [0.21, 0.54] (RRR: 66%) in favor of condom use compared with no condom use. Condom users were more likely to have more partners (but studies did not adjust for this confounding factor in their analyses). Considering the number of partners would, if anything, strengthen the effect estimate in favor of condom use.

Assessing Certainty in the Evidence by Outcome

Table: GRADE's approach to rating quality of evidence (aka confidence in effect estimates)

For each outcome based on a systematic review and across outcomes (lowest quality across the outcomes critical for decision making)

1. Establish initial level of confidence		2. Consider lowering or raising level of confidence		3. Final level of confidence rating
Study design	*Initial confidence in an estimate of effect*	*Reasons for considering lowering or raising confidence*		*Confidence in an estimate of effect across those considerations*
		↓ Lower if	↑ Higher if*	
Randomized trials →	High confidence	Risk of Bias Inconsistency Indirectness Imprecision Publication bias	Large effect Dose response All plausible confounding & bias • would reduce a demonstrated effect **or** • would suggest a spurious effect if no effect was observed	High ⊕⊕⊕⊕
				Moderate ⊕⊕⊕◯
Observational studies →	Low confidence			Low ⊕⊕◯◯
				Very low ⊕◯◯◯

*upgrading criteria are usually applicable to observational studies only.

Lowering certainty in RCTs

Table: GRADE's approach to rating quality of evidence (aka confidence in effect estimates)

For each outcome based on a systematic review and across outcomes (lowest quality across the outcomes critical for decision making)

1. Establish initial level of confidence		2. Consider lowering or raising level of confidence		3. Final level of confidence rating
Study design	*Initial confidence in an estimate of effect*	*Reasons for considering lowering or raising confidence*		*Confidence in an estimate of effect across those considerations*
		↓ Lower if	↑ Higher if*	
Randomized trials →	High confidence	Risk of Bias Inconsistency Indirectness Imprecision Publication bias	Large effect Dose response All plausible confounding would reduce a demonstrated effect or • would suggest a spurious effect if no effect was observed	High ⊕⊕⊕⊕
				Moderate ⊕⊕⊕◯
Observational studies →	Low confidence			Low ⊕⊕◯◯
				Very low ⊕◯◯◯

*upgrading criteria are usually applicable to observational studies only.

McMaster University
Inspiring Innovation and Discovery

Altering certainty in observational studies

Table: GRADE's approach to rating quality of evidence (aka confidence in effect estimates)

For each outcome based on a systematic review and across outcomes (lowest quality across the outcomes critical for decision making)

1. Establish initial level of confidence		2. Consider lowering or raising level of confidence		3. Final level of confidence rating
Study design	*Initial confidence in an estimate of effect*	*Reasons for considering lowering or raising confidence*		*Confidence in an estimate of effect across those considerations*
		↓ Lower if	↑ Higher if*	
Randomized trials →	High confidence	Risk of Bias Inconsistency Indirectness Imprecision Publication bias	Large effect Dose response All plausible confounding & bias • would reduce a demonstrated effect or • would suggest a spurious effect if no effect was observed	High ⊕⊕⊕⊕
				Moderate ⊕⊕⊕◯
Observational studies →	Low confidence			Low ⊕⊕◯◯
				Very low ⊕◯◯◯

*upgrading criteria are usually applicable to observational studies only.

McMaster University
Inspiring Innovation and Discovery

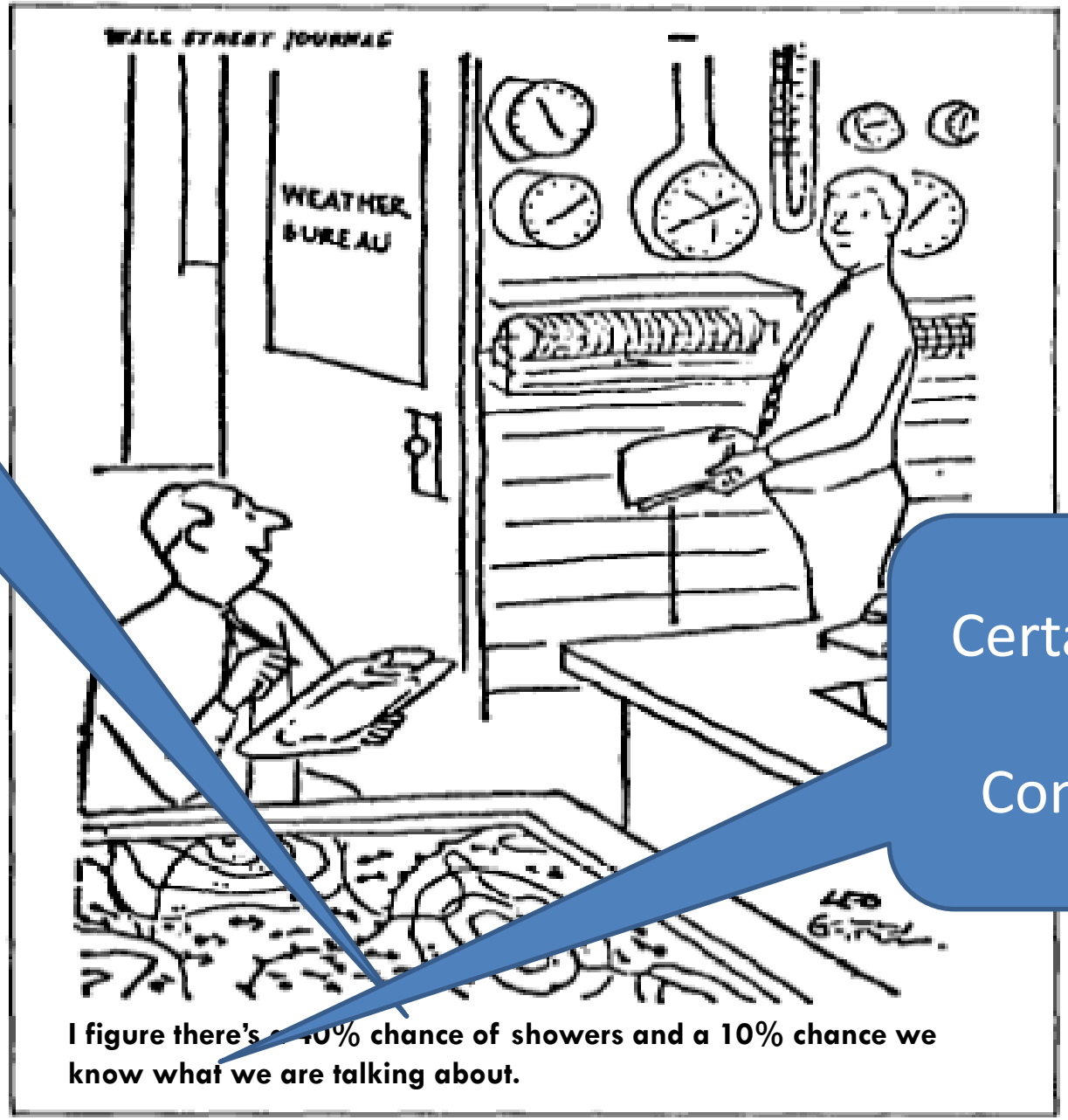
Grades of evidence and Interpretation

Symbol	Quality	Interpretation
⨁⨁⨁⨁	**High**	We are very confident that the true effect lies close to that of the estimate of the effect
⨁⨁⨁◯	**Moderate**	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⨁⨁◯◯	**Low**	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⨁◯◯◯	**Very low**	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

grades of evidence and Interpretation

Quality of evidence = certainty of the results

Magnitude of Effect



Likelihood of and certainty in the evidence or effect

Certainty or Quality of evidence
Confidence in effect

NEGRAR DI VALPOLICELLA
11-12 FEBBRAIO 2022

Centro Formazione IRCCS "Sacro Cuore-Don Calabria"

12 Febbraio 2022

09.00-10.00	Eterogeneità Michela CINQUINI
10.00-11.00	Summary of Findings Tables (1ª parte) Ivan MOSCHETTI
11.00-11.30	Coffee Break
11.30-12.00	Summary of Findings Tables (2ª parte) Ivan MOSCHETTI
12.00-13.00	Lavoro di gruppo *Summing-Up* (metodo: *What? So What? Now What?*) (valido come prova ECM)
13.00-13.15	Conclusione del Corso Stefania GORI - Giovanni L. PAPPAGALLO

NEGRAR DI VALPOLICELLA
11-12 FEBBRAIO 2022

Centro Formazione IRCCS "Sacro Cuore-Don Calabria"

12 Febbraio 2022

09.00-10.00	Eterogeneità Michela CINQUINI
10.00-11.00	Summary of Findings Tables (1ª parte) Ivan MOSCHETTI
11.00-11.30	Coffee Break
11.30-12.00	Summary of Findings Tables (2ª parte) Ivan MOSCHETTI
12.00-13.00	Lavoro di gruppo *Summing-Up* (metodo: *What? So What? Now What?*) (valido come prova ECM)
13.00-13.15	Conclusione del Corso Stefania GORI - Giovanni L. PAPPAGALLO