

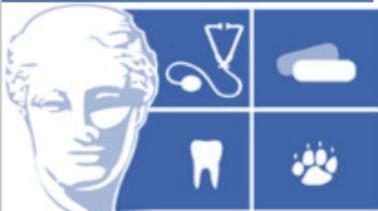


ARISTOTLE  
UNIVERSITY OF  
THESSALONIKI

FACULTY OF HEALTH SCIENCES - SCHOOL OF MEDICINE  
MSc Health Statistics and Data Analytics

# Systematic reviews & meta-analyses

**Thomas Karagiannis MD, MSc, PhD**  
Internal Medicine Physician – Postdoctoral Researcher  
Clinical Research & Evidence-Based Medicine Unit  
Aristotle University of Thessaloniki



# The story with rosiglitazone



1999: Έγκριση από την FDA



DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-071

Food and Drug Administration  
Rockville MD 20857

MAY 25 1999

SmithKline Beecham Pharmaceuticals  
Attention: G. Clare Kahn, Ph.D.  
Group Director, U.S. Regulatory Affairs  
P.O. Box 7929  
Philadelphia, PA 19101

Dear Dr. Kahn:

Please refer to your new drug application (NDA) dated November 25, 1998, received November 25, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avandia™ (rosiglitazone maleate tablets), 2, 4, and 8 mg.

We acknowledge receipt of your submissions dated January 28, February 4, 18, and 22, March 2, 18, and 31, April 2, 7, 12, 13, 20, and 28, and May 20, 21, 24, and 25, 1999.

This new drug application provides for the use of Avandia (rosiglitazone maleate tablets) as an adjunct to diet and exercise to improve glycemic control in patients with Type 2 diabetes mellitus as monotherapy or in combination with metformin.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/99/21071\\_Avandia\\_Approval.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21071_Avandia_Approval.pdf)





# Many individual trials

Emerging Treatments and Technologies  
ORIGINAL ARTICLE

## Once- and Twice-Daily Dosing With Rosiglitazone Improves Glycemic Control in Patients With Type 2 Diabetes

DIABETES CARE, VOLUME 24, NUMBER 2, FEBRUARY 2001

## Effect of Metformin and Rosiglitazone Combination Therapy in Patients With Type 2 Diabetes Mellitus

A Randomized Controlled Trial JAMA, April 5, 2000—Vol 283, No. 13

ORIGINAL ARTICLE



Addition of low-dose rosiglitazone to sulphonylurea therapy improves glycaemic control in Type 2 diabetic patients

B. H. R. Wolffenbuttel\*, R. Gomist, S. Squatrito†, N. P. Jones‡ and R. N. Patwardhan§

Rosiglitazone monotherapy improves glycaemic control in patients with type 2 diabetes: a twelve-week, randomized, placebo-controlled study

Diabetes, Obesity and Metabolism, 1, 1999, 165–172





# A systematic review and meta-analysis

## The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

JUNE 14, 2007

VOL. 356 NO. 24

### Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

#### **CONCLUSIONS**

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.



# Subsequent regulatory changes

## FDA

AUTHENTICATED  
US GOVERNMENT  
INFORMATION  
GPO  
77724

Federal Register / Vol. 73, No. 245 / Friday, December 19, 2008 / Notices

### DEPARTMENT OF HEALTH AND HUMAN SERVICES

#### Food and Drug Administration

[Docket No. FDA-2008-D-0118]

#### Guidance for Industry on Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes; Availability

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

## EMA



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

Medicines Human regulatory ▾ Veterinary regulatory ▾

Avandia  

*rosiglitazone*

Table of contents

- [Overview](#)
- [Authorisation details](#)
- [Product information](#)
- [Assessment history](#)



**WITHDRAWN**

This medicine is now withdrawn from use in the European Union.





# What is a systematic review?

A systematic review is a review of a **clearly formulated question** that uses **systematic and explicit methods** to **identify, select, and critically appraise** relevant research, and to **collect and analyze data** from the studies that are included in the review.





# What is a meta-analysis?

The use of **statistical techniques** in a systematic review  
to **integrate** the results of included studies and produce an  
**overall effect estimate**





# A type of meta-research

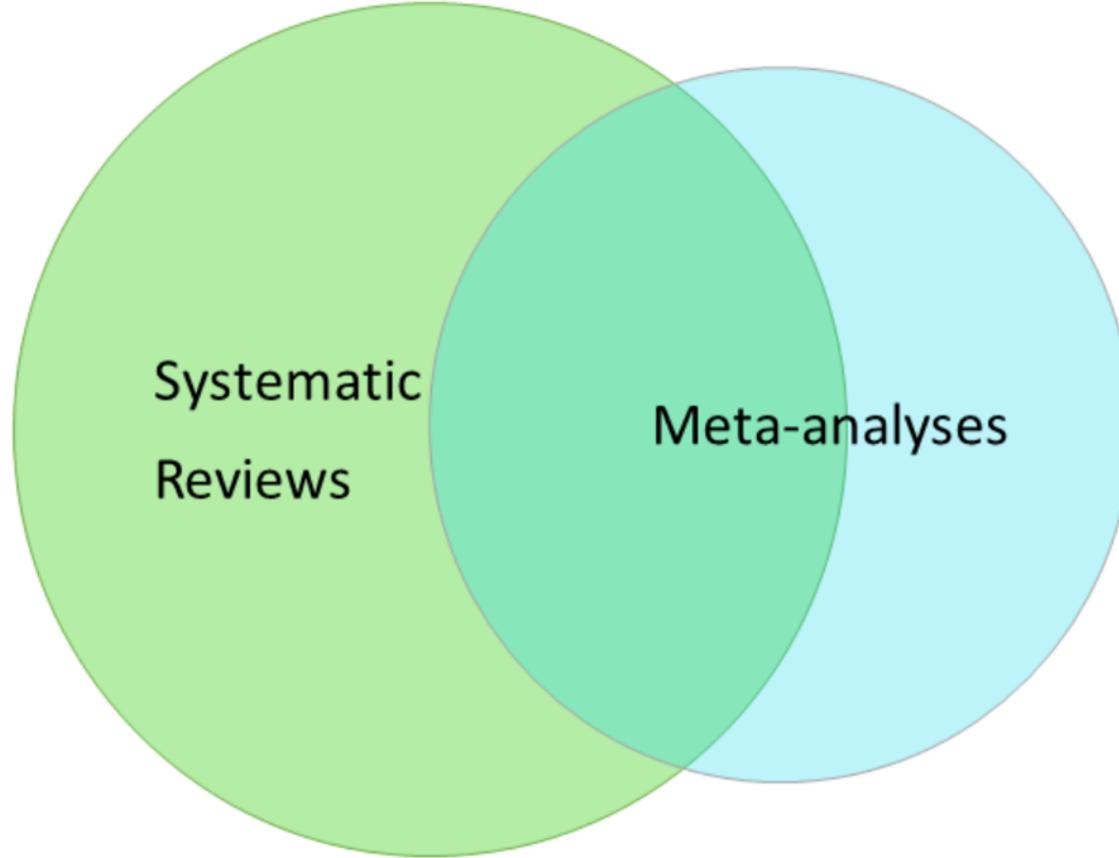
“What is meta-research? As the name suggests, **it is simply research on research**. This new field has **its roots in traditional meta-analysis and systematic reviews**, which aim to examine and combine all research on a scientific question. Meta-researchers apply **a wide variety of methodologies** to study **how research is done and interpreted**, in order to reach a rigorous understanding of what makes research reliable, or how it can be strengthened...”

<https://metrics.stanford.edu/>





# Relationship between systematic reviews & meta-analyses



## RESEARCH METHODS AND REPORTING

### Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline

Mhairi Campbell,<sup>1</sup> Joanne E McKenzie,<sup>2</sup> Amanda Sowden,<sup>3</sup> Srinivasa Vittal Katikireddi,<sup>1</sup> Sue E Brennan,<sup>2</sup> Simon Ellis,<sup>4</sup> Jamie Hartmann-Boyce,<sup>5</sup> Rebecca Ryan,<sup>6</sup> Sasha Shepperd,<sup>7</sup> James Thomas,<sup>8</sup> Vivian Welch,<sup>9</sup> Hilary Thomson<sup>1</sup>

#### SUMMARY POINTS

Systematic reviews of health related interventions often use alternative methods of synthesis to meta-analysis of effect estimates, methods often described as “narrative synthesis”

Serious shortcomings in reviews that use “narrative synthesis” have been identified, including a lack of description of the methods used; unclear links between the included data, the synthesis, and the conclusions; and inadequate reporting of the limitations of the synthesis

The Synthesis Without Meta-analysis (SWiM) guideline is a nine item checklist to promote transparent reporting for reviews of interventions that use alternative synthesis methods

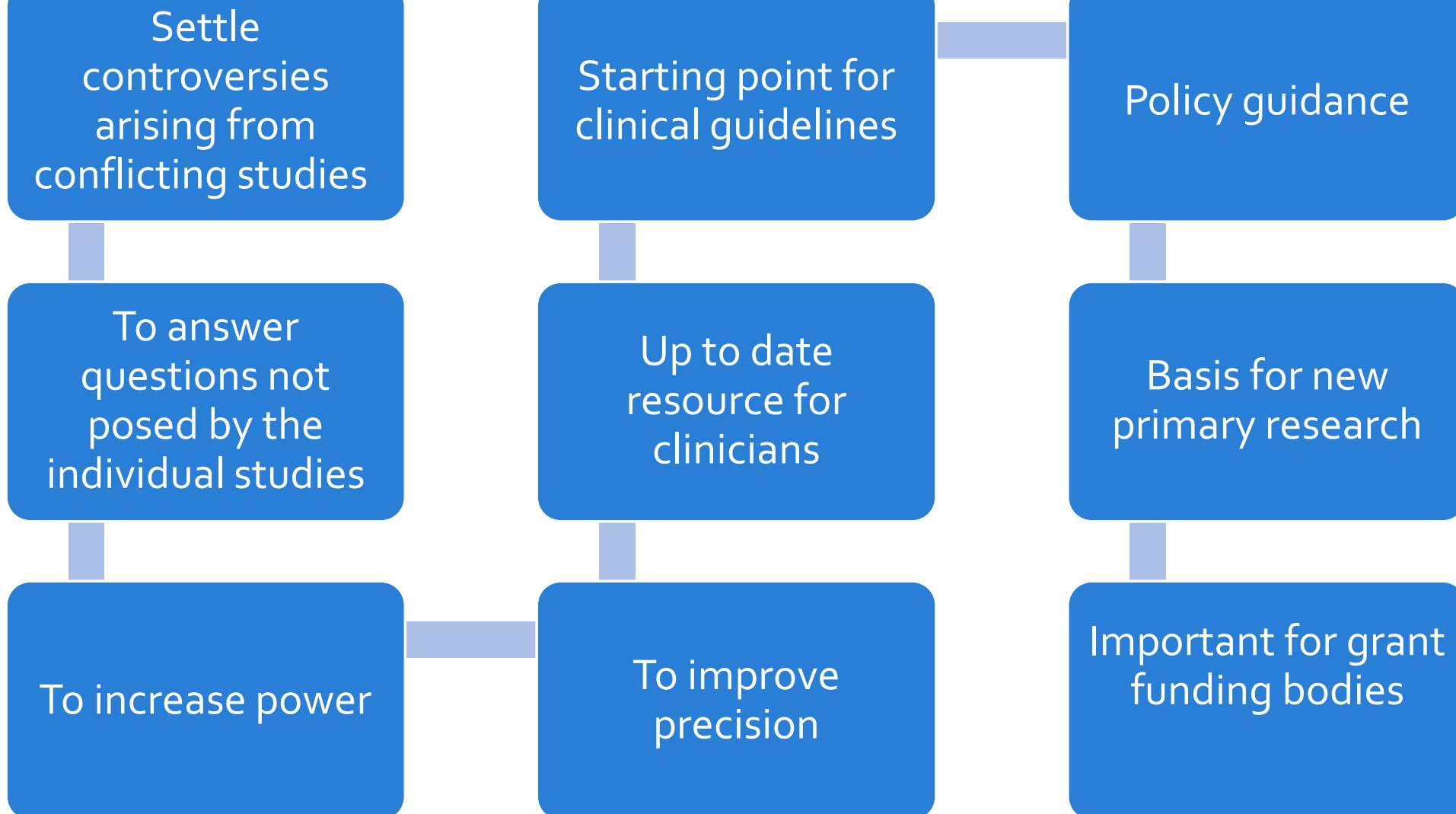
The SWiM items prompt users to report how studies are grouped, the standardised metric used for the synthesis, the synthesis method, how data are presented, a summary of the synthesis findings, and limitations of the synthesis  
The SWiM guideline has been developed using a best practice approach, involving extensive consultation and formal consensus

the **bmj** | BMJ 2020;368:l6890 | doi: 10.1136/bmj.l6890





# The importance of systematic reviews



# The value of systematic reviews



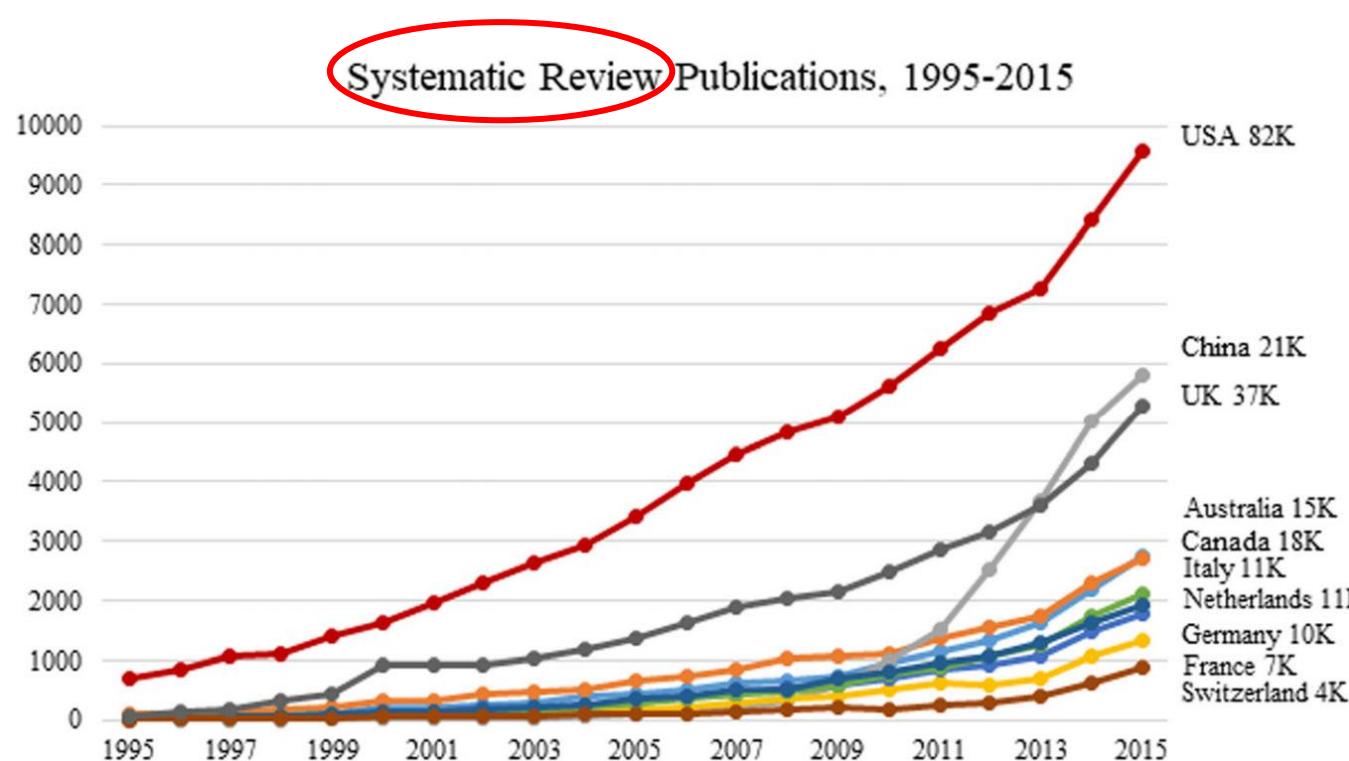
## Offline: The gravy train of systematic reviews

[www.thelancet.com](http://www.thelancet.com) Vol 394 November 16, 2019

Indranil Mukherjee/AFP/  
Getty Images

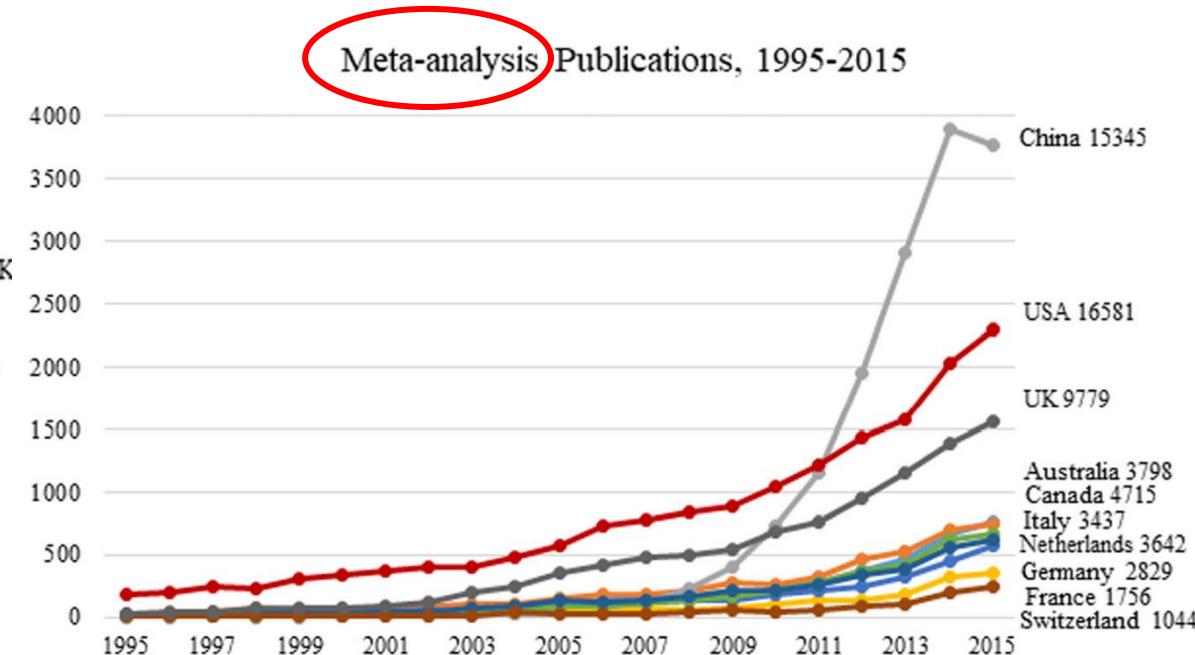


# The popularity of systematic reviews



A review of recent publication trends from top publishing countries

Fontelo and Liu *Systematic Reviews* (2018) 7:147  
<https://doi.org/10.1186/s13643-018-0819-1>





# Are systematic reviews time-consuming?

## BMC Medical Research Methodology

Research article

### Meta-analysis: Neither quick nor easy

Nancy G Berman<sup>\*1</sup> and Robert A Parker<sup>2</sup>

"Meta-analysis can be a very useful method to summarize data across many studies, but it requires careful thought, planning and implementation"



Journal of Clinical Epidemiology 121 (2020) 81–90

#### ORIGINAL ARTICLE

A full systematic review was completed in 2 weeks using automation tools: a case study

Justin Clark\*, Paul Glasziou, Chris Del Mar, Alexandra Bannach-Brown, Paulina Stehlik, Anna Mae Scott

Institute for Evidence-Based Healthcare, Bond University, Gold Coast, Australia

Accepted 18 January 2020; Published online 28 January 2020



2weekSR

@2weekSR



Ακολουθήστε

2week systematic reviews (2weekSR) = full sys revs done super-fast + other methods geekery: Anna Mae Scott, Justin Clark & Paul Glasziou. Tweets: Anna Mae Scott

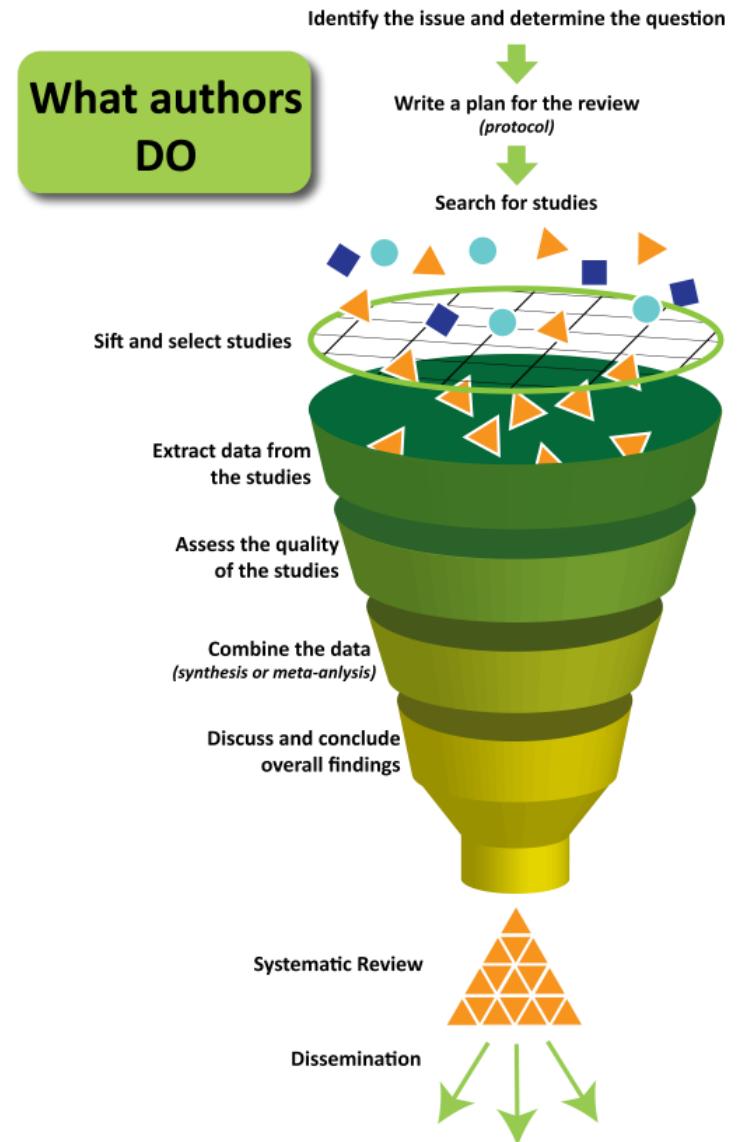
Μετάφραση βιογραφικού

✉ IEBH, Bond Univ., Australia Ⓢ [sr-accelerator.com/#/](http://sr-accelerator.com/#/)

Ἑγινε μέλος: Απρίλιος 2020

# If you want to do a systematic review...

1. **Develop** a focused **research question**
2. **Define** inclusion and exclusion **criteria**
3. **Search** the literature
4. **Select studies** based on the inclusion/exclusion criteria
5. **Extract** data
6. **Assess risk of bias** in included studies
7. **Synthesize** (*not always*) and **interpret** findings
8. **Write** the report





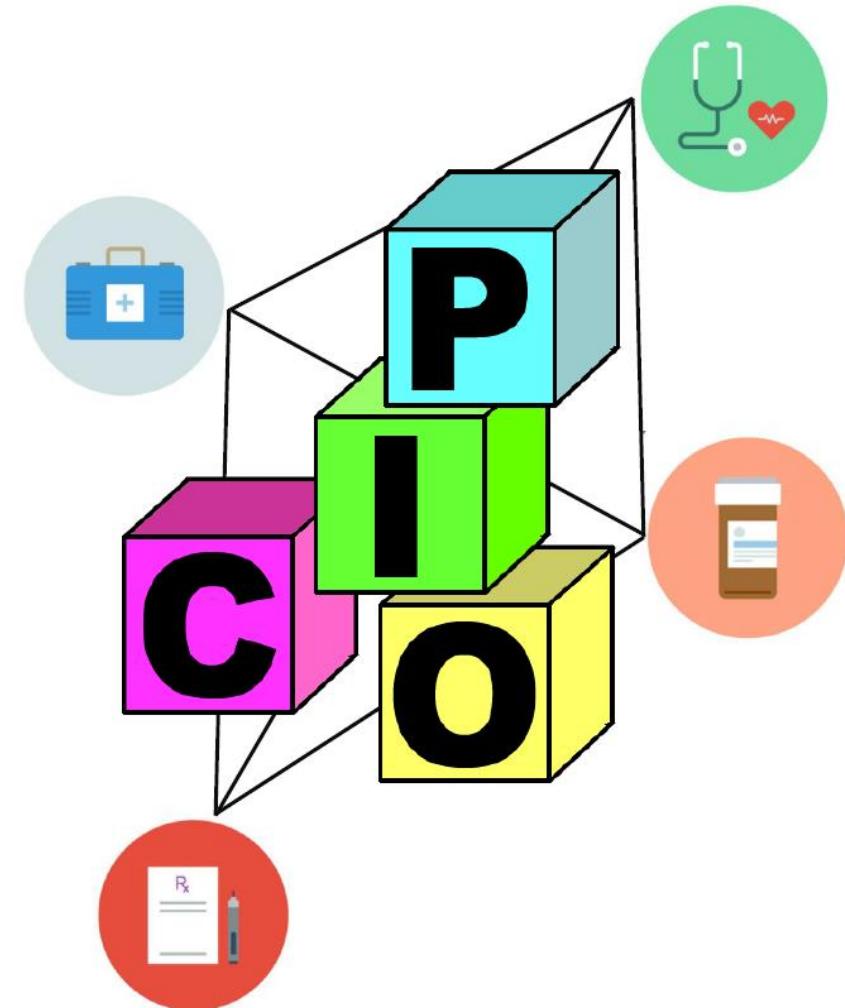
# Development of the review question

- A well formulated review question helps:
  - determine eligibility criteria
  - create search strategy
  - data extraction
  - presentation of results
- Review question should always be:
  - Clear
  - Unambiguous
  - Structured

“To assess the effects of [*intervention or comparison*] for  
[*health problem*] in [*types of people, disease or problem and setting if specified*]”

# PICOS format

- Who are the **Participants** you want to study ?
- What is the **Intervention** you want to examine ?
- What do you want to **Compare** against your intervention of interest ?
- What are the **Outcomes** you want to measure ?
- Which **Study design** do you want to include ?



# A PICOS example

Question:



PICOS format:

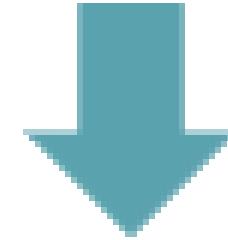
Do e-cigarettes help  
in smoking cessation compared to  
nicotine patch  
in adult smokers?

- Population, Problem: adult smokers
- Intervention: e-cigarette
- Comparison/Control: nicotine patch
- Outcome: smoking cessation
- Studies: e.g RCTs



# Literature Search

- A systematic review must contain all available evidence answering the review question.
- Even a single missing study can affect the results of the whole review.



- A systematic approach is vital, to include
  - a wide variety of literature sources.
  - sources of unpublished studies (grey literature).



# Major bibliographic databases

The three bibliographic databases generally considered to be the most important sources to search for trials are:

## 1. MEDLINE



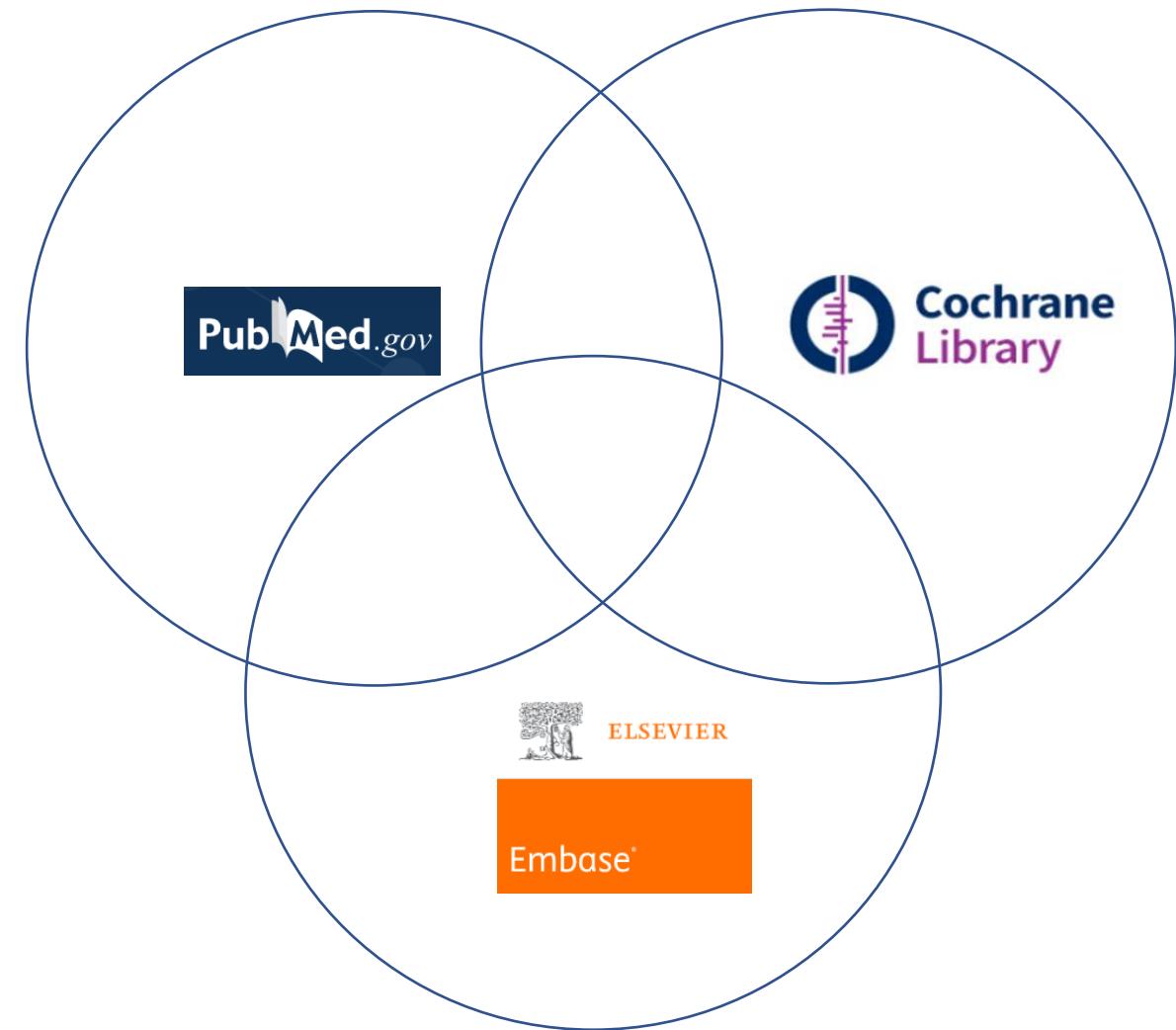
## 2. Embase



## 3. Cochrane Central Register of Controlled Trials **(CENTRAL)**, which is published within the Cochrane Library



Trusted evidence.  
Informed decisions.  
Better health.





# Medline

- As of 2020, MEDLINE contains over 30 million references to journal articles.
- More than 5200 journals in about 40 languages.
- **PubMed** provides access to a free version of MEDLINE that also includes up-to-date citations not yet indexed for MEDLINE.



- MEDLINE is also available on subscription from a number of other database vendors, such as **Ovid**.

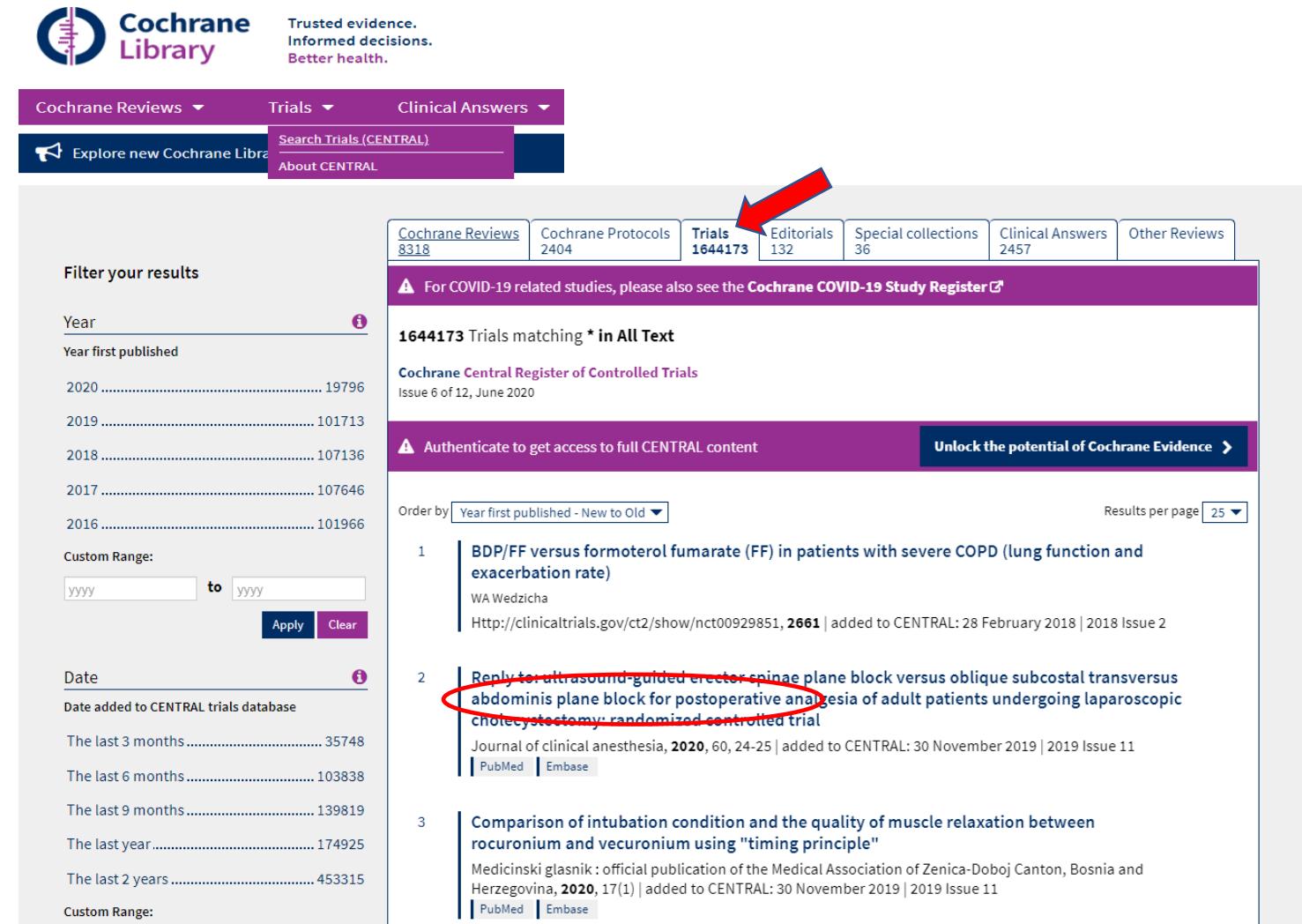


<https://www.ovid.com/about-ovid.html>

Ovid

# CENTRAL

- The Cochrane Central Register of Controlled Trials (CENTRAL) has been recognized as the most comprehensive source of reports of randomized trials.
- As of June 2020, it contains over 1.6 million records of trials.
- CENTRAL includes randomized trials that are not indexed in MEDLINE, Embase or other bibliographic databases and reports that are available only in **conference proceedings** or **trials registers**.



Trusted evidence.  
Informed decisions.  
Better health.

Cochrane Reviews Trials Clinical Answers

Explore new Cochrane Library Search Trials (CENTRAL) About CENTRAL

Filter your results

Year

Year first published

2020 ..... 19796  
2019 ..... 101713  
2018 ..... 107136  
2017 ..... 107646  
2016 ..... 101966

Custom Range: yyyy to yyyy Apply Clear

Date

Date added to CENTRAL trials database

The last 3 months ..... 35748  
The last 6 months ..... 103838  
The last 9 months ..... 139819  
The last year ..... 174925  
The last 2 years ..... 453315

Custom Range:

Cochrane Reviews 8318 Cochrane Protocols 2404 Trials 1644173 Editorials 132 Special collections 36 Clinical Answers 2457 Other Reviews

For COVID-19 related studies, please also see the [Cochrane COVID-19 Study Register](#)

1644173 Trials matching \* in All Text

Cochrane Central Register of Controlled Trials  
Issue 6 of 12, June 2020

Authenticate to get access to full CENTRAL content

Unlock the potential of Cochrane Evidence

Order by Year first published - New to Old Results per page 25

1 BDP/FF versus formoterol fumarate (FF) in patients with severe COPD (lung function and exacerbation rate)  
WA Wedzicha  
[Http://clinicaltrials.gov/ct2/show/nct00929851](http://clinicaltrials.gov/ct2/show/nct00929851), 2661 | added to CENTRAL: 28 February 2018 | 2018 Issue 2

2 Reply to: ultrasound-guided erector spinae plane block versus oblique subcostal transversus abdominis plane block for postoperative analgesia of adult patients undergoing laparoscopic cholecystectomy: randomized controlled trial  
Journal of clinical anesthesia, 2020, 60, 24-25 | added to CENTRAL: 30 November 2019 | 2019 Issue 11  
PubMed | Embase

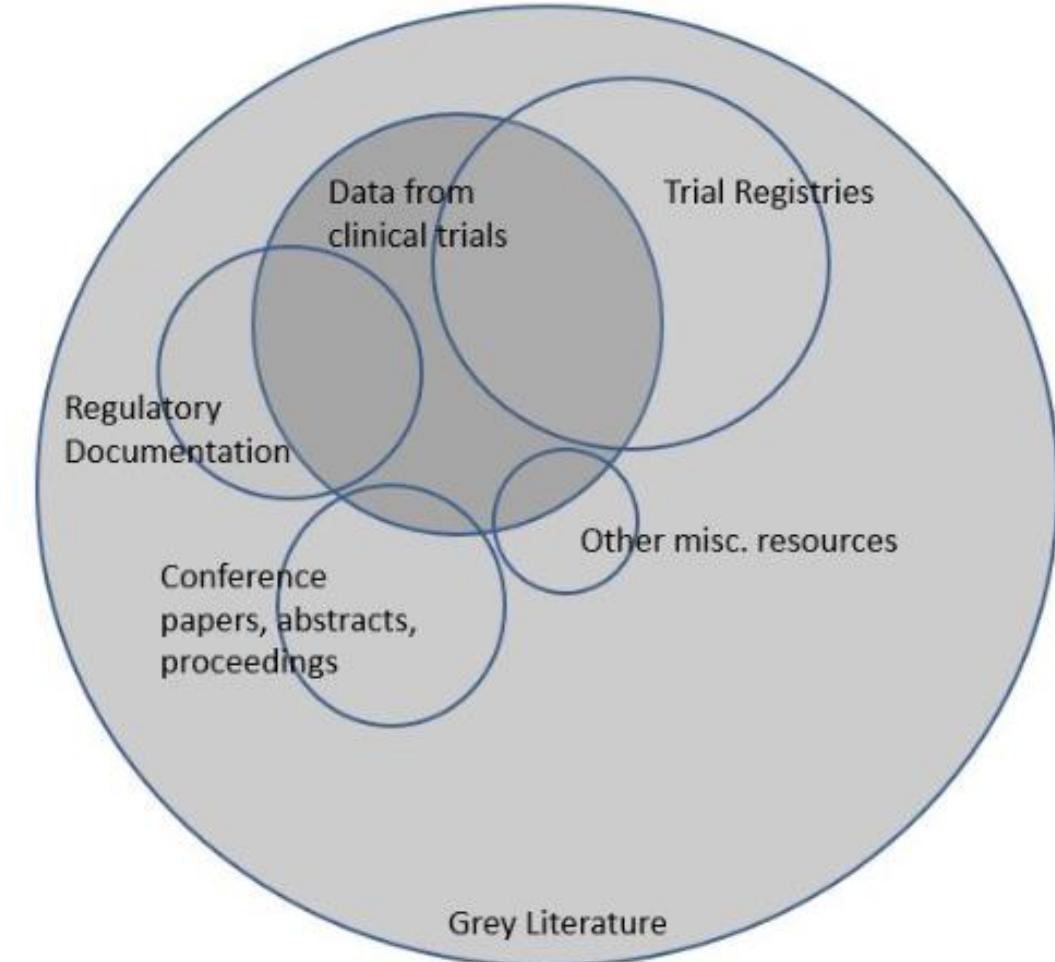
3 Comparison of intubation condition and the quality of muscle relaxation between rocuronium and vecuronium using "timing principle"  
Medicinski glasnik : official publication of the Medical Association of Zenica-Doboj Canton, Bosnia and Herzegovina, 2020, 17(1) | added to CENTRAL: 30 November 2019 | 2019 Issue 11  
PubMed | Embase

<https://www.cochranelibrary.com/>

# Sources of unpublished studies (“grey literature”)

There are many definitions of grey literature, but it is usually understood to mean “literature that is not formally published in sources such as books or journal articles”. This includes:

1. Conference abstracts
2. International trial registries
3. Pharmaceutical industry trial registries
4. Regulatory authorities clinical study reports



# Conference abstracts

- Over one-half of trials reported in conference abstracts never reach full publication.
- Many conference proceedings are published as journal supplements, which are retrieved from the search of main databases
- Others can be searched online in specific websites (e.g. for diabetes):



The screenshot shows the EASD Virtual Meeting website interface. At the top, there is a blue header bar with the text "EASD VIRTUAL MEETING". Below the header, there is a row of thumbnails for previous EASD annual meetings from 2018 to 2011. To the right of the thumbnails, there is a search bar with the placeholder "Search" and a search icon. Below the search bar, there are three filter options: "Select by group:", "Filter by Event:", and "Filter by Resource type:". Under "Select by group:", there is a dropdown menu with the option "Webcasts, ePosters, Abstracts, Interviews" selected. Under "Filter by Event:", there is a dropdown menu with the option "Berlin 2018" selected. Under "Filter by Resource type:", there is a dropdown menu with the option "Abstract" selected. Below these filters, there is a section titled "Filter by Keyword:" with a placeholder "Select a keyword" and a "Clear Filter →" button. At the bottom of the search results, there is a message "1215 results found" and a "Sort by:" dropdown menu set to "Year (newest first)".



# International trial registries

- Clinicaltrials.gov: Identify completed unpublished, terminated, or ongoing trials
- EU Clinical Trials Register - <https://www.clinicaltrialsregister.eu/ctr-search/search>
- WHO International Clinical Trials Registry Platform (ICTRP) - <http://apps.who.int/trialsearch/>

NIH U.S. National Library of Medicine

**ClinicalTrials.gov**

Find Studies ▾ About Studies ▾ Submit Studies ▾ Resources ▾ About Site ▾

ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world.

## EU Clinical Trials Register

Home & Search Joining a trial Contacts About

### Clinical trials

The European Union Clinical Trials Register allows you to search for protocol and results information on:

- interventional clinical trials that are conducted in the European Union (EU) and the European Economic Area (EEA);
- clinical trials conducted outside the EU / EEA that are linked to European paediatric-medicine development.

World Health Organization

International Clinical Trials Registry Platform Search Portal

Data Providers

Data sets from [data providers](#) are updated every Friday evening according to the following schedule:  
Every week:

- Australian New Zealand Clinical Trials Registry, last data file imported on **11 February 2019**
- Chinese Clinical Trial Registry, last data file imported on **3 June 2019**
- ClinicalTrials.gov, last data file imported on **3 June 2019**
- EU Clinical Trials Register (EU-CTR), last data file imported on **14 January 2019**
- ISRCTN, last data file imported on **27 May 2019**
- The Netherlands National Trial Register, last data file imported on **3 June 2019**

Every 4 weeks:

- Brazilian Clinical Trials Registry (ReBec), last data file imported on **15 January 2019**
- Clinical Trials Registry - India, last data file imported on **21 May 2019**
- Clinical Research Information Service - Republic of Korea, last data file imported on **20 May 2019**
- Cuban Public Registry of Clinical Trials, last data file imported on **15 January 2019**
- German Clinical Trials Register, last data file imported on **21 May 2019**
- Iranian Registry of Clinical Trials, last data file imported on **21 May 2019**
- Japan Primary Registries Network, last data file imported on **21 May 2019**
- Pan African Clinical Trial Registry, last data file imported on **20 May 2019**
- Sri Lanka Clinical Trials Registry, last data file imported on **21 May 2019**
- Thai Clinical Trials Registry (TCTR), last data file imported on **22 May 2019**
- Peruvian Clinical Trials Registry (REPEC), last data file imported on **25 February 2019**

# Design a search strategy

"Everything should be made as simple as possible, but not simpler." A. Einstein

- Three main steps:

**1. Build your general search structure  
(Define main PICO<sub>S</sub> domains)**

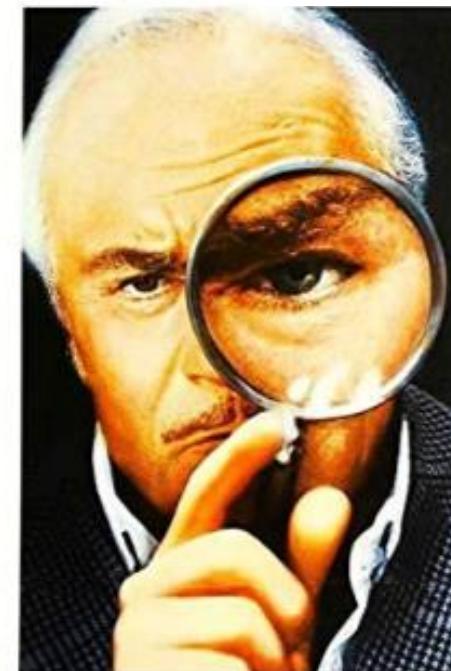


**2. Identify all relevant search terms  
for each domain**

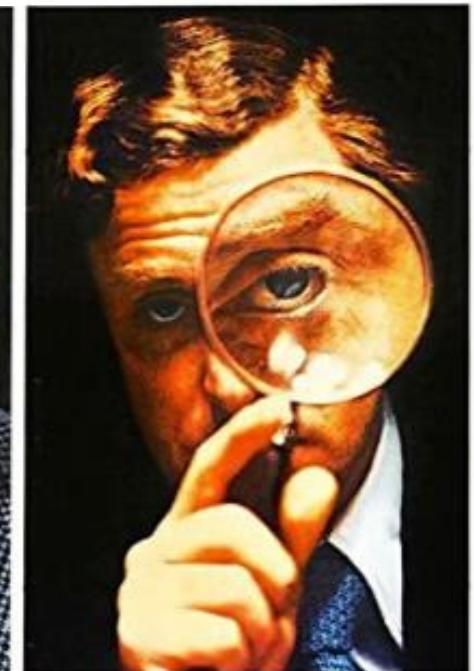


**3. Combine your search terms**

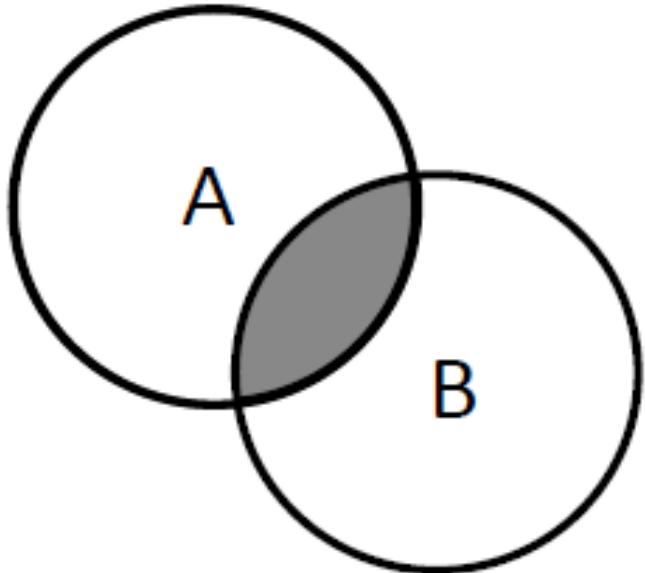
*Think of the  
perfect search...*



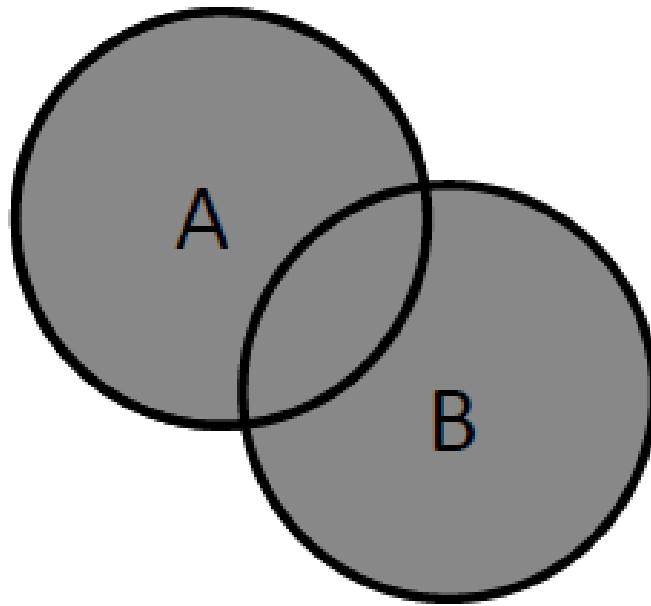
*Then go  
one step further.*



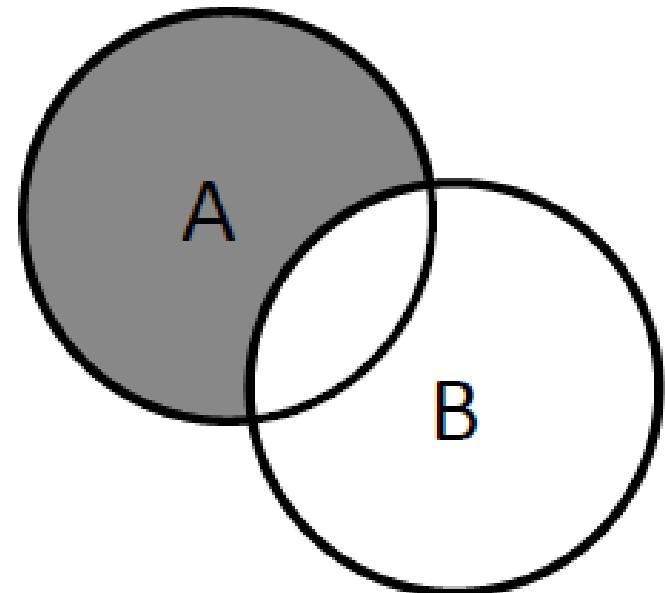
# Boolean operators



A AND B



A OR B



A NOT B

# Search quiz

- Search for:
  1. Diabetes → • 675k
  2. Metformin → • 20k
  3. diabetes AND metformin → • 660k
  4. diabetes OR metformin → • 680k
  5. diabetes NOT metformin → • 15k
  6. metformin NOT diabetes → • 5k
- Search results:



# Translate your search across databases

The screenshot shows the 'Polyglot' section of the Systematic Review Accelerator. On the left is a vertical navigation menu with icons for Dashboard, Login, SearchRefinery, Polyglot Search, Deduplicator, Screenatron, Disputatron, SpiderCite, RevMan Replicant, Help, Recommended Tools, What's new, About Us, Citing us, Contact Us, and Collapse. The main area has a dark header with the title 'Polyglot'. Below it is a large input field labeled 'Your query' containing the number '1'. To the right of the input field are several icons: a checkbox for 'Replace Line References', a magnifying glass, a clipboard, a delete button, and a dropdown arrow. A sub-instruction below the input field says 'Type a PubMed or Ovid MEDLINE query in the box above to see its translations (or click here to see an example)'. At the bottom of the main area are three buttons: 'Open Query in SearchRefiner', 'Import Search From .txt File', and three expandable sections for 'PubMed', 'Ovid MEDLINE', and 'Cochrane Library', each with a copy icon. The top right corner of the page includes the Bond University logo, the Institute for Evidence-Based Healthcare logo, a login link, and 'Cite' and 'Help' buttons.

<https://sr-accelerator.com/#/polyglot>



# An example of a search strategy

Medline (via Pubmed)	#47 NVPLAF237	#95 "pioglitazone"(Supplementary Concept)	#145 insulin glulisine
#1 Metformin	#48 canagliflozin	#96 AD-4833	#146 "insulin glulisine"(Supplementary Concept)
#2 "Metformin"(Mesh)	#49 "Canagliflozin"(Mesh)	#97 AD4833	#147 insulin lispro
#3 LA-6023	#50 JNJ-28431754	#98 U72107A	#148 "Insulin Lispro"(Mesh)
#4 LA6023	#51 JNJ28431754	#99 U-72107A	#149 "isophane insulin, insulin lispro drug combination 50:50"(Supplementary Concept)
#5 glimepiride	#52 TA-7284	#100 U72,107A	#150 "insulin lispro, isophane insulin lispro drug combination (25:75)"(Supplementary Concept)
#6 "glimepiride"(Supplementary Concept)	#53 TA7284	#101 Acarbose	#151 LY-275585
#7 HOE-490	#54 empagliflozin	#102 "Acarbose"(Mesh)	#152 LY275585
#8 HOE490	#55 "empagliflozin"(Supplementary Concept)	#103 BAY-G-5421	#153 SAR-342434
#9 gliclazide	#56 BI-10773	#104 BAYG5421	#154 SAR342434
#10 "Gliclazide"(Mesh)	#57 BI10773	#105 BAY-G 5421	#155 insulin isophane
#11 S-1702	#58 dapagliflozin	#106 miglitol	#156 insulin NPH
#12 S1702	#59 "2-(3-(4-ethoxybenzyl)-4-chlorophenyl)-6-hydroxymethyltetrahydro-2H-pyran-3,4,5-triol"(Supplementary Concept)	#107 "miglitol"(Supplementary Concept)	#157 insulin neutral protamine Hagedorn
#13 S-852	#60 BMS-512148	#108 BAY-m-1099	#158 "Insulin, Isophane"(Mesh)
#14 S852	#61 BMS512148	#109 BAY-m 1099	#159 insulin regular
#15 glipizide	#62 ertugliflozin	#110 BAYm1099	#160 insulin human
#16 "Glipizide"(Mesh)	#63 "5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-hydroxymethyl-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol"(Supplementary Concept)	#111 nateglinide	#161 "Insulin, Regular, Human"(Mesh)
#17 K-4024	#64 PF-04971729	#112 "nateglinide"(Supplementary Concept)	#162 MK-1293
#18 K4024	#65 PF04971729	#113 AY-4166	#163 MK1293
#19 glyburide	#66 sotagliflozin	#114 AY4166	#164 MYL-1501D
#20 glibenclamide	#67 "(2S, 3R, 4R, 5S, 6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol"(Supplementary Concept)	#115 repaglinide	#165 MYL1501D
#21 "Glyburide"(Mesh)	#68 LX4211	#116 "repaglinide"(Supplementary Concept)	#166 OR #1-165
#22 HB-419	#69 LX-4211	#117 AG-EE-623-ZW	#167 randomized controlled trial(pt)
#23 HB419	#70 Liraglutide	#118 AG-EE-388	#168 controlled clinical trial(pt)
#24 HB-420	#71 "Liraglutide"(Mesh)	#119 AG-EE-388-ZW	#169 randomized(tiab)
#25 HB420	#72 NN-2211	#120 AGEE623ZW	#170 placebo(tiab)
#26 alogliptin	#73 NN2211	#121 AGEE388	#171 clinical trials as topic(mesh: noexp)
#27 "alogliptin"(Supplementary Concept)	#74 2211, NN	#122 AGEE388ZW	#172 randomly(tiab)
#28 SYR-322	#75 lixisenatide	#123 insulin degludec	#173 trial(ti)
#29 SYR322	#76 "lixisenatide"(Supplementary Concept)	#124 "insulin degludec, insulin aspart drug combination"(Supplementary Concept)	#174 OR #167-173
#30 Linagliptin	#77 AVE-010	#125 "insulin degludec"(Supplementary Concept)	#175 animals(mh) NOT humans(mh)
#31 "Linagliptin"(Mesh)	#78 AVE-0010	#126 NN-1250	#176 #174 NOT #175
#32 BI1356	#79 AVE0010	#127 NN1250	#177 #166 AND #176
#33 BI-1356	#80 AVE010	#128 insulin detemir	
#34 1356, BI	#81 dulaglutide	#129 "Insulin Detemir"(Mesh)	
#35 saxagliptin	#82 "dulaglutide"(Supplementary Concept)	#130 NN-304	
#36 "saxagliptin"(Supplementary Concept)	#83 LY-2189265	#131 NN304	
#37 BMS-477118	#84 LY2189265	#132 insulin glargine	
#38 BMS477118	#85 exenatide	#133 ("Insulin Glargin"(Mesh)	
#39 sitagliptin	#86 "exenatide"(Supplementary Concept)	#134 "LY2963016 insulin glargin"(Supplementary Concept)	
#40 "Sitagliptin Phosphate"(Mesh)	#87 AC-2993	#135 HOE-901	
#41 MK-0431	#88 semaglutide	#136 HOE901	
#42 MK0431	#89 "semaglutide"(Supplementary Concept)	#137 901, HOE	
#43 0431, MK	#90 NN-9535	#138 LY2963016	
#44 vildagliptin	#91 NN9535	#139 insulin aspart	
#45 "vildagliptin"(Supplementary Concept)	#92 NN9924	#140 "Insulin Aspart"(Mesh) OR "insulin aspart, insulin aspart protamine drug combination 30:70"(Supplementary Concept)	
#46 NVP-LAF237	#93 NN-9924	#141 "insulin degludec, insulin aspart drug combination"(Supplementary Concept)	
	#94 Pioglitazone	#142 NN-1218	
		#143 NN1218	
		#144 INA-X14	

<https://dom-pubs.onlinelibrary.wiley.com/doi/10.1111/dom.14451>



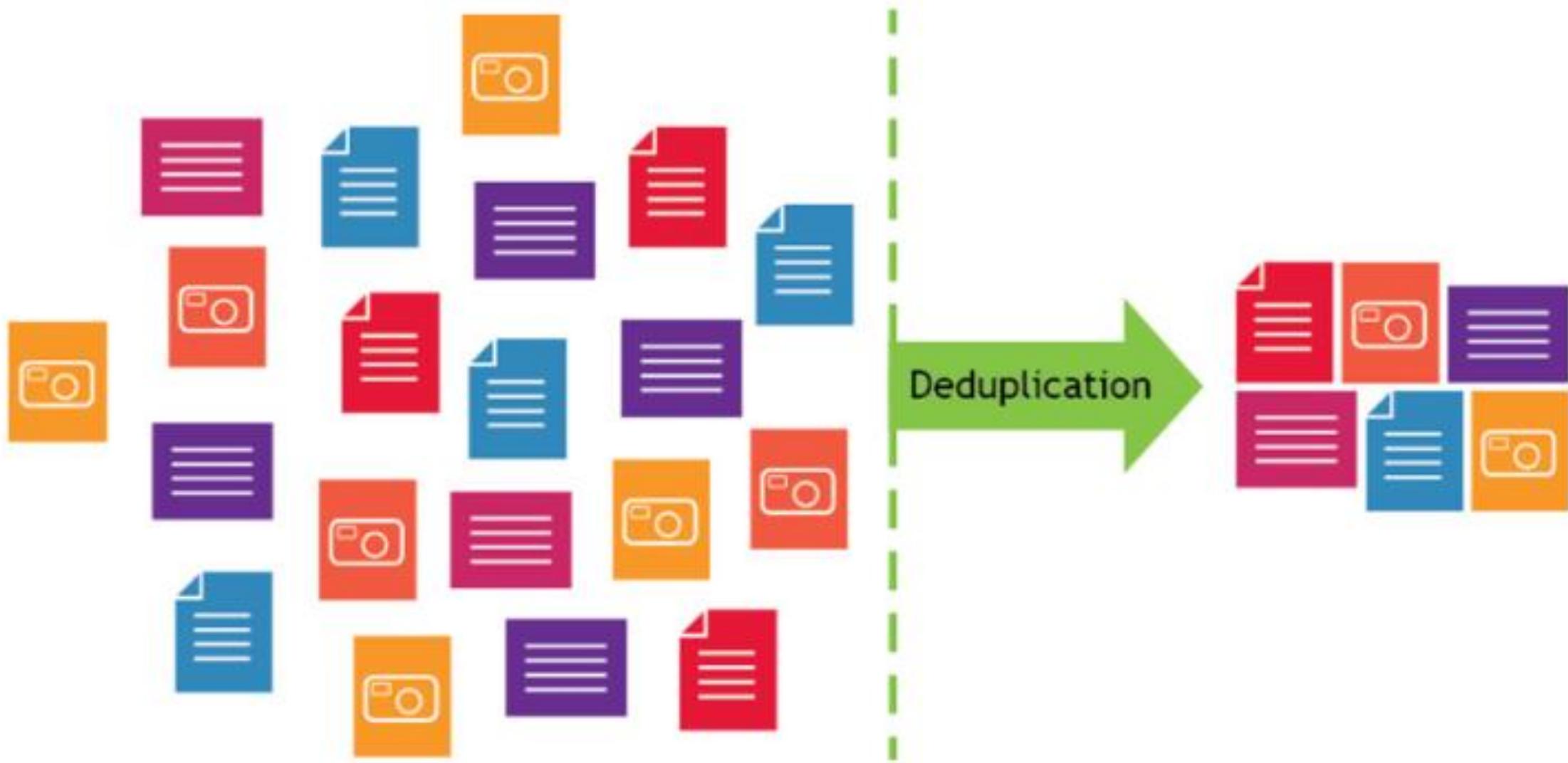
# Import search results



Your personal  
research assistant

Zotero is a free, easy-to-use tool to help you  
collect, organize, cite, and share research.

# Deduplication of references



# Study selection



Once you have imported and merged your search results from electronic databases using reference management software...

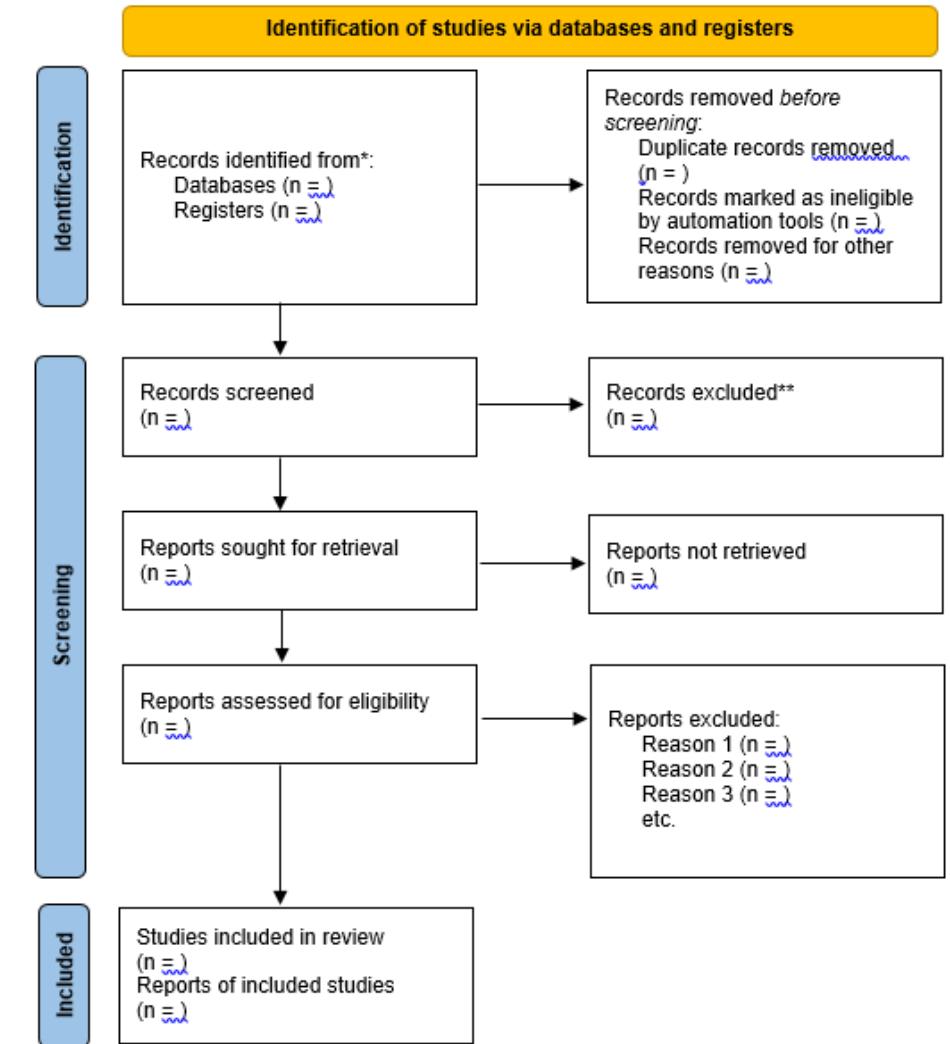
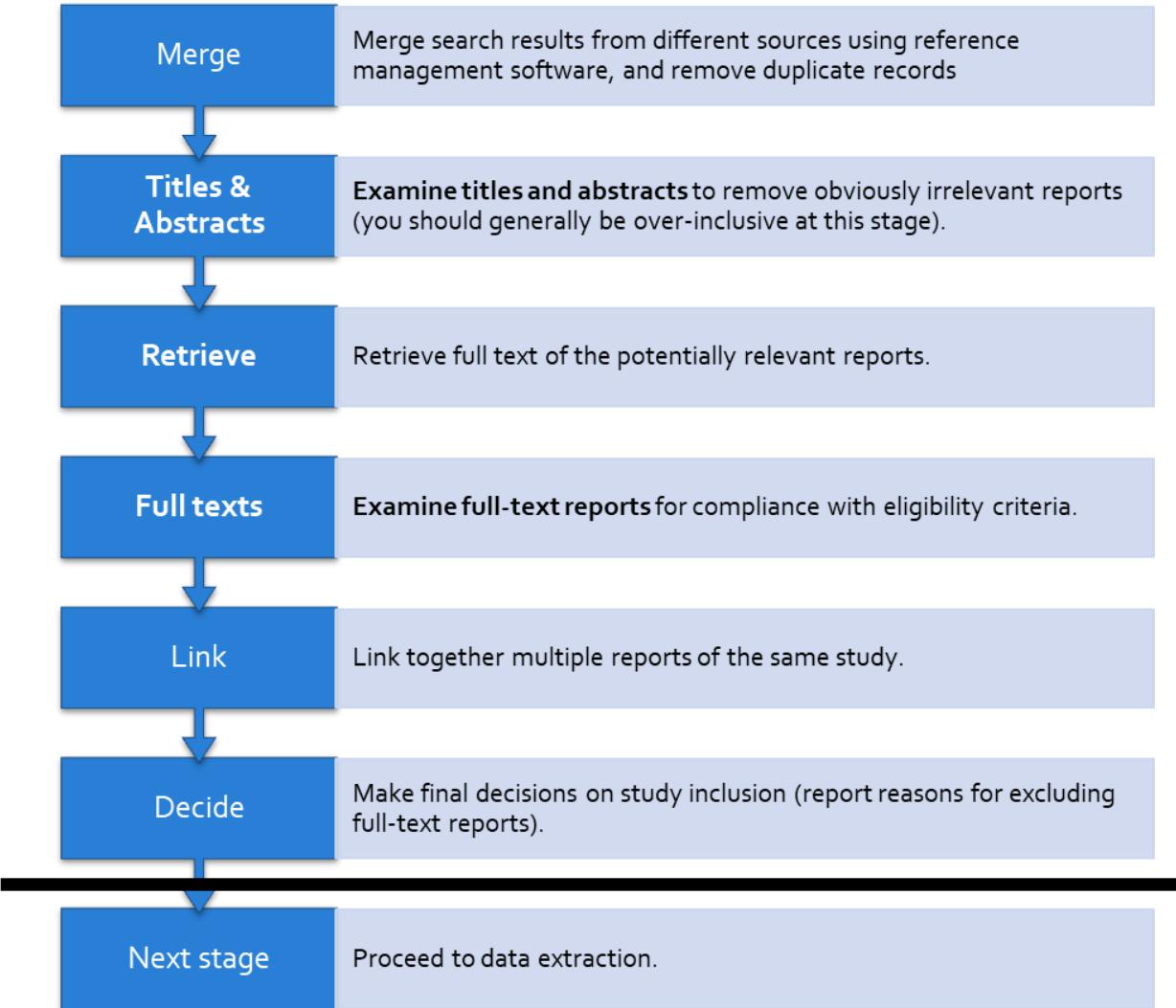


...and have removed duplicate records of the same report (records retrieved from more than one database) then...



... you have to **screen the remaining reports** in order to select which will be included in the systematic review.

# Flow diagram of the selection process



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

# Reports (records) vs Studies

## Studies (not reports) are the unit of interest

-  A **study** may have been reported in several published articles, abstracts or other **reports**.
-  You have to **link together** multiple reports of the same study.
-  This “collation of reports” process is usually done after the full text screening, but often it is also continued during the data extraction process.
-  Sometimes it may be difficult to detect multiple reports of the same study, and some “detective work” may be required.

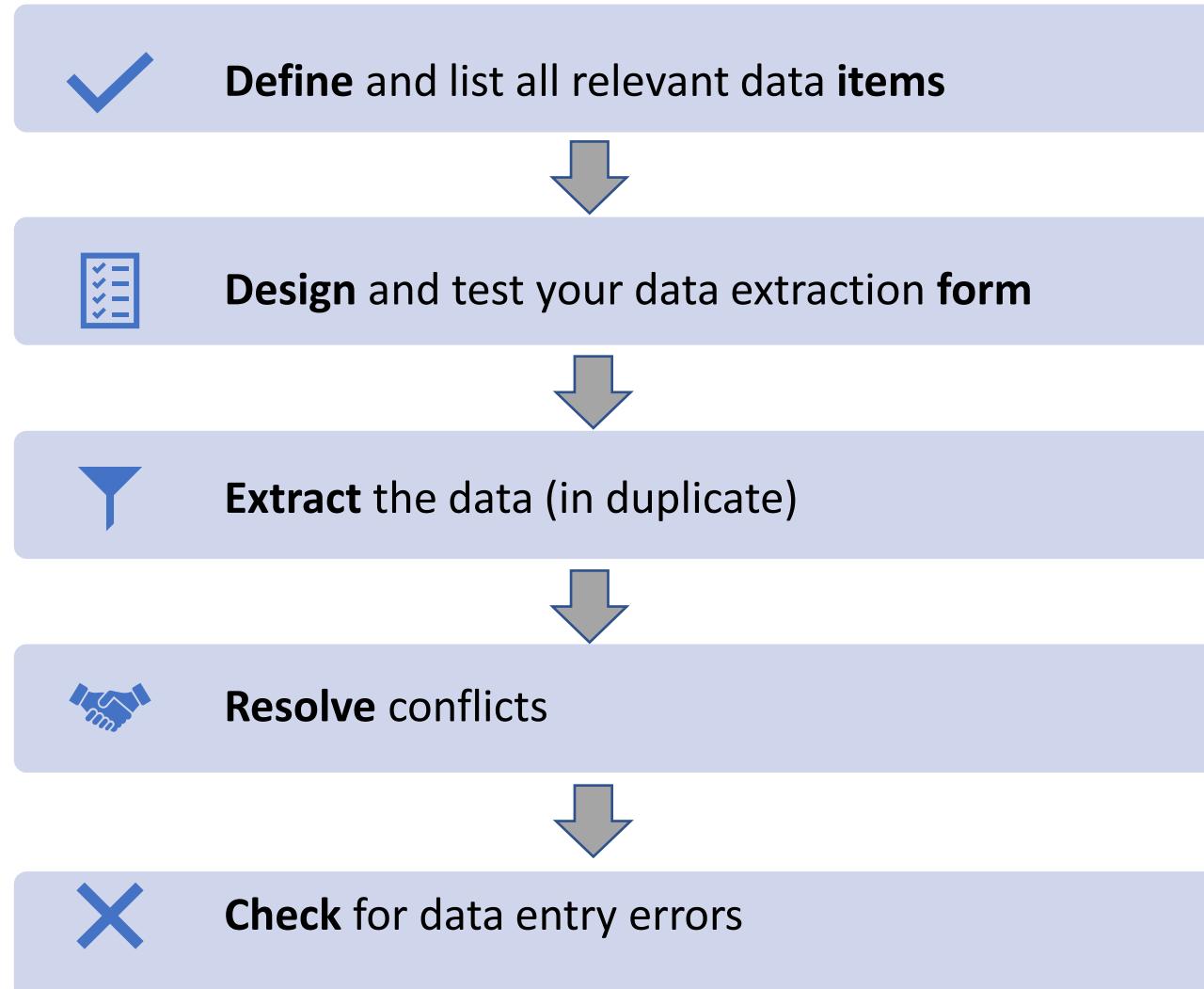
# Data extraction

The process of collecting and organizing all relevant data from each eligible study



Refid	Author_Year	Trial characteristics						agent	Intervention characteristics			mean change from baseline	SD	n
		Study design	Blinding status	Drug-naïve status?	Pharma industry sponsored	Duration	Duration measured		drugclass					
2	Aschner 2015	Parallel	Open-label	No	Yes	24 Weeks	24 Weeks	Basal insulin	Basal insulin			1.1	9999	455
3	Aschner 2006	Parallel	Double-blind	No	Yes	24 Weeks	24 Weeks	DPP-4 inhibitors	DPP-4 inhibitors			-0.2	2.77	192
5	Aschner 2010	Parallel	Double-blind	Yes	Yes	24 Weeks	24 Weeks	Metformin	Metformin			-1.9	2.69	446
6	Aschner 2012	Parallel	Open-label	No	Yes	24 Weeks	24 Weeks	Basal insulin	Basal insulin			0.44	3.31	227
7	Acronfit 2000	Parallel	Double-blind	No	Yes	26 Weeks	26 Weeks	Pioglitazone	Pioglitazone			1.78	3.39	245
8	Aroda 2016	Parallel	Open-label	No	Yes	30 Weeks	30 Weeks	Lixisenatide	GLP-1 RAs			-0.7	3.83	366
9	Aroda 2017	Parallel	Open-label	No	Yes	30 Weeks	30 Weeks	Basal insulin	Basal insulin			1.15	4.36	360
10	Aroda 2016	Parallel	Double-blind	No	Yes	26 Weeks	26 Weeks	Basal insulin	Basal insulin			2	1.55	173
11	Angona Ferreira 2013	Parallel	Double-blind	No	Yes	54 Weeks	54 Weeks	Sulphonylureas	Sulphonylureas			1.2	3.65	148
12	Angona Ferreira 2013	Parallel	Double-blind	No	Yes	54 Weeks	54 Weeks	Sulphonylureas	Sulphonylureas			0.8	4.25	41
13	Arechavaleta 2011	Parallel	Double-blind	No	Yes	30 Weeks	30 Weeks	DPP-4 inhibitors	DPP-4 inhibitors			-0.8	3.3	465
14	Apovion 2010	Parallel	Double-blind	No	Yes	24 Weeks	24 Weeks	Placebo	Placebo			-3.6	9999	36
15	Alvrisson 2003	Parallel	Not reported	Yes	No	312 Weeks	312 Weeks	Sulphonylureas	Sulphonylureas			1.5	4.67	18
16	Athren 2017	Parallel	Double-blind	No	Yes	56 Weeks	56 Weeks	Semaglutide SC	GLP-1 RAs			-5.2	5.23	818
17	Athren 2013	Parallel	Double-blind	No	Yes	24 Weeks	24 Weeks	Lixisenatide	GLP-1 RAs			-2	3.74	510
18	Athren 2014	Parallel	Double-blind	No	Yes	156 Weeks	156 Weeks	DPP-4 inhibitors	DPP-4 inhibitors			-2.05	4.11	89
19	Athren 2014	Parallel	Double-blind	No	Yes	156 Weeks	156 Weeks	Sulphonylureas	Sulphonylureas			0.98	4.76	102
20	Athren 2004	Parallel	Double-blind	No	No	52 Weeks	52 Weeks	DPP-4 inhibitors	DPP-4 inhibitors			-0.2	9999	56
21	Ahmann 2018	Parallel	Open-label	No	Yes	56 Weeks	56 Weeks	Semaglutide SC	GLP-1 RAs			-5.6	5.83	404
22	Ahmann 2015	Parallel	Double-blind	No	Yes	26 Weeks	26 Weeks	Placebo	Placebo			-0.42	3.91	216
23	Moses 2015	Parallel	Double-blind	No	Yes	54 Weeks	54 Weeks	DPP-4 inhibitors	DPP-4 inhibitors			-0.3	3.87	190
24	Probstfield 2016	Parallel	Open-label	No	Yes	26 Weeks	26 Weeks	Exenatide	GLP-1 RAs			-4.8	3.3	45
25	Rosenstock 2016	Parallel	Open-label	No	Yes	26 Weeks	26 Weeks	Lixisenatide	GLP-1 RAs			-0.6	5.15	295
26	Belli 2014	Parallel	Double-blind	No	Yes	24 Weeks	24 Weeks	Lixisenatide	GLP-1 RAs			-2.65	5	313
27	Belli 2007	Parallel	Double-blind	No	Yes	52 Weeks	52 Weeks	DPP-4 inhibitors	DPP-4 inhibitors			0.2	3.44	295
28	Bellinder 2012	Parallel	Double-blind/single-blind	No	Yes	102 Weeks	102 Weeks	Dapagliflozin	SGLT-2 inhibitors			-4.54	4.26	89
29	Bode 2013	Parallel	Double-blind	No	Yes	104 Weeks	104 Weeks	Placebo	Placebo			-0.6	0.41	237
30	Bosi 2011	Parallel	Double-blind	No	Yes	52 Weeks	52 Weeks	Pioglitazone	Pioglitazone			1.6	3.88	399
31	Bosi 2009	Parallel	Double-blind	Yes	Yes	24 Weeks	24 Weeks	Metformin	Metformin			-1.62	3.71	285
32	Bosi 2007	Parallel	Double-blind	No	Yes	24 Weeks	24 Weeks	Placebo	Placebo			-1	3.42	130
33	Bi 2013	Parallel	Open-label	Yes	Yes	24 Weeks	24 Weeks	Sulphonylureas	Sulphonylureas			-0.1	2.51	70

# The data extraction process



# Characteristics of a data extraction form

- A good data extraction form balances **detail** with **utility**:
- An **Overly Inclusive** form is **impractical** and **time-consuming** (lots of useless data)
- An **Overly Minimalist** form may require revisiting the articles, in order to populate the form with **additional items**



VS



# Outcome data output for statistical analysis

	A	B	C	D	E	F	G	H	I	J	K	L	M
1	Refid	agent1	drugclass1	event1	n1	agent2	drugclass2	event2	n2	agent3	drugclass3	event3	n3
2		5 Metformin	Metformin		0	522	DPP-4 inhibit	DPP-4 inhibit	1	528			
3		22 Premixed ins	Premixed ins		2	23	Sulphonylure	Sulphonylure	1	26			
4		64 Metformin	Metformin		0	292	DPP-4 inhibit	DPP-4 inhibit	0	297			
5		67 Metformin	Metformin		0	68	Sulphonylure	Sulphonylure	0	70			
6		75 Sulphonylure	Sulphonylure		0	30	Placebo	Placebo	0	16			
7		92 Dapagliflozin	SGLT-2 inhibit		0	68	Placebo	Placebo	0	68			
8		113 $\alpha$ -glucosidase	$\alpha$ -glucosidase		0	62	Placebo	Placebo	0	62			
9		123 Metformin	Metformin		0	24	Sulphonylure	Sulphonylure	0	24			
10		136 DPP-4 inhibit	DPP-4 inhibit		0	29	Placebo	Placebo	0	30			
11		145 $\alpha$ -glucosidase	$\alpha$ -glucosidase		0	55	Placebo	Placebo	0	57			
12		150 Meglitinide	Meglitinide		0	62	Sulphonylure	Sulphonylure	0	62			
13		153 Metformin	Metformin		0	67	Pioglitazone	Pioglitazone	0	69			
14		154 $\alpha$ -glucosidase	$\alpha$ -glucosidase		0	96	Placebo	Placebo	0	92			
15		162 DPP-4 inhibit	DPP-4 inhibit		0	468	Placebo	Placebo	0	157			
16		170 DPP-4 inhibit	DPP-4 inhibit		0	132	Placebo	Placebo	0	64			
17		188 DPP-4 inhibit	DPP-4 inhibit		0	21	Placebo	Placebo	0	19			
18		209 $\alpha$ -glucosidase	$\alpha$ -glucosidase		1	279	Placebo	Placebo	0	93			
19		211 Metformin	Metformin		0	210	DPP-4 inhibit	DPP-4 inhibit	1	214			
20		212 Metformin	Metformin		0	30	Placebo	Placebo	0	30			
21		231 DPP-4 inhibit	DPP-4 inhibit		6	546	Sulphonylure	Sulphonylure	9	546			
22		236 $\alpha$ -glucosidase	$\alpha$ -glucosidase		0	398	Placebo	Placebo	0	97			
23		239 Metformin	Metformin		0	75	Dapagliflozin	SGLT-2 inhibit	2	351			
24		241 Metformin	Metformin	1		56	Empagliflozin	SGLT-2 inhibit	0	215			
25		243 Metformin	Metformin		0	29	Liraglutide	GLP-1 RA	0	29	Sulphonylure	Sulphonylure	0
26		244 $\alpha$ -glucosidase	$\alpha$ -glucosidase		0	108	Sulphonylure	Sulphonylure	0	111			
27		246 Metformin	Metformin		0	55	Pioglitazone	Pioglitazone	0	55			
28		247 Meglitinide	Meglitinide		0	88	Sulphonylure	Sulphonylure	0	87			
29		249 Metformin	Metformin		0	20	Pioglitazone	Pioglitazone	0	20	Sulphonylure	Sulphonylure	0
30		273 Metformin	Metformin	3		540	DPP-4 inhibit	DPP-4 inhibit	0	179			
31		292 DPP-4 inhibit	DPP-4 inhibit		0	146	Placebo	Placebo	0	74			



# Risk of bias assessment (Cochrane RoB 2 tool)

## Current version of RoB 2

### Current version

Download the 22 August 2019 version:

- The [full guidance document](#).
- The [gridsheet summarizing the tool](#).
- A [template for completing the assessment](#).
- An [Excel tool to implement RoB 2](#) (contains macros; download to your computer before using; some text is slightly out of date).

<https://www.riskofbias.info>



RoB 2 assessment for individual randomized, parallel group trials

Assessment ID: Ref. or label: Assessor: 21/5/1

Study ID: Experimental: Comparator: Specify which outcome: Specify the numerical result:

Is the review team's aim for this result to assess...? Weight for analysis:  
assignment to intervention (the 'intention-to-treat' effect)

If the aim is to assess the effect of adhering to intervention... (select one at least):

occurrence of non-protocol interventions  
 failures in implementing the intervention that could have affected the outcome  
 non-adherence to their assigned intervention by trial participants

assessment? (tick as many as apply)

Journal article(s)  
 Trial protocol  
 Statistical analysis plan (SAP)  
 Non-commercial trial registry record (e.g. ClinicalTrials.gov record)  
 Company-owned trial registry record (e.g. GSK Clinical Study Register record)  
 "Grey literature" (e.g. unpublished thesis)  
 Conference abstract(s) about the trial  
 Regulatory document (e.g. Clinical Study Report, Drug Approval Package)  
 Research ethics application  
 Grant database summary (e.g. NIH RePORTER, Research Councils UK Gateway to Research)

inform the risk-of-bias

Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Overall bias | Randomisation process

Signalling questions Response Description

1.1 Was the allocation sequence random?  
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?  
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?

Risk of bias judgement

Algorithm result Assessor's judgement

Algorithm

Double click on this column to create the support for judgement for this risk of bias domain from descriptions

Optional: What is the predicted direction of bias arising from the randomization process?

Guidance (Internet access) CLOSE SAVE



# Cochrane Risk Of Bias tool v.2 (RoB2)

RoB 2 assessment for individual randomized, parallel group trials

Assessment ID: [redacted] Assessor: 21/5/6 22:48

Study ID: [redacted] Ref. or label: [redacted]

Experimental: [redacted] Comparator: [redacted]

Specify which outcome: [redacted] Specify the numerical result: [redacted]

Is the review team's aim for this result to assess...? Weight for analysis: [redacted]

assignment to intervention (the 'intention-to-treat' effect) If the aim is to assess the effect of adhering to intervention... (select one at least)

occurrence of non-protocol interventions  
 failures in implementing the intervention that could have affected the outcome  
 non-adherence to their assigned intervention by trial participants

**Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Overall bias**

**Randomisation process**

Signalling questions Response Description

1.1 Was the allocation sequence random? [dropdown]  
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? [dropdown]  
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process? [dropdown]

Risk of bias judgement

Algorithm result: Algorithm Assessor's judgement: [dropdown]

Double click on this column to create the support for judgement for this risk of bias domain from descriptions

Optional: What is the predicted direction of bias arising from the randomization process? [dropdown]

GUIDANCE (Internet access) CLOSE SAVE

## Domain

### Domain 1: Randomization process

### Domain 2: Deviations from intended interventions

### Domain 3: Missing outcome data

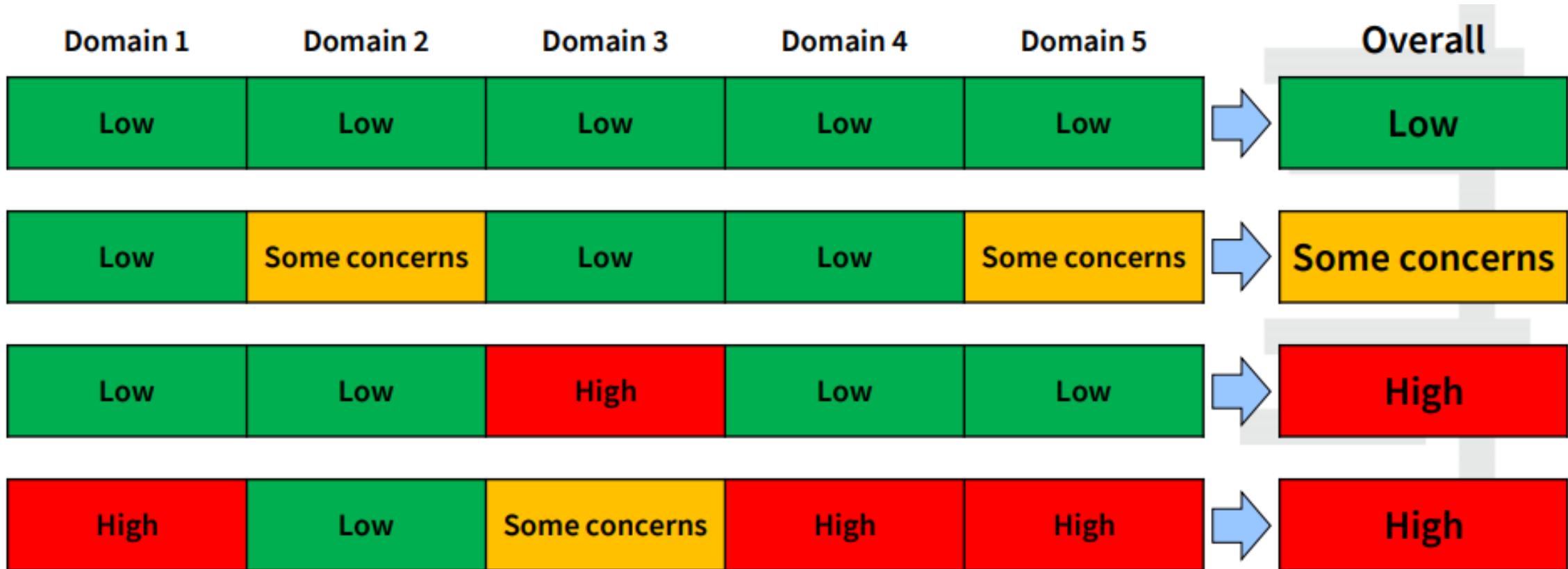
### Domain 4: Measurement of the outcome

### Domain 5: Selection of reported results

<https://www.riskofbias.info/>



# Cochrane Risk Of Bias tool v.2 (RoB2)





# Two is better than one





# Software for systematic reviews & meta-analyses

## SR TOOL BOX

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### Advanced Search

Software Tools  Other Tools [Add a New Tool](#)

Select an underlying approach:

Select a discipline:

Select a Cost:

Check 'Any' if not concerned about any specific features:

Any

OR

Select features you want a tool to support:

Protocol Development  
 Automated Search  
 Study Selection  
 Quality Assessment  
 Data Extraction  
 Automated Analysis  
 Text Analysis  
 Meta-Analysis  
 Report Write-Up  
 Collaboration  
 Document Management

**Search**

### Advanced Search Results:

Search criteria:  
- Underlying Approach: "any" | Discipline: "any" | Cost: "any" | Features: "Study Selection"

37 (Software) Tools have been found.

**Abstrackr** - An online tool for the task of citation screening for systematic reviews.

**BioReader (Biomedical Research Article Distiller)** - BioReader is a tool that enables users to perform classification of scientific literature by text mining-based classification of article abstracts. The tool is trained by uploading article corpora for two training categories - e.g. one positive and one negative for content of interest - as well as one corpus of abstracts to be classified and/or a search string to query PubMed for articles. The corpora are submitted as lists of PubMed IDs and the abstracts are automatically downloaded from PubMed, preprocessed, and the unclassified corpus is classified using the best performing classification algorithm out of ten implemented algorithms. BioReader is freely available as a web service.

**CADIMA** - CADIMA supports the conduct of systematic reviews and evidence/systematic maps by the provision of a freely available online tool that: 1. guides review authors through the evidence synthesis process, 2. facilitates the coordination of cooperating team members, 3. eases steps with considerable workload and 4. guarantees for its thorough documentation. The evidence synthesis tool was established and is further developed in a close collaboration between the Julius Kühn-Institut and the Collaboration for Environmental Evidence

**Colandr** - Colandr is an open access, machine-learning assisted tool for conducting evidence synthesis. This tool uses machine learning, natural language processing, and text-mining functions to partially automate finding relevant citations and extract desired data from PDF articles.

**Covidience** - A web-based software platform that streamlines the production of systematic reviews, including Cochrane Reviews. Citation screening, Full text review, Risk of Bias assessment, Extraction of study characteristics and other study data, Export of data into RevMan. Nonprofit organization, open source software

**DBpedia** - A resource description framework repository to support automated selection of primary studies.

**DistillerSR** - A web based reference screening, data extraction and reporting solution for systematic reviews.

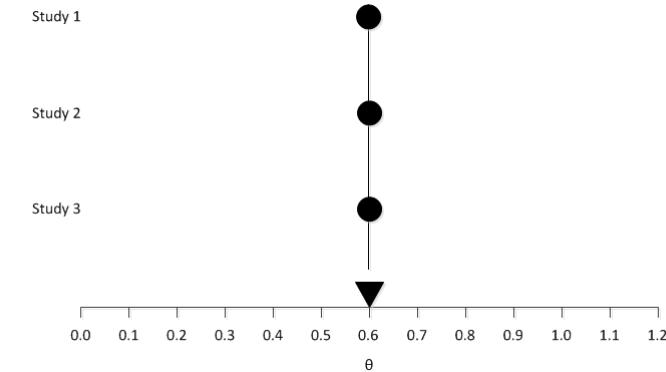
<http://systematicreviewtools.com/>

# Data synthesis (meta-analysis)

## ✓ Main Analysis

- Effect measures (e.g. mean difference, odds ratio)
- Confidence Interval (95% CI)
- Statistical approach (fixed OR random effects)
- Heterogeneity assessment

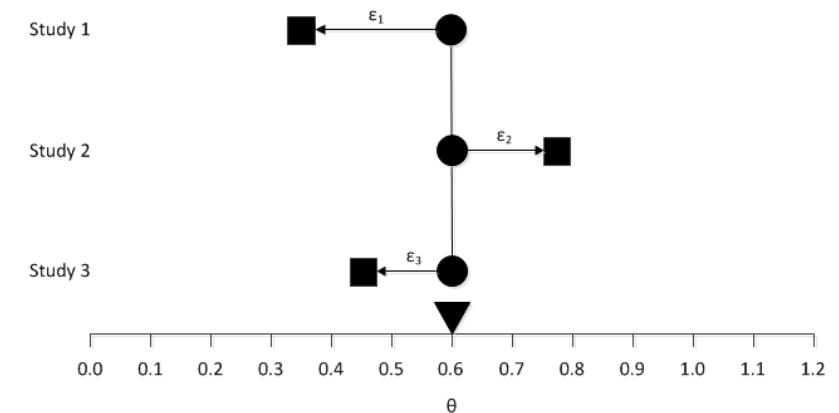
Fixed Effects



## ✓ Additional analyses

- Subgroup analyses
- Sensitivity analyses

Random Effects



# Forest plot

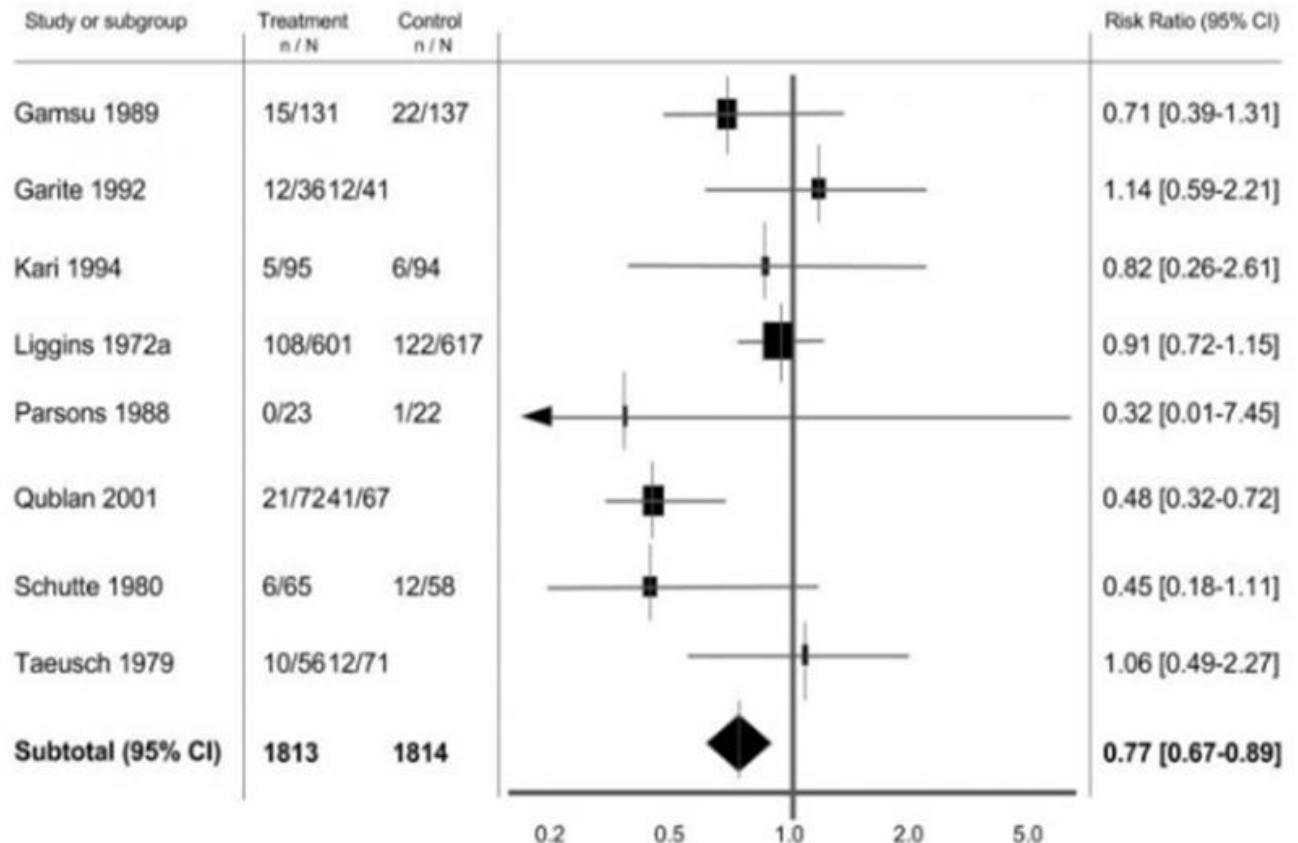
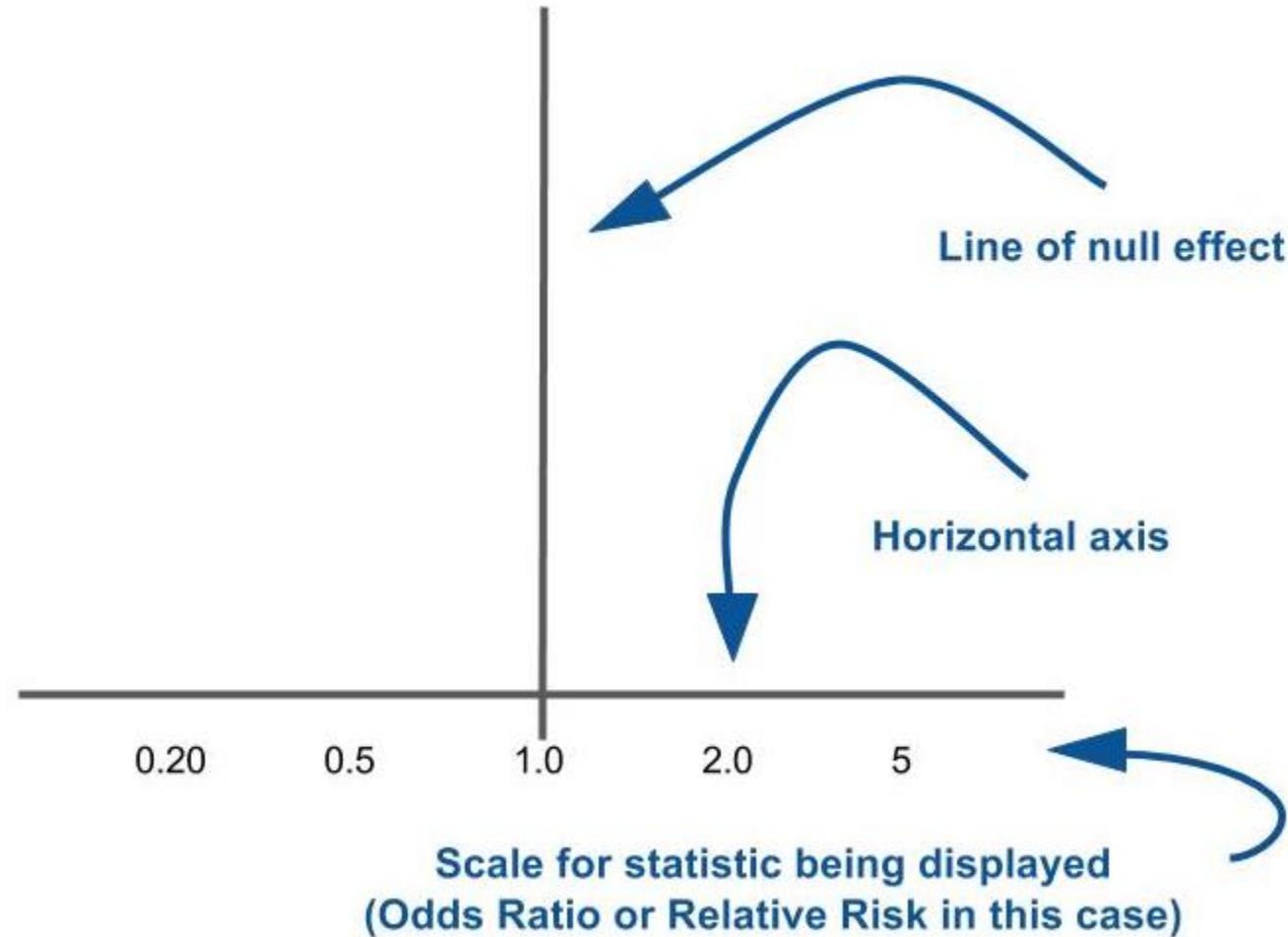
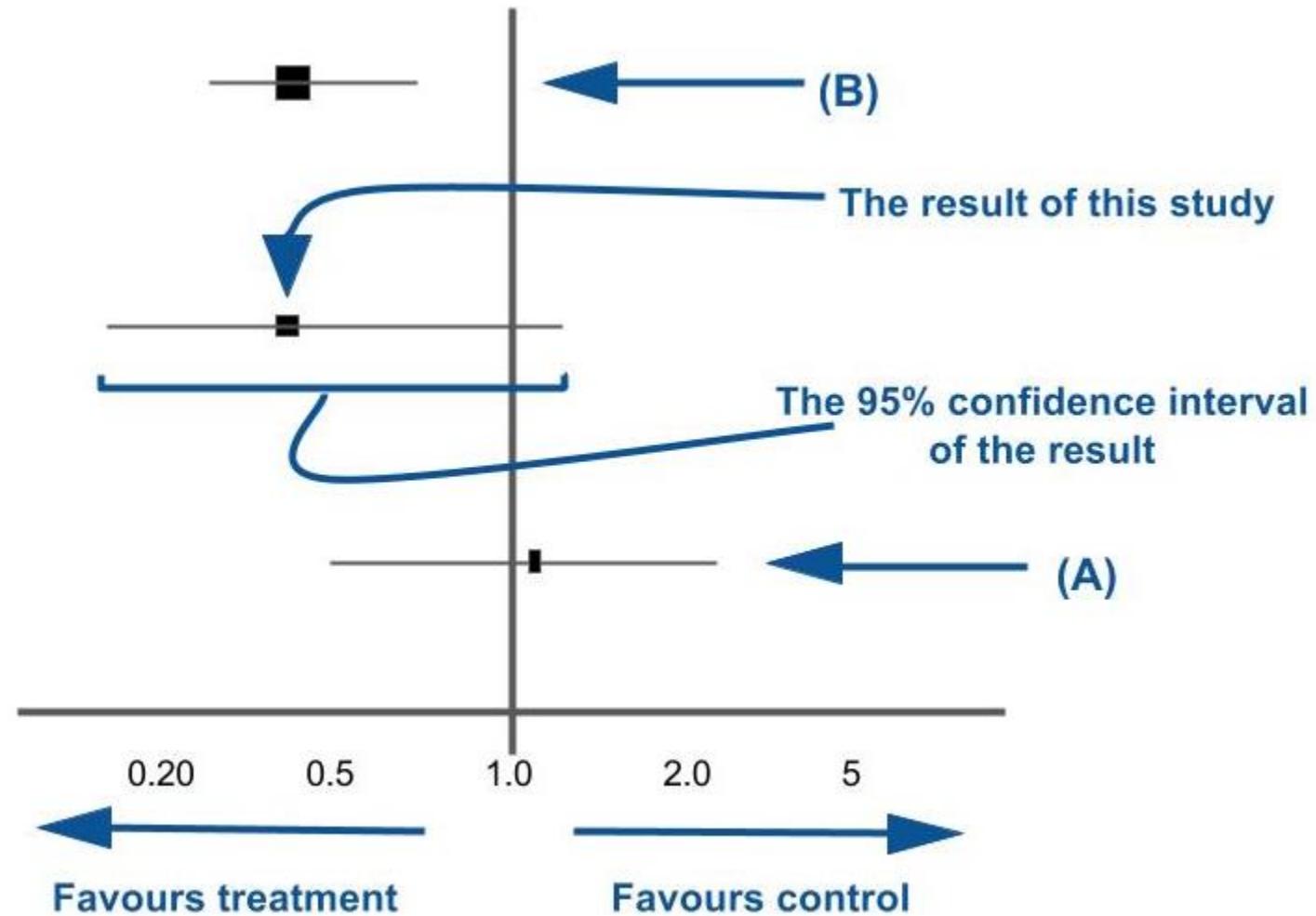


Figure 1. An example of a forest plot. Image adapted from Table 4 Roberts et al. (2006). [1]

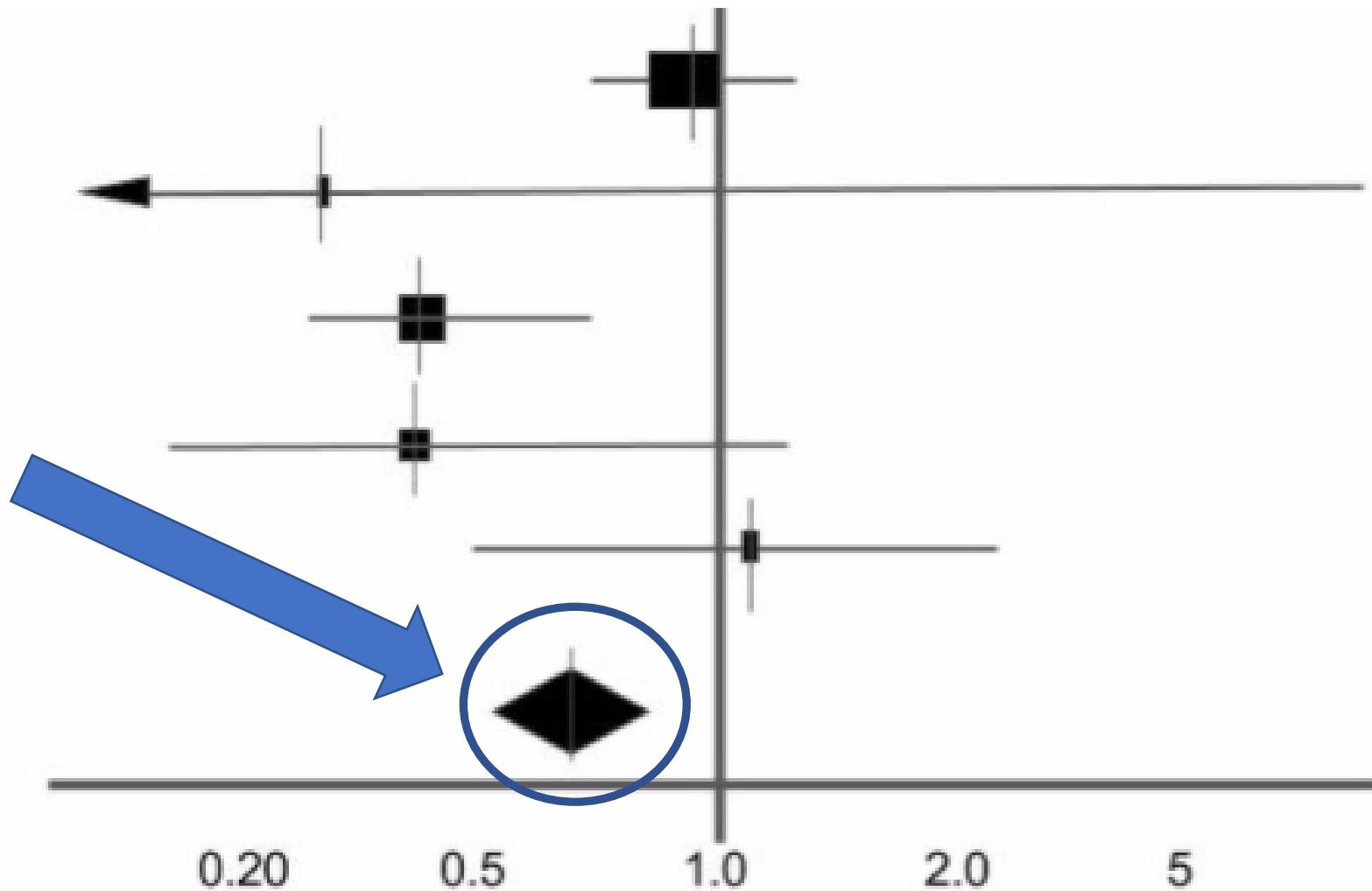
# The basics of forest plots



# Individual trial effect estimates



# Producing a summary effect estimate



# How do you interpret this forest plot?

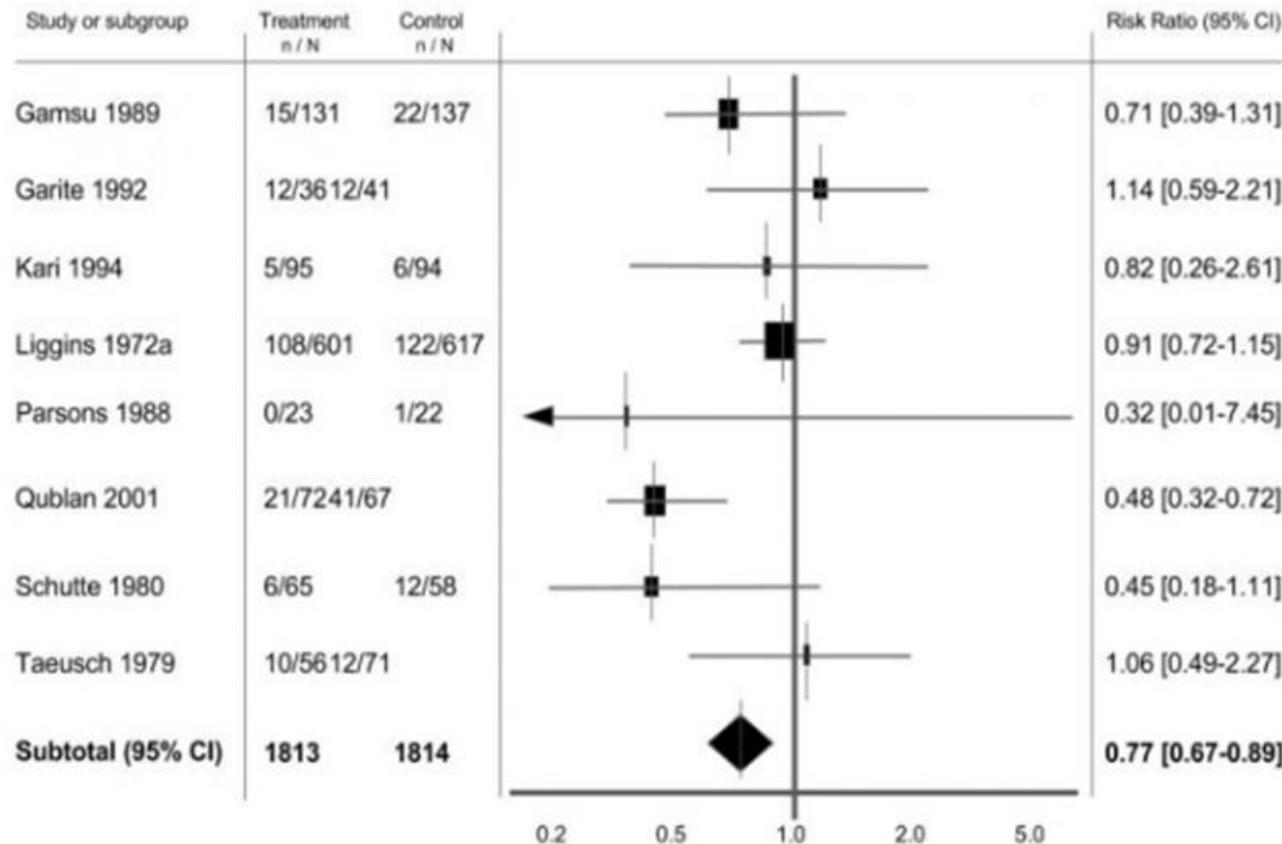
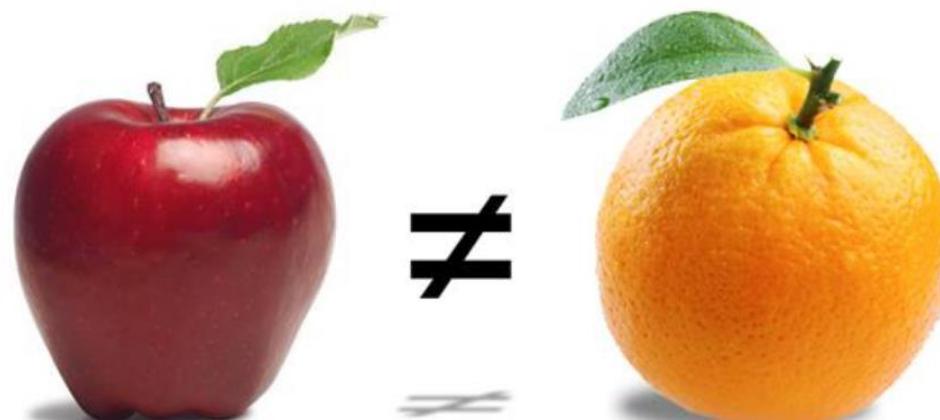


Figure 1. An example of a forest plot. Image adapted from Table 4 Roberts et al. (2006). [1]

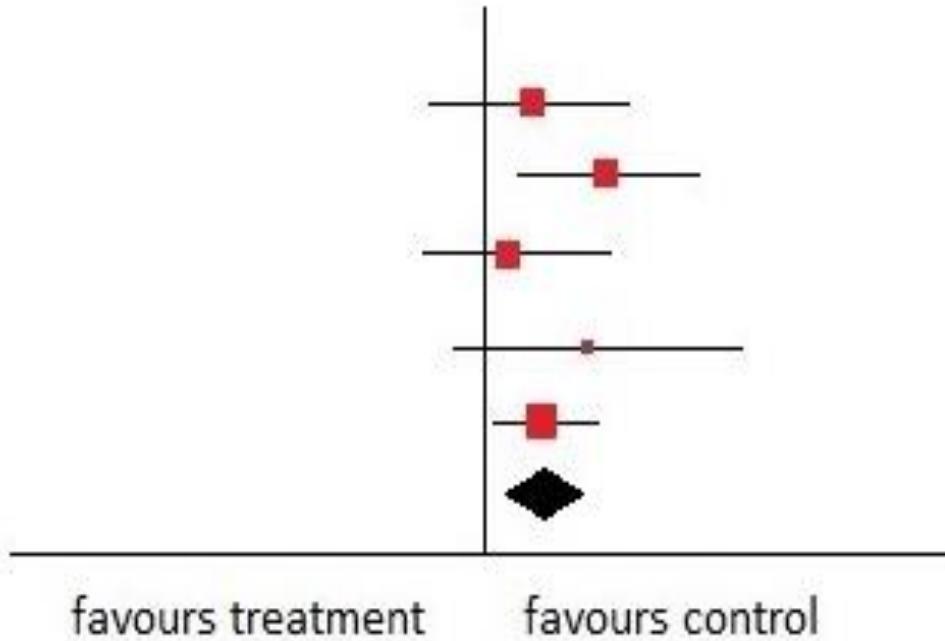
# Heterogeneity

- Difference (variation) in the results of the individual studies.
  - Clinical (e.g. differences in participants)
  - Methodological (e.g. Low vs high risk of bias)
  - Statistical (Variation in intervention effects or results)

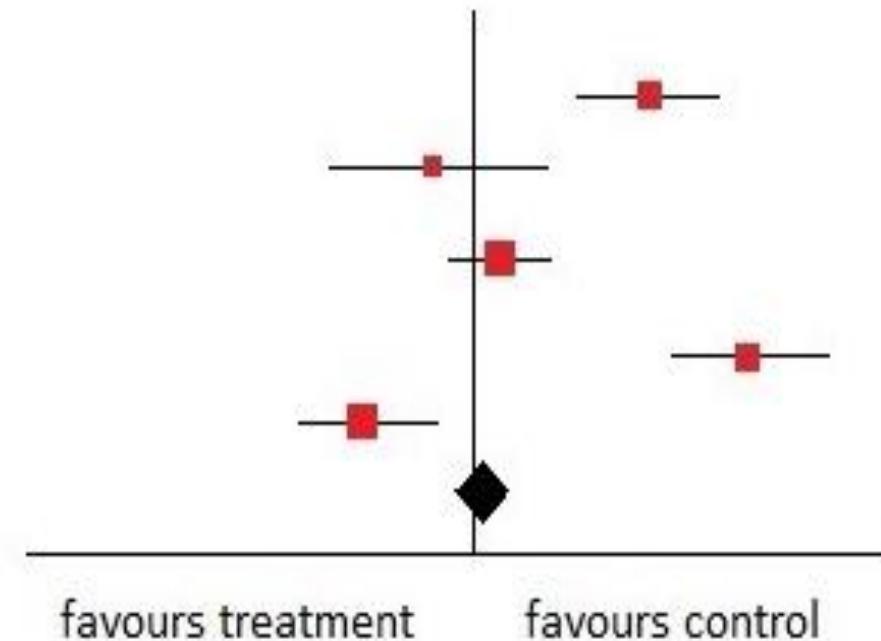


# Identifying statistical heterogeneity – The «eyeball» test

1



2





# Quantifying heterogeneity – the $I^2$ test

A rough guide to interpretation:

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

<https://training.cochrane.org/handbook/current/chapter-10#section-10-11>



# Cochrane Handbook for Systematic Reviews of Interventions



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## Cochrane Handbook for Systematic Reviews of Interventions

- ◆ Overview
- ◆ Part 1: About Cochrane Reviews
- ◆ Part 2: Core methods
- ◆ Part 3: Specific perspectives in reviews
- ◆ Part 4: Other topics

### Part 1: About Cochrane Reviews

- I. [Introduction](#)
- II. [Planning a Cochrane Review](#)
- III. [Reporting the review](#)
- IV. [Updating the review](#)
- V. [Overviews of Reviews](#)

### Part 2: Core methods

1. [Starting a review](#)
2. [Determining the scope and questions](#)
3. [Inclusion criteria & grouping for synthesis](#)

### Part 3: Specific perspectives in reviews

16. [Equity](#)
17. [Intervention complexity](#)
18. [Patient-reported outcomes](#)
19. [Adverse effects](#)
20. [Economic evidence](#)
21. [Qualitative evidence](#)

### Part 4: Other topics

22. [Prospective approaches](#)
23. [Variants on randomized trials](#)

<https://training.cochrane.org/handbook/current>



# Reporting of systematic reviews (PRISMA 2020)

OPEN ACCESS

Check for updates

## The PRISMA 2020 statement: an updated guideline for reporting systematic reviews

Matthew J Page,<sup>1</sup> Joanne E McKenzie,<sup>1</sup> Patrick M Bossuyt,<sup>2</sup> Isabelle Boutron,<sup>3</sup> Tammy C Hoffmann,<sup>4</sup> Cynthia D Mulrow,<sup>5</sup> Larissa Shamseer,<sup>6</sup> Jennifer M Tetzlaff,<sup>7</sup> Elie A Akl,<sup>8</sup> Sue E Brennan,<sup>1</sup> Roger Chou,<sup>9</sup> Julie Glanville,<sup>10</sup> Jeremy M Grimshaw,<sup>11</sup> Asbjørn Hróbjartsson,<sup>12</sup> Manoj M Lalu,<sup>13</sup> Tianjing Li,<sup>14</sup> Elizabeth W Loder,<sup>15</sup> Evan Mayo-Wilson,<sup>16</sup> Steve McDonald,<sup>1</sup> Luke A McGuinness,<sup>17</sup> Lesley A Stewart,<sup>18</sup> James Thomas,<sup>19</sup> Andrea C Tricco,<sup>20</sup> Vivian A Welch,<sup>21</sup> Penny Whiting,<sup>17</sup> David Moher<sup>22</sup>

For numbered affiliations see end of the article.

Correspondence to: MJ Page  
matthew.page@monash.edu  
(ORCID 0000-0002-4242-7526)

Additional material is published online only. To view please visit the journal online.

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<http://dx.doi.org/10.1136/bmj.n71>

Accepted: 4 January 2021

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement, published in 2009, was designed to help systematic reviewers transparently report why the review was done, what the authors did, and what they found. Over the past decade, advances in systematic review methodology and terminology have necessitated an update to the guideline. The PRISMA 2020 statement replaces the 2009 statement and includes new reporting guidance that reflects advances in methods to identify, select, appraise, and synthesise studies. The structure and presentation of the items have been modified to facilitate implementation. In this article, we present the PRISMA 2020 27-item checklist, an expanded checklist that details reporting recommendations for each item, the PRISMA 2020 abstract checklist, and

the revised flow diagrams for original and updated reviews.

Systematic reviews serve many critical roles. They can provide syntheses of the state of knowledge in a field, from which future research priorities can be identified; they can address questions that otherwise could not be answered by individual studies; they can identify problems in primary research that should be rectified in future studies; and they can generate or evaluate theories about how or why phenomena occur. Systematic reviews therefore generate various types of knowledge for different users of reviews (such as patients, healthcare providers, researchers, and policy makers).<sup>1,2</sup> To ensure a systematic review is valuable to users, authors should prepare a transparent, complete, and accurate account of why the review was done, what they did (such as how studies were identified and selected) and what they found (such as characteristics of contributing studies and results of meta-analyses). Up-to-date reporting guidance facilitates authors achieving this.<sup>3</sup>

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement published in 2009 (hereafter referred to as PRISMA 2009)<sup>4–10</sup> is a reporting guideline designed to address poor reporting of systematic reviews.<sup>11</sup> The PRISMA 2009 statement comprised a checklist of 27 items recommended for reporting in systematic reviews and an “explanation and elaboration” paper<sup>12–16</sup> providing additional reporting guidance for each item, along with exemplars of reporting. The recommendations have been widely endorsed and adopted, as evidenced by

- “We identified possible modifications to the PRISMA 2009 statement by reviewing 60 documents providing reporting guidance for systematic reviews”
- “Systematic review methodologists and journal editors were invited to complete the online survey”
- “...we circulated an initial draft and five revisions of the checklist and explanation and elaboration paper to co-authors for feedback.”

**BMJ 2021; 372 doi: <https://doi.org/10.1136/bmj.n71>**

## SUMMARY POINTS

# Systematic reviews of observational studies

## RESEARCH

OPEN ACCESS

Check for updates

### Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis

Elpida Vounzoulaki,<sup>1,2</sup> Kamlesh Khunti,<sup>1,2</sup> Sophia C Abner,<sup>1,2</sup> Bee K Tan,<sup>3</sup> Melanie J Davies,<sup>1</sup> Clare L Gillies<sup>1,2</sup>

#### ABSTRACT

#### OBJECTIVE

To estimate and compare progression rates to type 2 diabetes mellitus (T2DM) in women with gestational diabetes mellitus (GDM) and healthy controls.

#### DESIGN

Systematic review and meta-analysis.

#### DATA SOURCES

Medline and Embase between January 2000 and December 2019, studies published in English and conducted on humans.

#### ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Observational studies investigating progression to T2DM. Inclusion criteria were postpartum follow-up for at least 12 months, incident physician based diagnosis of diabetes, T2DM reported as a separate outcome rather than combined with impaired fasting glucose or impaired glucose tolerance, and studies with both a group of patients with GDM and a control group.

#### RESULTS

This meta-analysis of 20 studies assessed a total of 1 332 373 individuals (67 956 women with GDM and 1 264 417 controls). Data were pooled by random effects meta-analysis models, and heterogeneity was assessed by use of the  $I^2$  statistic. The pooled relative

for T2DM was almost 10 times higher in women with previous GDM than in healthy controls (9.51, 95% confidence interval 7.14 to 12.67,  $P<0.001$ ). In populations of women with previous GDM, the cumulative incidence of T2DM was 16.46% (95% confidence interval 16.16% to 16.77%) in women of mixed ethnicity, 15.58% (13.30% to 17.86%) in a predominantly non-white population, and 9.91% (9.39% to 10.42%) in a white population. These differences were not statistically significant between subgroups (white v mixed populations,  $P=0.26$ ; white v non-white populations,  $P=0.54$ ). Meta-regression analyses showed that the study effect size was not significantly associated with mean study age, body mass index, publication year, and length of follow-up.

#### CONCLUSIONS

Women with a history of GDM appear to have a nearly 10-fold higher risk of developing T2DM than those with a normoglycaemic pregnancy. The magnitude of this risk highlights the importance of intervening to prevent the onset of T2DM, particularly in the early years after pregnancy.

#### SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42019123079.

#### Introduction

Gestational diabetes mellitus (GDM) is glucose

BMJ: first published as 10.1136/bmj.m1361 on 18 May 2020. Downloaded from http://www

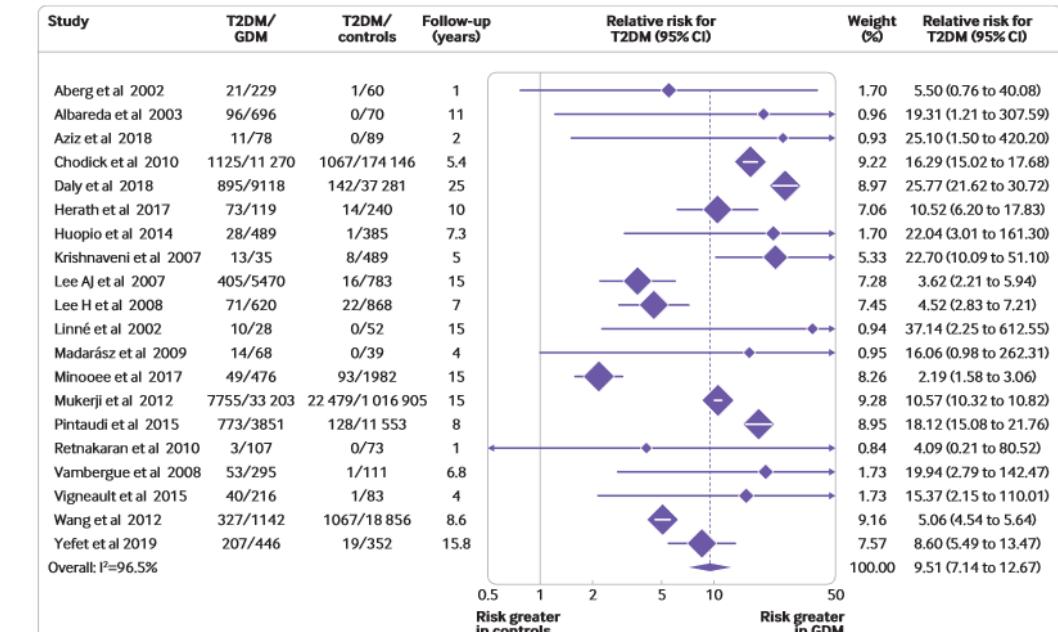
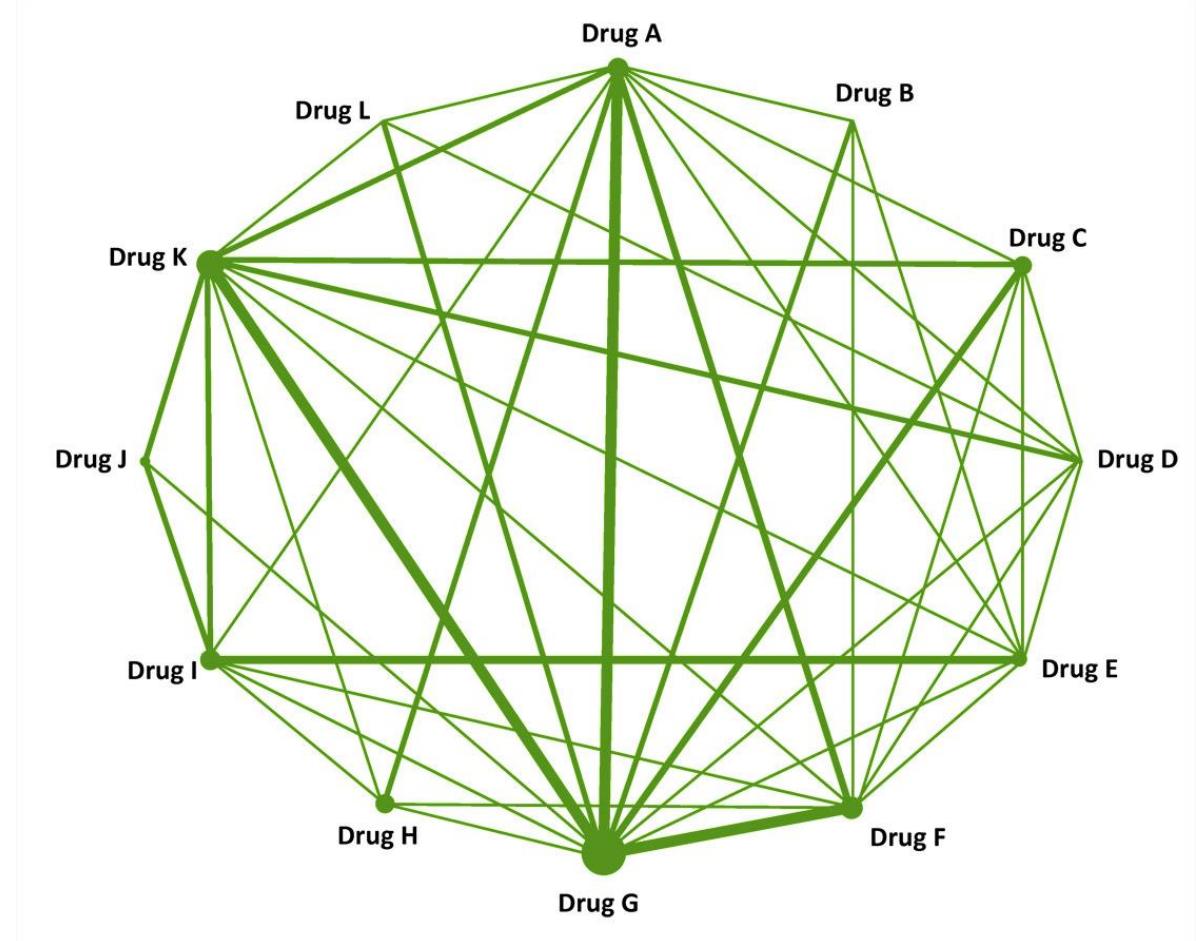
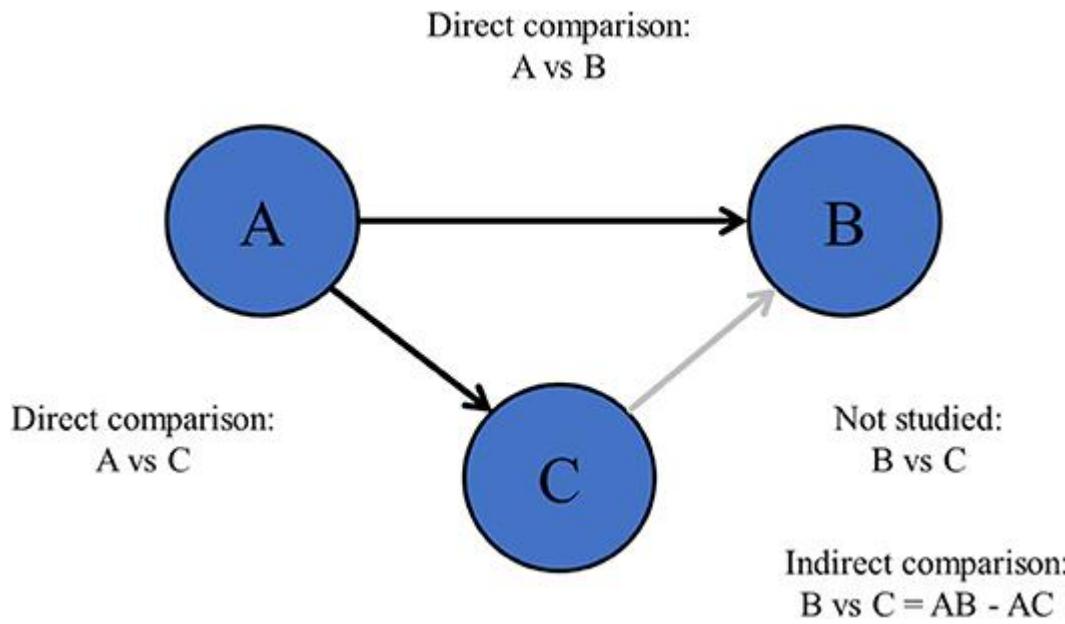


Fig 2 | Relative risk of type 2 diabetes mellitus (T2DM) in women with gestational diabetes mellitus (GDM) compared with healthy controls

BMJ 2020;369:m1361

# Network meta-analyses





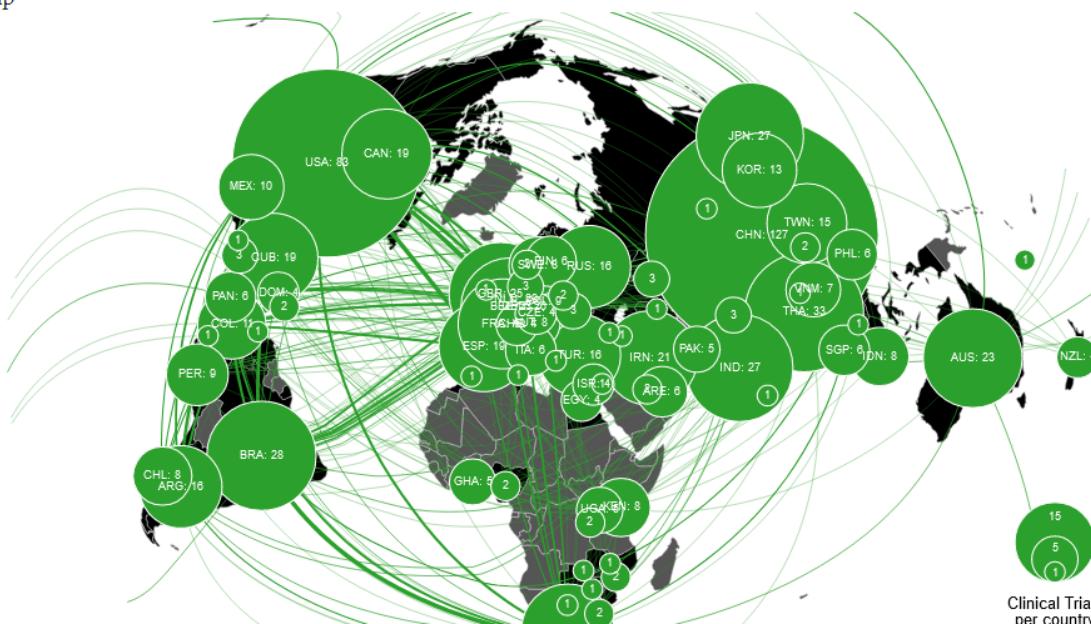
# Living systematic reviews & meta-analyses

As of December 15, 2021 the [Covid-19 - living NMA initiative](#) collected 461 RCTs and 222 non-randomised studies of **vaccines** from the [ICTRP](#). 321 of these trials are recruiting patients.

## ▼ User Guide

- To see how to explore the mapping, check [our tutorial](#).
- Make your browser window as wide as possible for a 2-column display.
- Click on the map or any of the graphs to create filters on the data.
- All the filters are applied jointly, refining your selection.
- Click **Reset all** to remove the filters.
- Click on the arrows to open or close any section.
- For any questions or remarks, please [contact us](#).

## ▼ Map

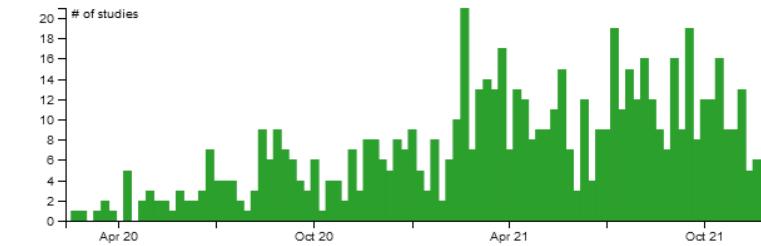


## Filters

All trials selected (683) | Reset all

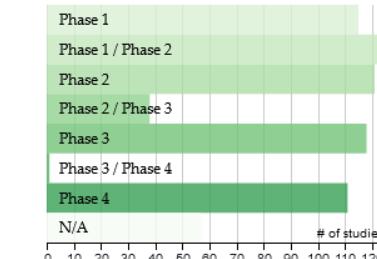
Search...  
Ex: RNA, Adenovirus, Oxford...

### ▼ Registration date by week

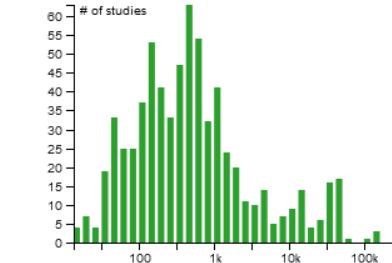


To filter by Registration dates, click and drag to create a range.

### ▼ Phase



### ▼ Sample size



### ▼ Recruitment status

- Recruiting (321 studies) 
- Not recruiting (317 studies) 
- Completed (38 studies) 

### ▼ Publication status

- Not published (598 studies)
- Published (85 studies) 

<https://covid-nma.com/>