Meta-analysis Workshop

TRANSLATIONAL MEDICINE
Meta-Analysis

Coordinator: Zsolt Szakács

27th February, 2019

University of Pécs
Pécs

Schedule for today

1.	Erőss Bálint	**Voting,** The role of meta-analyses in translational medicine
2.	Mikó Alexandra	Questions and hypotheses
3.	Márta Katalin	Meta-analysis guidelines
4.	Solymár Margit	Protocols and reporting bias
5.	Pécsi Dániel	Systematic search **Break**
6.	Balaskó Márta	Selection of records
7.	Hanák Lilla	Data collection - statistical aspects
8.	Erőss Bálint	Data collection - practical aspects
9.	Szakács Zsolt	Bias **Break**
10.	Soós Alexandra	Statistics of meta-analyses
11.	Szakács Zsolt	Grade of evidence
12.	Szakács Zsolt	Limitations and implications
13.	Szakács Zsolt	Future perspectives, **voting**

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Break

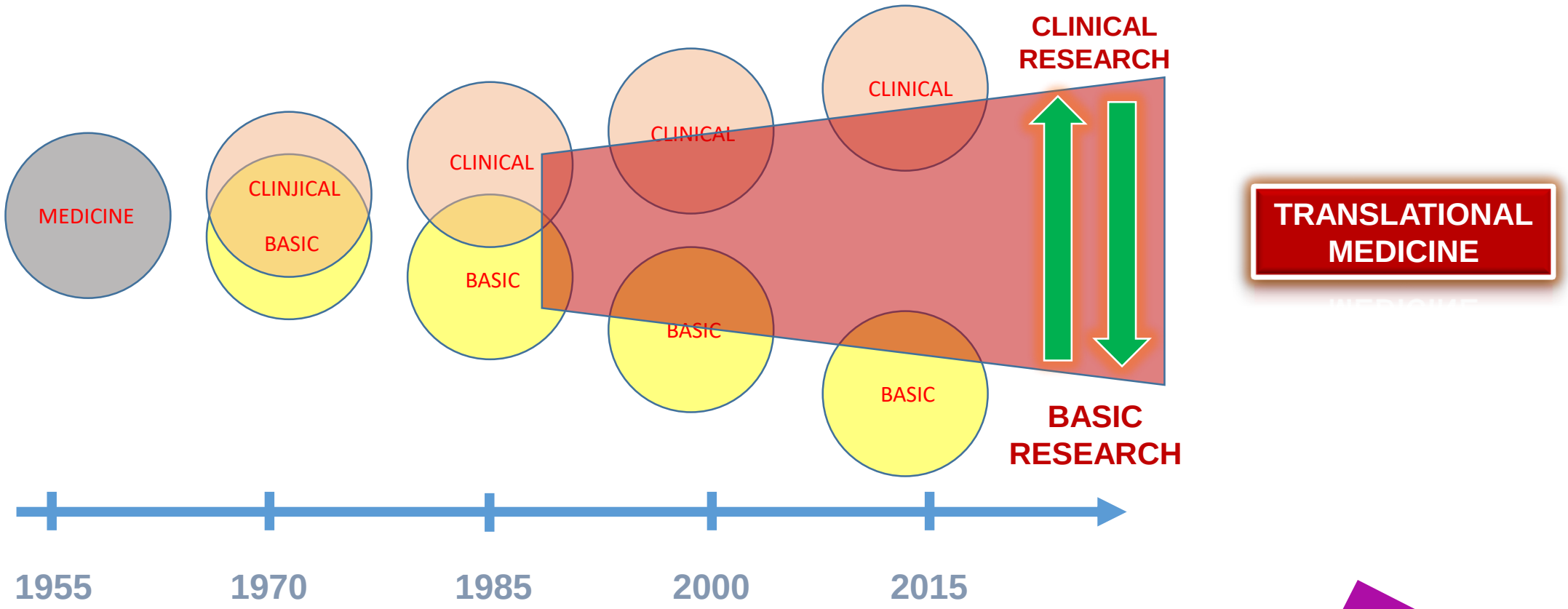
Break

Aims for today

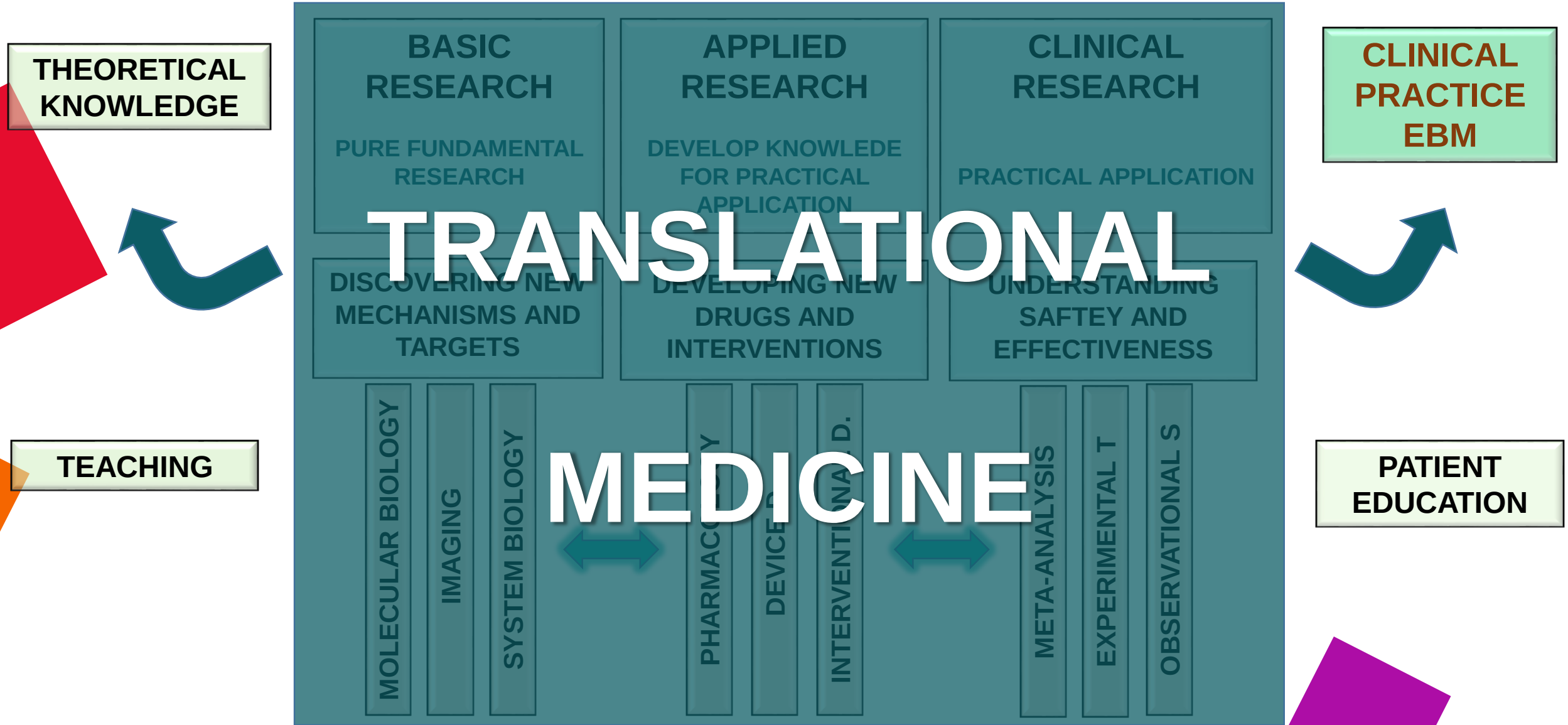
to provide **basic knowledge** of meta-analysis and systematic reviews

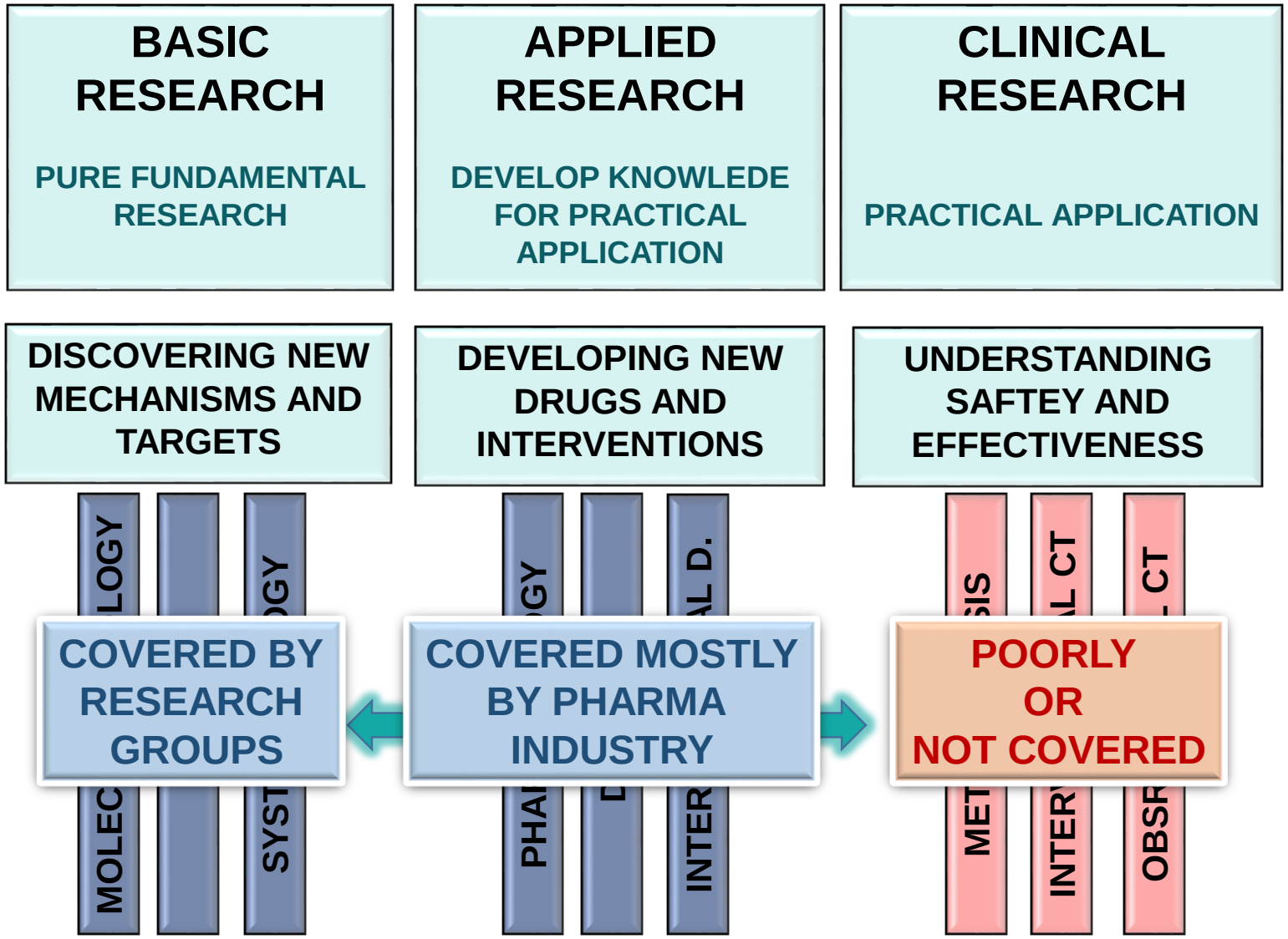
to guide how to **read** and **critically appraise** meta-analysis and systematic reviews

The role of translational medicine



The role of translational medicine




BASIC RESEARCH
PURE FUNDAMENTAL RESEARCH
APPLIED RESEARCH
DEVELOP KNOWLEDE FOR PRACTICAL APPLICATION
CLINICAL RESEARCH
PRACTICAL APPLICATION
DISCOVERING NEW MECHANISMS AND TARGETS
DEVELOPING NEW DRUGS AND INTERVENTIONS
UNDERSTANDING SAFTEY AND EFFECTIVENESS
COVERED BY RESEARCH GROUPS
COVERED MOSTLY BY PHARMA INDUSTRY
POORLY OR NOT COVERED

TRANSLATIONAL MEDICINE

THEORETICAL KNOWLEDGE

BASIC RESEARCH

PURE FUNDAMENTAL RESEARCH

APPLIED RESEARCH

DEVELOP KNOWLEDE FOR PRACTICAL APPLICATION

CLINICAL RESEARCH

PRACTICAL APPLICATION

CLINICAL PRACTICE EBM

DISCOVERING NEW MECHANISMS AND TARGETS

DEVELOPING NEW DRUGS AND INTERVENTIONS

UNDERSTANDING SAFTEY AND EFFECTIVENESS

TEACHING

MOLECULAR BIOLOGY

IMAGING

SYSTEM BIOLOGY

PHARMACOLOGY

DEVICE D.

INTERVENTIONAL D.

META-ANALYSIS

INTERVENTIONAL CT

OBSERVATIONAL CT

PATIENT EDUCATION

Meta-analysis, definition

„Systematic reviews are a type of literature review that uses systematic methods to collect secondary data, critically appraise research studies, and synthesize findings qualitatively or quantitatively.„

- Armstrong R et al "Cochrane Update. 'Scoping the scope' of a cochrane review". Journal of Public Health. 2011;33 (1): 147–50.

Meta analysis: „The statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings.”

- Glass GV. Primary, secondary and meta-analysis of research. Educational Researcher. 1976;5:3–8.

Meta-analysis, definition

Systematic review

1. Specific question
2. Comprehensive search and selection
3. **Narrative summary** of evidence
4. Answer to the question (if there is any)

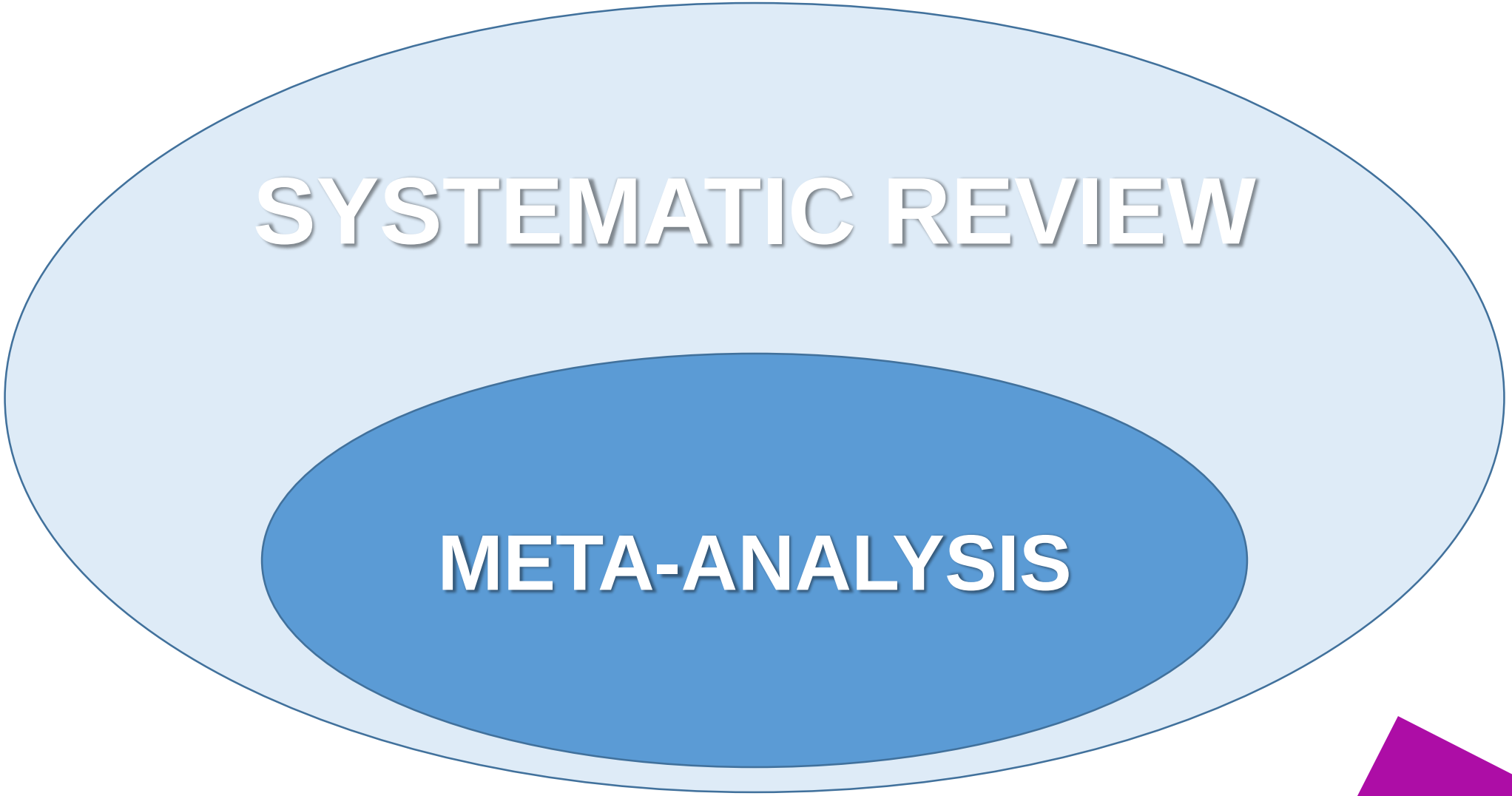
Qualitative synthesis

Meta-analysis

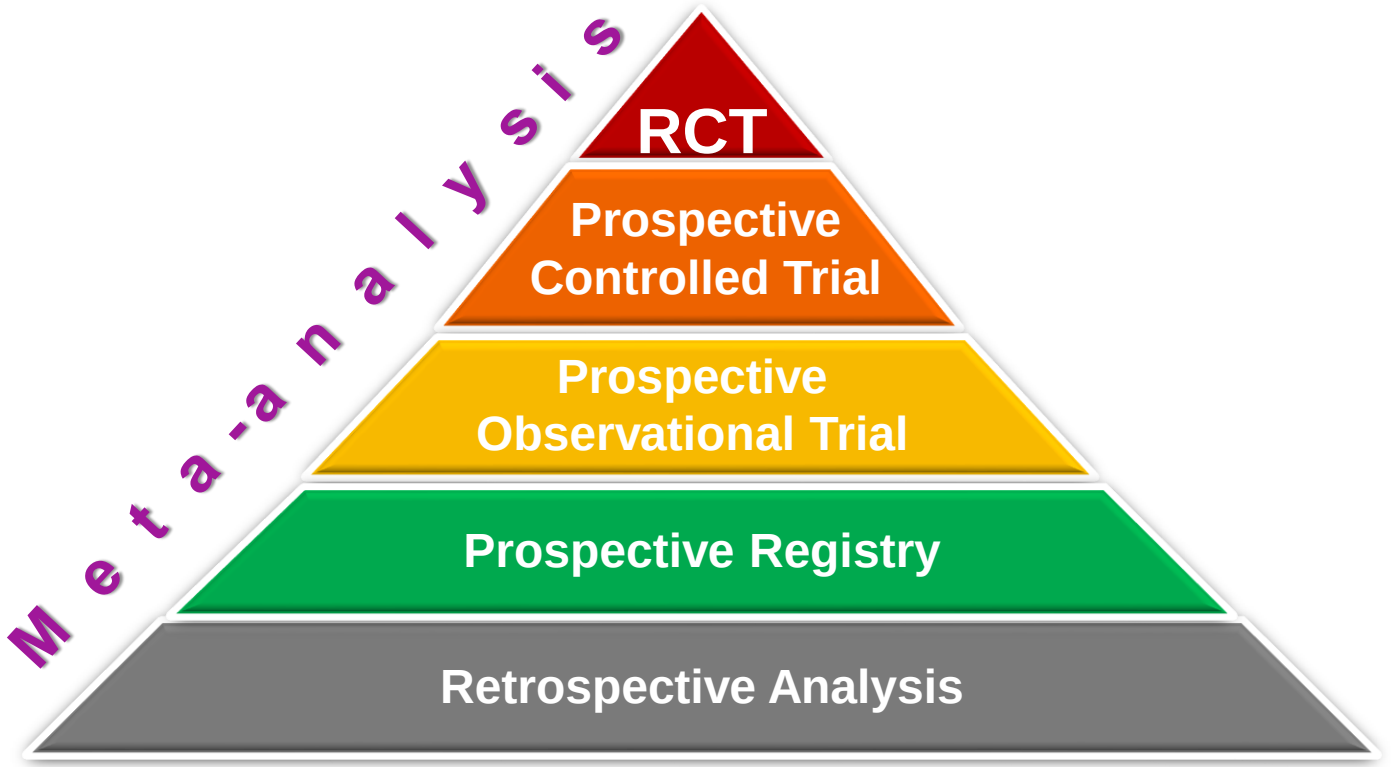
1. Specific question
2. Comprehensive search and selection
3. **Statistical summary** of evidence
4. Answer to the question (if there is any)

Quantitative synthesis

Meta-analysis, definition



What is the evidence level of meta-analysis?



RECOMMENDATION

ESGE recommends endoscopic drainage over percutaneous or surgical treatment for uncomplicated CP-related pseudocysts that are within endoscopic reach.
Strong recommendation, moderate quality evidence.

A meta-analysis of 7 retrospective studies (490 patients with various types of pancreatic fluid collections [PFCs]) found that, compared with percutaneous drainage, endoscopic drainage was associated with a higher clinical success rate, fewer re-interventions, shorter hospital stay, and similar morbidity and recurrence rates [118]. Although percutaneous drainage has mostly been abandoned for the definitive treatment of CP-related pseudo[illegible]s in an external fistula [119], it [illegible]y measure (e.g., for infected PPC[illegible]drainage in a frail patient).

10/165

A meta-analysis (5 comparative studies including one RCT, 255 patients) found that, compared with endoscopic therapy, surgery has a higher success rate (odds ratio [OR] 0.43, 95%CI 0.20–0.95), but is associated with a longer length of hospital stay and higher hospital costs as well as similar rates of morbidity (18.0% vs. 11.5%) and recurrence (3.2% vs. 3.1%) [120]. A more recent multicenter prospective cohort study (71 patients) reported a similar overall success rate and a shorter hospital stay for endoscopic therapy vs. surgery [121].

Guideline

Thieme

Endosc
Europe
Update
ideline –

ESGE

Authors
Jean-Marc Du
Thierry Vayss
Enrique Dom
Jeanin E. van
z-Yague[5],
ière[2], Juan
shwar Reddy[13],

Recommendations to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms

Recommendations	Class [a]	Level [b]	Ref [c]
Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life.	I	A	126, 129, 150, 151
Treatment with statins is recommended in patients with or at high-risk of CAD whether or not they have LV systolic dysfunction, in order to prevent or delay the onset of HF and pr	I	A	137–140, 152
Counselling and treatment for smoking cessation and alcohol inta or people who smoke or who consume excess alcohol in order to prevent or delay the onset of HF.	I	C	131–134
Treating other risk factors of HF (e.g. obesity, dysglycaemia) should be considered in order to prevent or delay the onset of HF.	IIa	C	130, 141, 153–155
Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.	IIa	B	130
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life.	I	A	5, 144, 145

74/659

PubMed

142 000 items

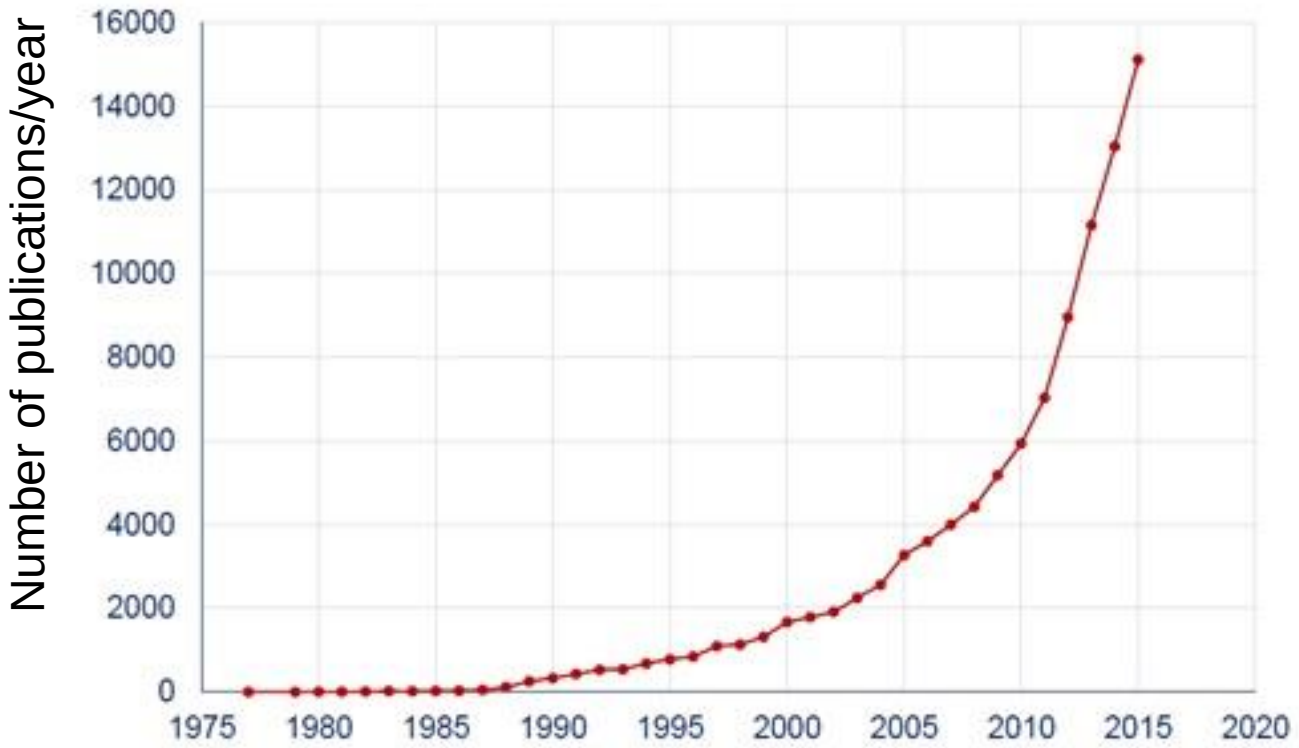
4 months

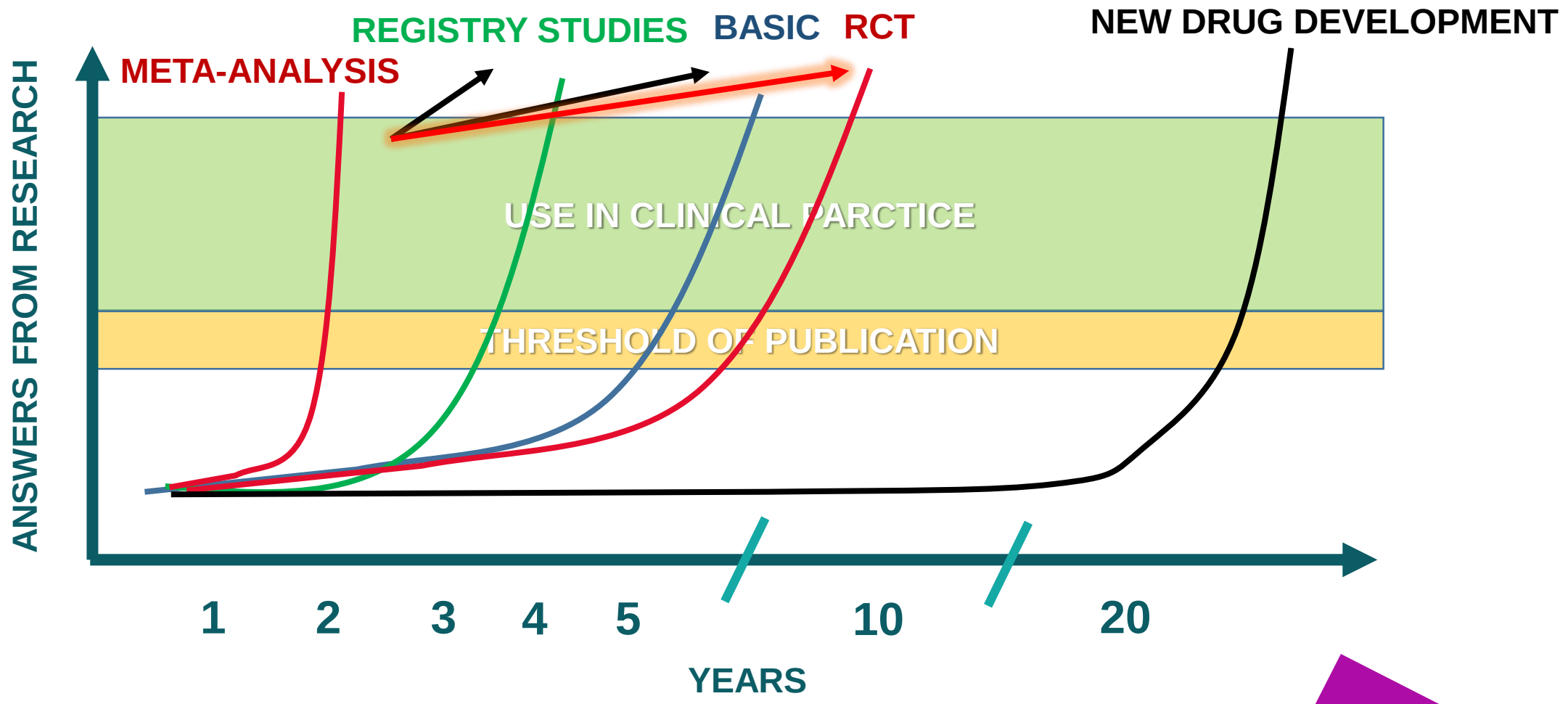
PubMed

150 000 items

(October, 2018)

Meta-analysis burst




REGISTRY STUDIES
BASIC
RCT
NEW DRUG DEVELOPMENT
META-ANALYSIS
USE IN CLINICAL PARCTICE
THRESHOLD OF PUBLICATION
ANSWERS FROM RESEARCH
1
2
3
4
5
10
20
YEARS

- NO RESTRICTIONS (BASIC OR CLINICAL)
- EASY TO LEARN
- HELPS TO IDENTIFY THE GAPS IN OUR KNOWLEDGE
- EXCELLENT LEARNING METHOD
  OF THE RIGOROUS REPORTING PRACTICE
- QUICK ANSWER

- NO RESTRICTIONS (BASIC OR CLINICAL)
- **EASY TO LEARN**
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- EXCELLENT LEARNING METHOD
  OF THE RIGOROUS REPORTING PRACTICE
- QUICK ANSWER

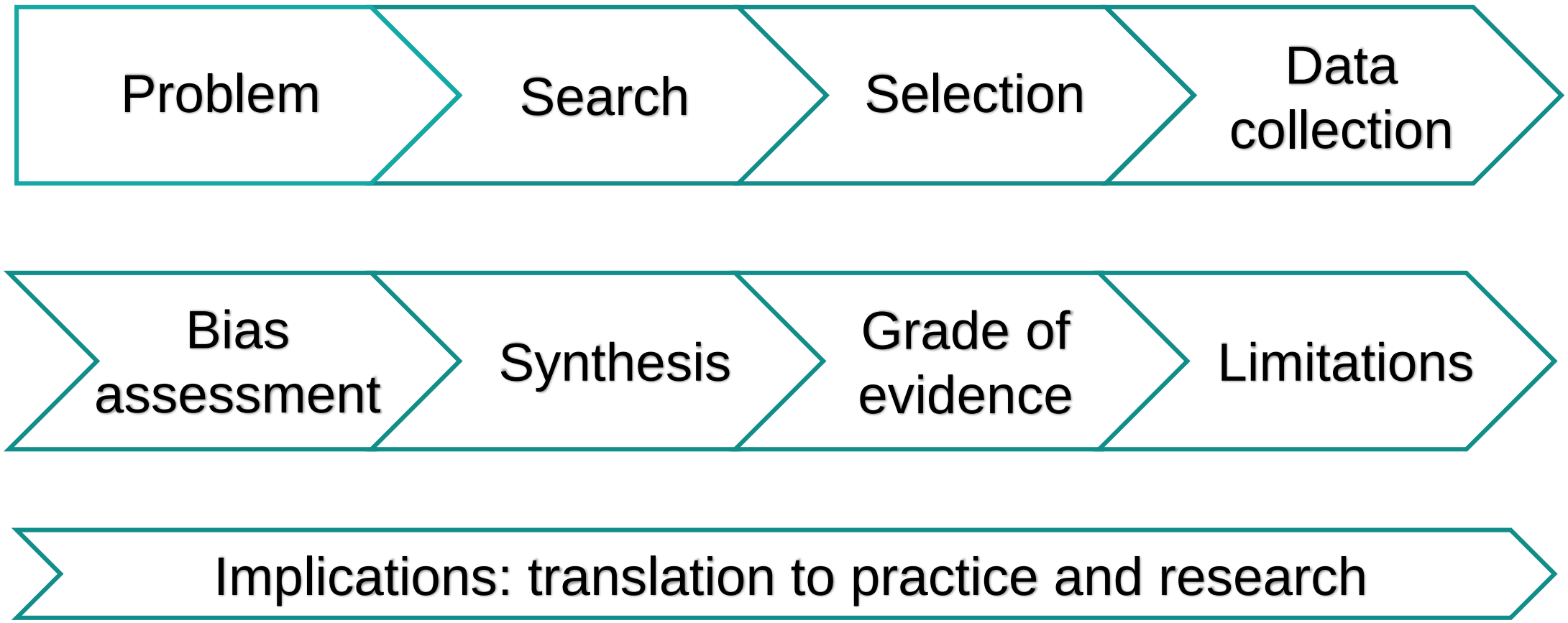
Our meta-analytical work:

since January 2016

93 ⟹ **36**

IF: 115 and 150 citations

Flowchart


Problem
Search
Selection
Data collection
Bias assessment
Synthesis
Grade of evidence
Limitations
Implications: translation to practice and research

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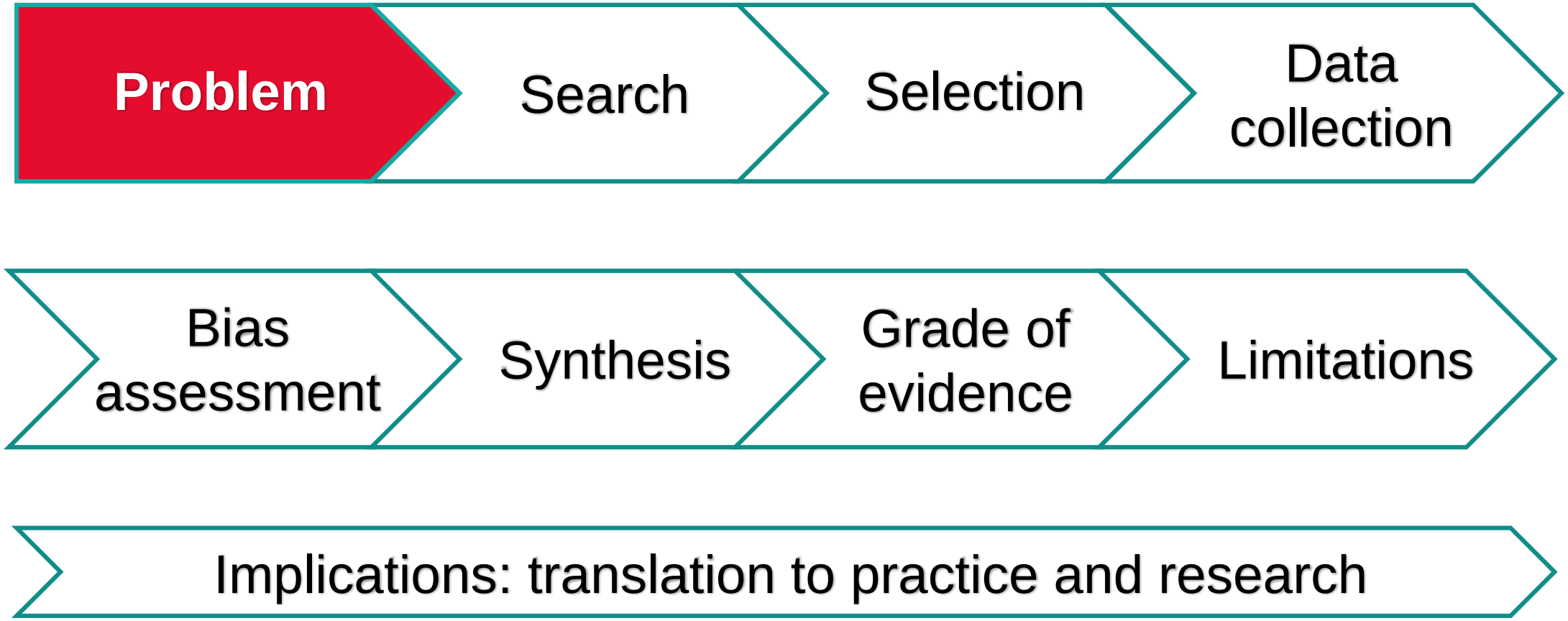
Flowchart


Problem
Search
Selection
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Scientific questions

Aim: to construct a well-designed, relevant scientific question

Benefit: a question appropriate for systematic review and meta-analysis

Good scientific questions

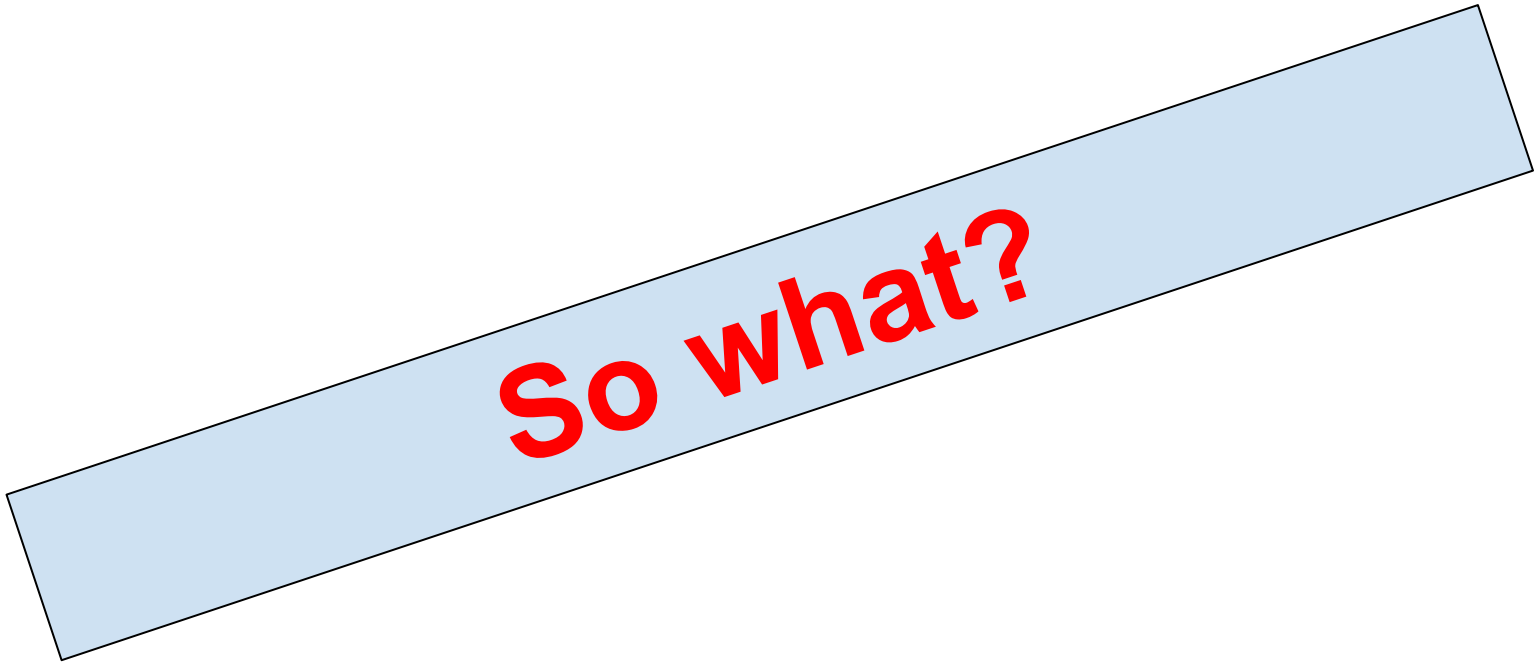
What is a good scientific question?

„Those questions that are **clearly related to a clinical decision** about whether to use a therapeutic, preventive, or diagnostic intervention are the ones that warrant the most time.” JAMA, 1993

Implication for practice

Implication for research

Good scientific questions



Inspirations for questions

Scientific community calls for it

Your practice calls for it

Your research calls for it

Gaps in guidelines call for it

An update…

PICO framework

designed to make the process of defining **interventional questions**

Population/Problem

Intervention

Comparison

Outcome

+ Study design

+ Methodology

PICO framework

Population/Problem

Consider the following characteristics:
-disease/condition, including localization, duration, type of symptoms
-age
-gender
-standard diagnostic criteria

**18-80 ys old female with mild (by revised Atlanta classification)
biliary acute pancreatitis (by IAP/APA guideline)
without cholangitis (by Tokyo guideline)**

PICO framework

Intervention

Comparator

The following should be described:
-type of intervention
-intensity of intervention
-frequency of intervention
-duration of intervention

Intravenous ceftriaxon therapy 100 mg/ kg/dosi, 4x daily, for 7 days

PICO framework

Outcome

-**primary/secondary**

-explicit outcome measures and tools

-standardized, validated, established outcome measures appropriate for disease condition

-focus on outcomes that are **important** (have relevance)

-hard vs. soft outcomes

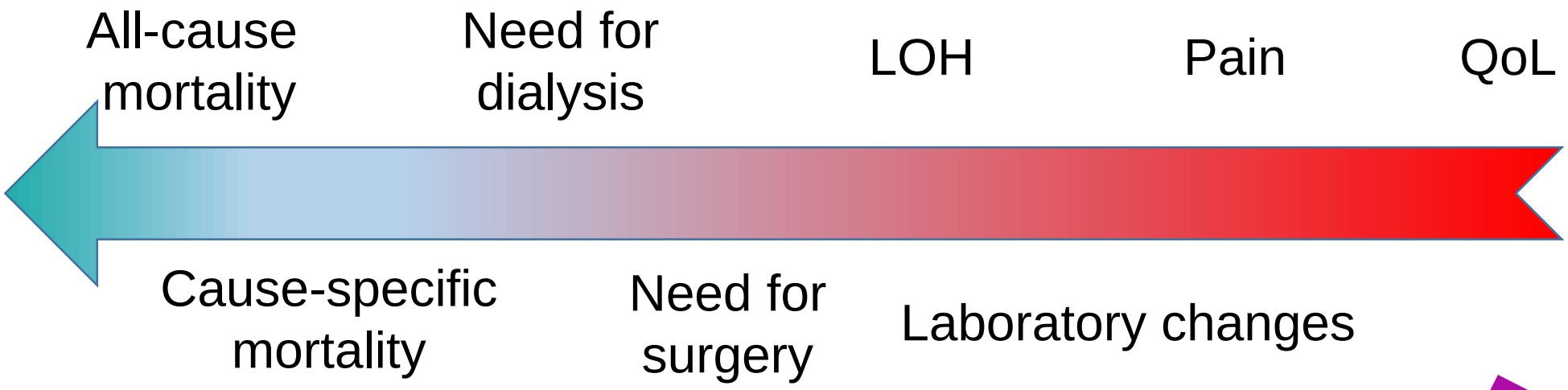
-**efficacy and safety**

PICO framework

Hard vs. **Soft**

- Objective
- Certain

- Might be subjective
- Less certain



PICO framework

Study design

	Type of question	Study design
60-70%	**Interventional**	**Experimental or observational studies**
3-5%	**Diagnostic**	**Observational studies (diagnostic accuracy studies)**
5-10%	**Prognostic/predictive**	**Observational studies (prognostic studies)**
20-30%	**Epidemiological**	**Descriptive studies**

Example for an interventional question

Patient, Problem

Acute appendicitis

Intervention

Antibiotics

Comparator

Appendectomy

Outcome

Morbidity/mortality

Should we chose antibiotics or appendectomy in acute appendicitis?

Huston JM., et al., Surg Infect (Larchmt) . 2017 Jul;18(5):527-535.
Kessler U., et al., Arch Dis Child. 2017 Dec;102(12):1118-1124

Hypothesis in a lay point of view…

What answer do you expect to your question?

Main features:

1. **refers to the question**
2. **testable**

Accept or reject

Colleagues who attend „Meta-analysis workshop” have higher chance to perform meta-analysis than those who skip this.

Scientific questions

COMMON MISTAKE

1. **The question is not relevant (SO WHAT???)**
2. **The question is poorly structured**
3. **No hypothesis formation when planning the study**

Scientific questions

TAKE HOME MESSAGE

1. PICO: patients/intervention/comparator/outcome
2. Pay attention to hypothesis generation

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Publication types

Adaptive Clinical Trial
Address
Autobiography

Case Reports
Classical Article
Clinical Conference
Clinical Study
Clinical Trial
Clinical Trial, Phase I
Clinical Trial, Phase II
Clinical Trial, Phase III
Clinical Trial, Phase IV
Clinical Trial Protocol
Clinical Trial, Veterinary
Collected Works
Comparative Study
Congress
Consensus Development Conference
Controlled Clinical Trial

Observational Study
Observational Study, Veterinary

Lecture
Legal Case
Legislation
Letter

Meta-Analysis
Multicenter Study
News
Newspaper Article

Validation Studies
Video-Audio Media
Webcasts

Scientific Integrity Review
Study Characteristics
Support of Research
Systematic Review

Technical Report
Twin Study

Dataset
Dictionary
Directory

Historical Article
Interactive Tutorial
Interview
Introductory Journal Article

Patient Education Handout
Periodical Index
Personal Narrative
Portrait
Practice Guideline
Pragmatic Clinical Trial
Publication Components

Bibliography
Biography

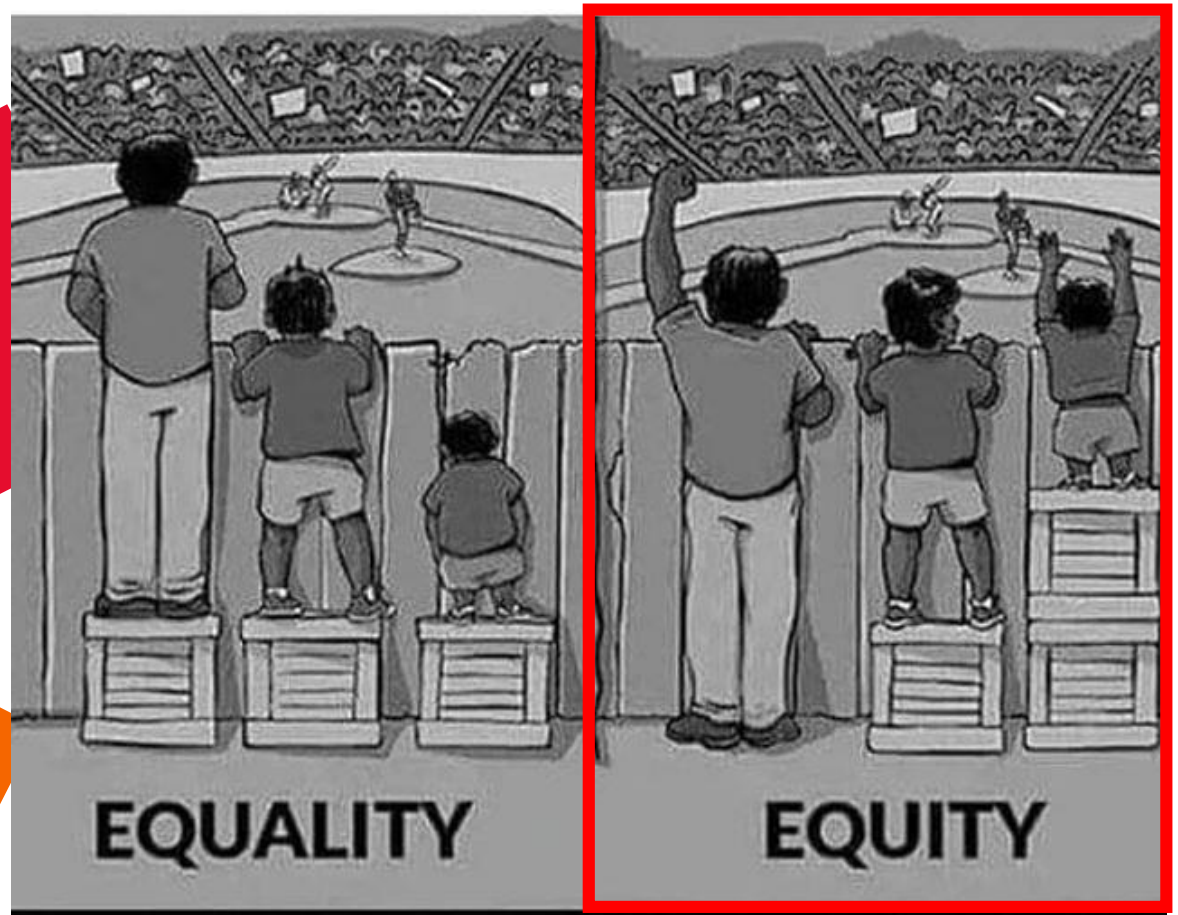
Editorial
English Abstract
Equivalence Trial
Evaluation Studies
Expression of Concern

Randomized Controlled Trial
Research Support, American Recovery and Reinvestment Act
Research Support, N.I.H., Extramural
Research Support, N.I.H., Intramural
Research Support, Non-U.S. Gov't Research Support, U.S. Gov't,
Research Support, U.S. Gov't, P.H.S.
Review

Government Document
Guideline

NIH U.S. National Library of Medicine

Guideline



1. Equality: is giving people the same thing/s.
2. Equity: is fairness in very situation.

Publication types

Adaptive Clinical Trial
Address
Autobiography
Observational Study
Observational Study, Veterinary
Scientific Integrity Review
Study Characteristics
Support of Research
Systematic Review
Historical Article
Interactive Tutorial
Interview
Introductory Journal Article
Case Reports
Classical Article
Clinical Conference
Clinical Study
Clinical Trial
Clinical Trial, Phase I
Clinical Trial, Phase II
Clinical Trial, Phase III
Clinical Trial, Phase IV
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Randomized Controlled Trial
Research Support, American Recovery and Reinvestment Act
Research Support, N.I.H., Extramural
Research Support, N.I.H., Intramural
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Government Document
Guideline

NIH U.S. National Library of Medicine

Guideline

equator network

Enhancing the QUAlity and Transparency Of health Research

Reporting guidelines for main study types

Randomised trials	CONSORT	Extensions
Observational studies	STROBE	Extensions
Systematic reviews	PRISMA	Extensions
Study protocols	SPIRIT	PRISMA-P
Diagnostic/prognostic studies	STARD	TRIPOD
Case reports	CARE	Extensions
Clinical practice guidelines	AGREE	RIGHT
Qualitative research	SRQR	COREQ
Animal pre-clinical studies	ARRIVE	
Quality improvement studies	SQUIRE	
Economic evaluations	CHEERS	

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

Guideline

equator network

Enhancing the QUAlity and Transparency Of health Research

Reporting guidelines for main study types

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Economic evaluations	CHEERS	

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

Formal protocols

REPRODUCIBILITY

MOOSE

(Meta-analysis Of Observational Studies in Epidemiology)

PMID: 10789670 JAMA 2000 Citations: 11608

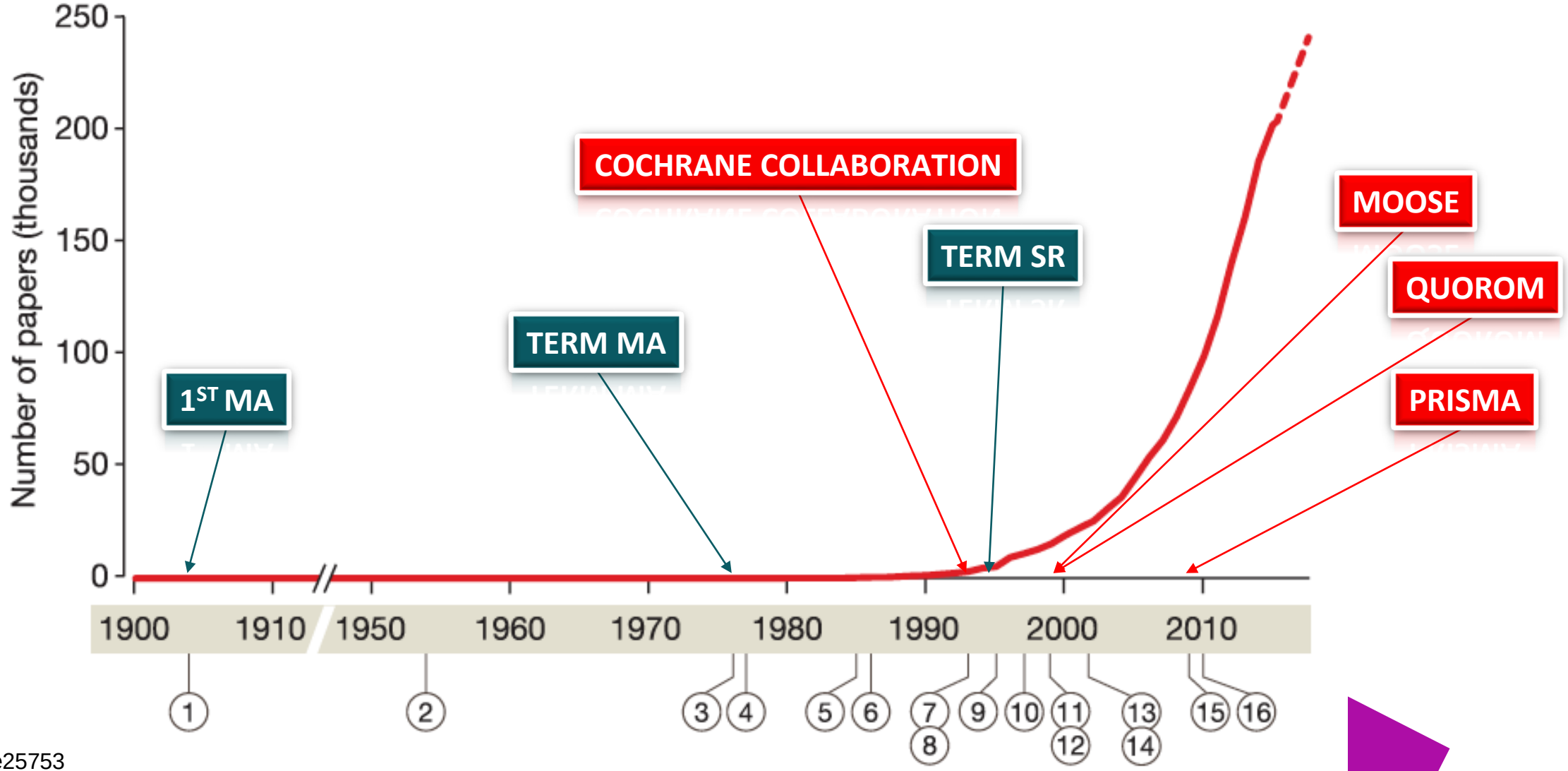
QUORUM

(Quality of Reporting of Meta-analyses)

PMID: 10703836 Lancet 2000 Citations: 105

PRISMA

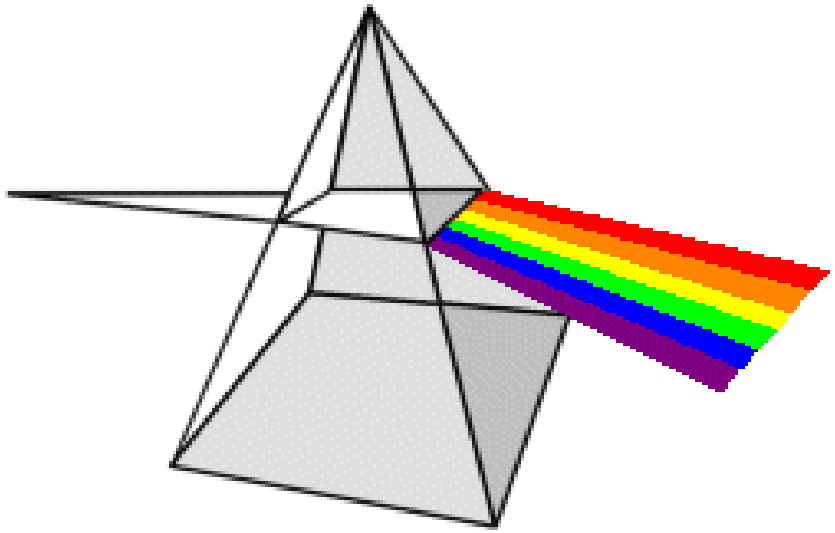
Quality



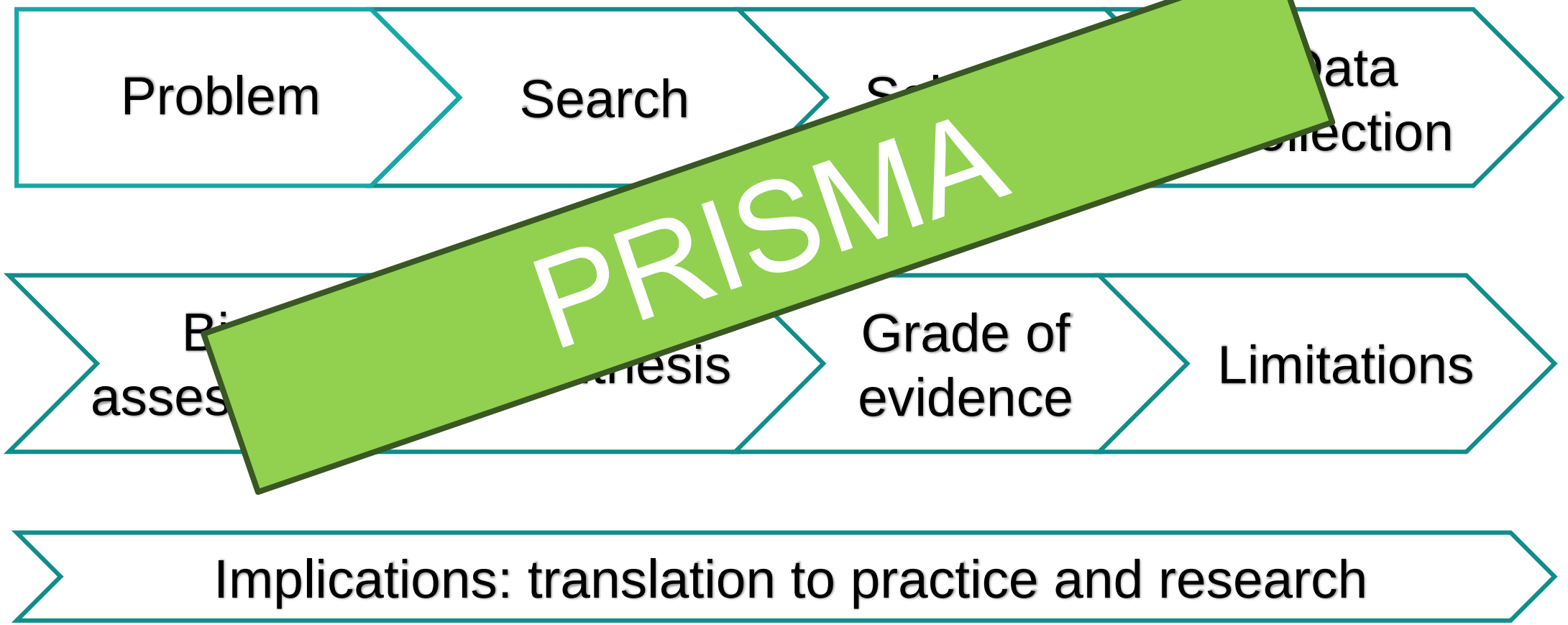
doi:10.1038/nature25753

PRISMA

Preferred
Reporting
I tems for
Systematic reviews
Meta -
Analysis



Flowchart


Problem
Search
PRISMA
Grade of evidence
Limitations
Implications: translation to practice and research

Aim: to provide a guide with the minimum set of items for planning

Benefit: a proper review protocol

PRISMA

Statement

PMID 20171303

Citations: 39441

Explanation and Elaboration (E&E)

PMID 19631507

Citations: 16434

Checklist

Extensions…

Flow diagram

PRISMA Checklist

TRANSLATIONAL MEDICINE

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

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.	

		Reported on page #
sment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective udies).		
of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating ecified.		
tudies screened, assessed for eligibility, and included in the review, with reasons for exclusions at with a flow diagram.		
esent characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and ns.		
sk of bias of each study and, if available, any outcome level assessment (see item 12).		
onsidered (benefits or harms), present, for each study: (a) simple summary data for each (b) effect estimates and confidence intervals, ideally with a forest plot.		
each meta-analysis done, including confidence intervals and measures of consistency.		
any assessment of risk of bias across studies (see Item 15).		
litional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).		
ain findings including the strength of evidence for each main outcome; consider their relevance to ealthcare providers, users, and policy makers).		
at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of , reporting bias).		
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.

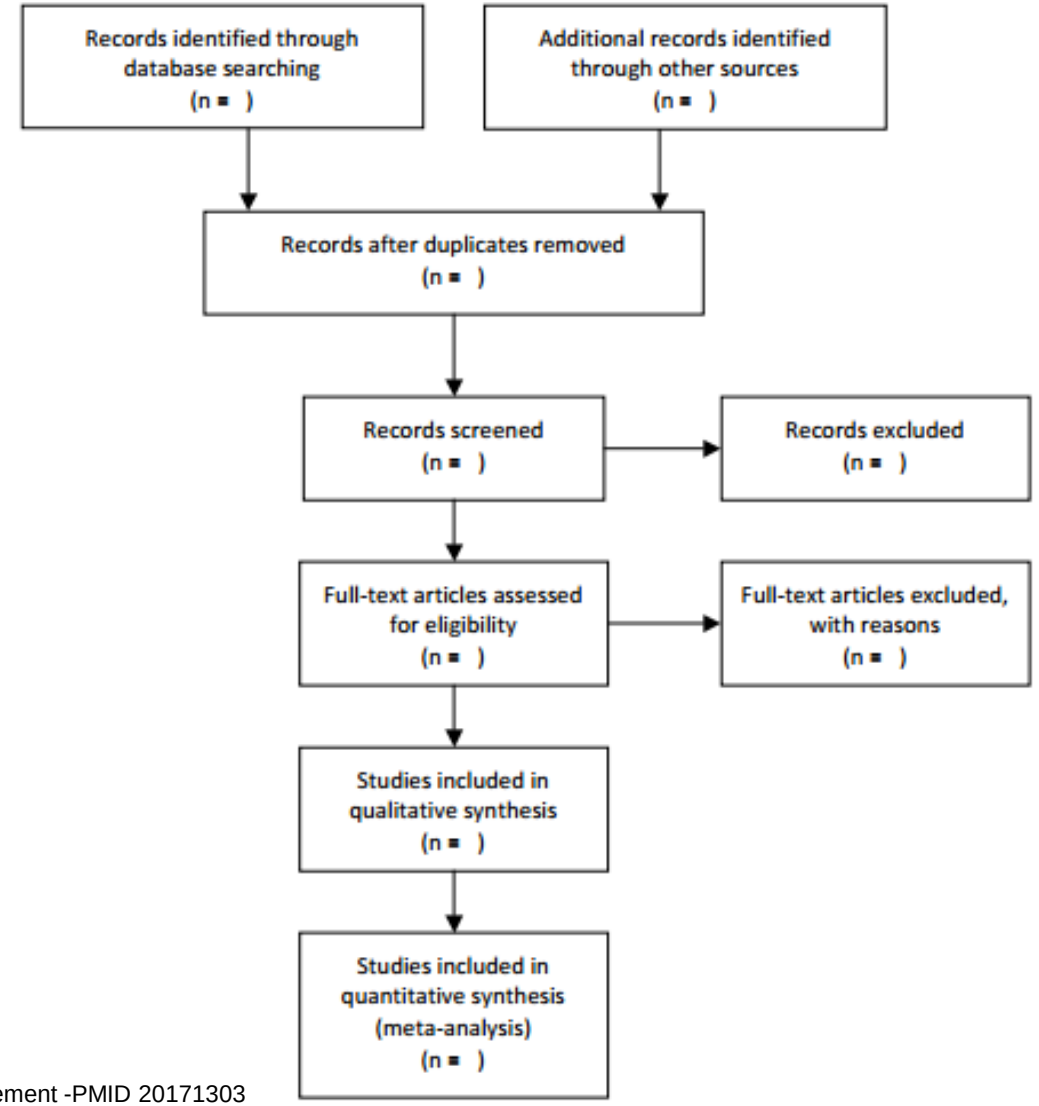
TRANSPARENT

Moher D et al. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and meta-analyses: The PRISMA statement PMID 20171303

PRISMA Flowchart

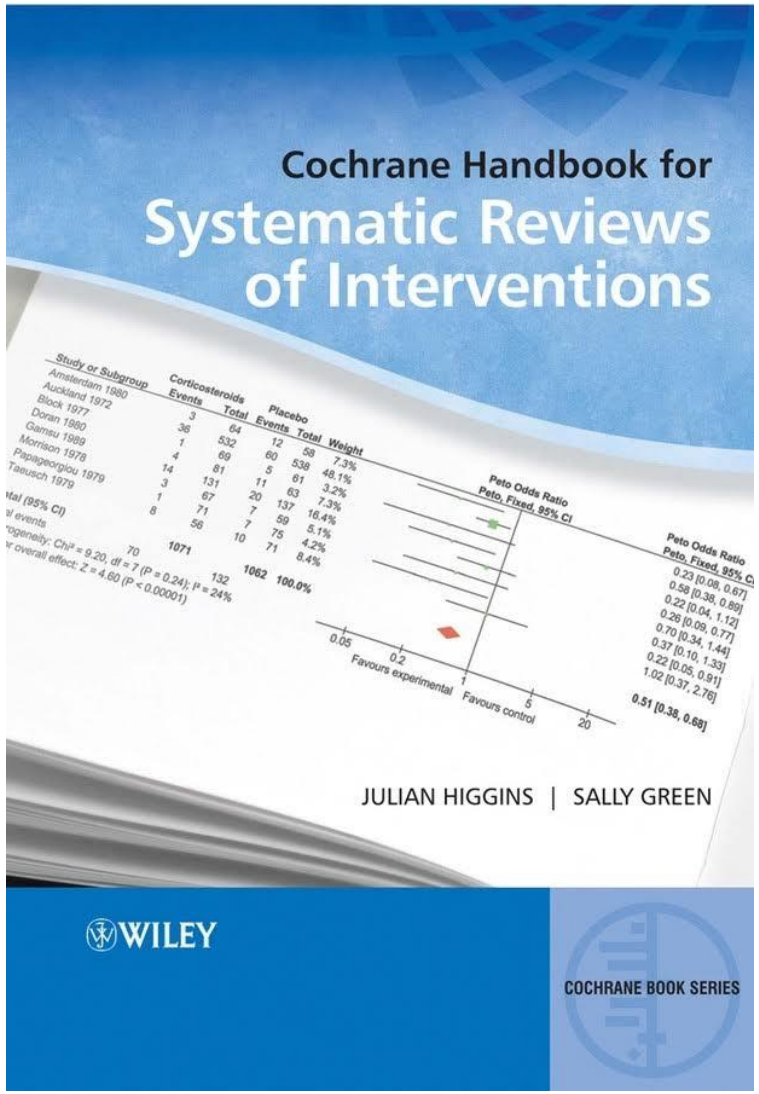
http://www.prisma-statement.org/

"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." (Checklist 17.)



Moher D et al. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and meta-analyses: The PRISMA statement -PMID 20171303

PRISMA Flowchart



https://training.cochrane.org/handbook

5th Edition
(6th is coming…)

Schedule for today

1.	Erőss Bálint	**Voting,** The role of meta-analyses in translational medicine
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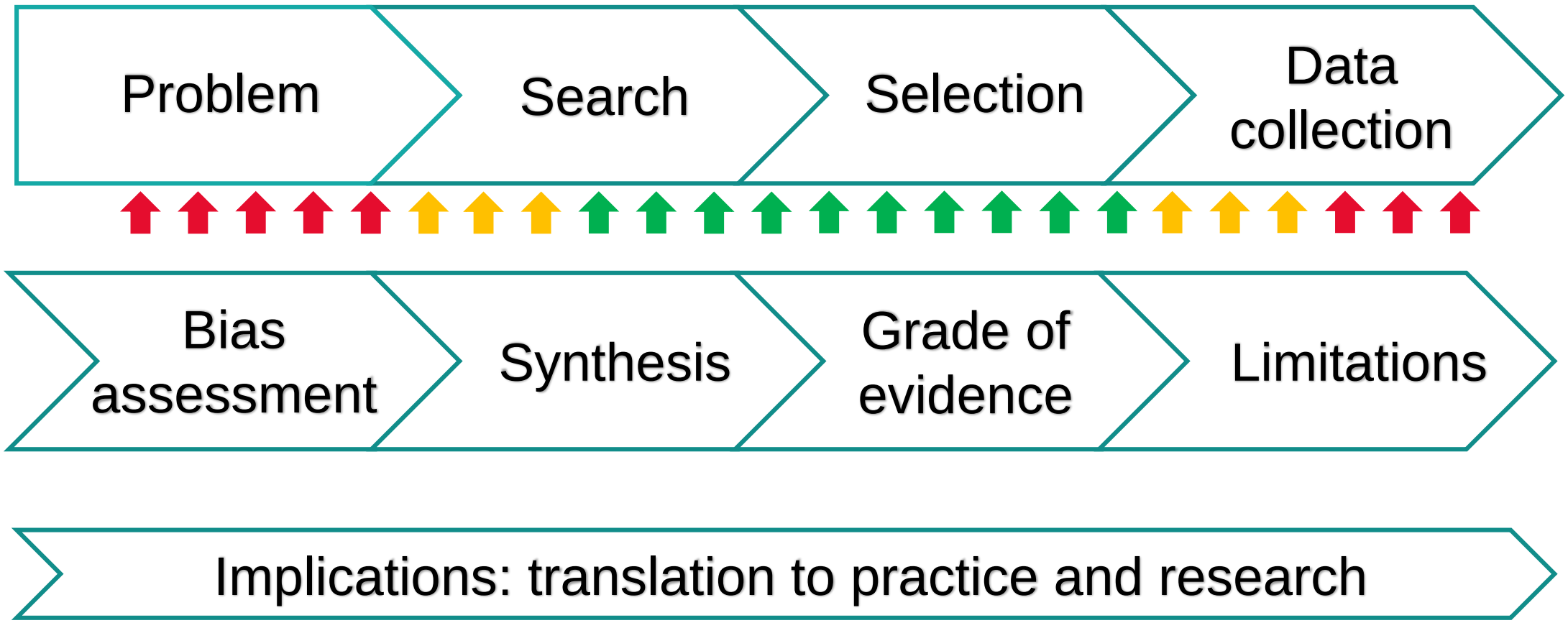
Protocol registration



Protocol registration

Aims:

1. to facilitate careful planning
2. to avoid duplication
3. to reduce reporting bias

What is PROSPERO?

PROSPERO is an international database of prospectively registered systematic reviews in health and social care.

Key features from the review protocol are recorded and maintained as a permanent record.

Systematic reviews should be registered at inception (i.e. at the protocol stage) to **help avoid unplanned duplication** and to **enable comparison of reported review methods with what was planned in the protocol**.

PROSPERO database

International prospective register of systematic reviews

PROSPERO database:

- http://www.crd.york.ac.uk/PROSPERO/
- prospectively registered systematic reviews with health related outcome
- „open access” system
- PRISMA-P recommendation

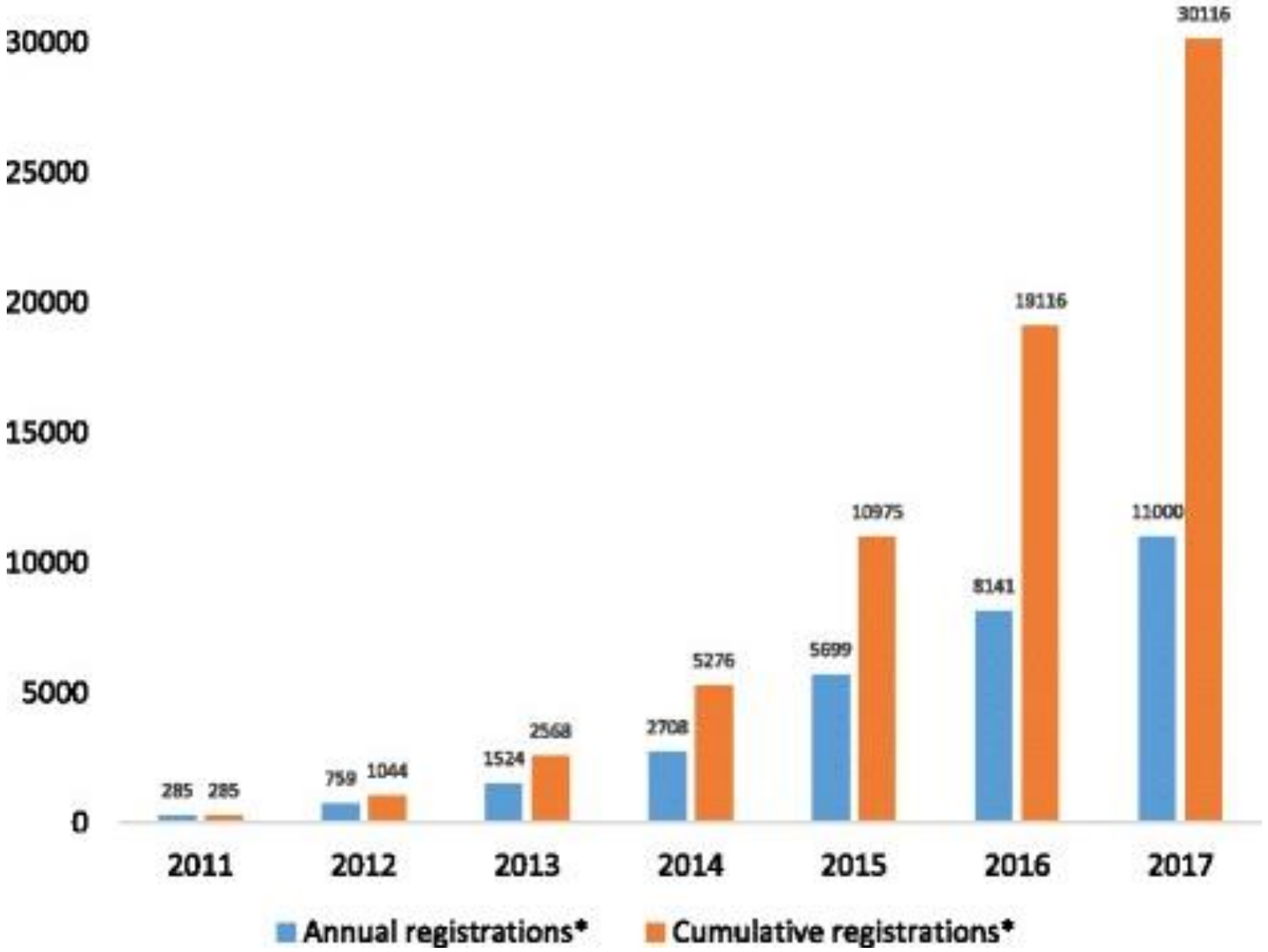
Importance:

- promotes and maintains **transparency**
- minimizes the **risk of reporting bias**
- avoids unnecessary **duplication**

Protocol registration:

- free of charge
- English
- a citable registration number
- 40 questions:
  - 22 mandatory items
  - 18 optional fields
- ~ 30-60 min
- changes/ updates:
  - only with brief explanation
  - public record

PROSPERO registrations between 2011–2017



- The question is how closely published SRs adhere to the planned methods, whether greater pre-specification of outcomes prevents selective inclusion and reporting of study results.
- **Registration in the international prospective register of systematic reviews (PROSPERO) of systematic review protocols was associated with increased review quality.**

Journal of clinical epidemiology, *100:103-110. 2018.*

How to do it?

- Step 1 Check the inclusion criteria
- Step 2 Ensure that your review protocol is in its (near) final form
- Step 3 Search PROSPERO to ensure that your review has not already been registered by another member of your team
- Step 4 Search PROSPERO to ensure that you are not unnecessarily duplicating a review that is being done by another team or has been registered previously
- Step 5 Start registering your review

Step 1 - inclusion criteria

- Step 1 Check the inclusion criteria to make sure that your review is eligible for inclusion in PROSPERO
- health related outcome
- studies of any design including reviews of animal studies for human health studies
- must be in English
- reviews of methodological issues need to contain at least one outcome of direct patient or clinical relevance
- reviews should be registered before screening against eligibility criteria

Step 2 - plan your protocol

- Step 2 Ensure that your review protocol is in its (near) final form and that no major changes are anticipated at this stage

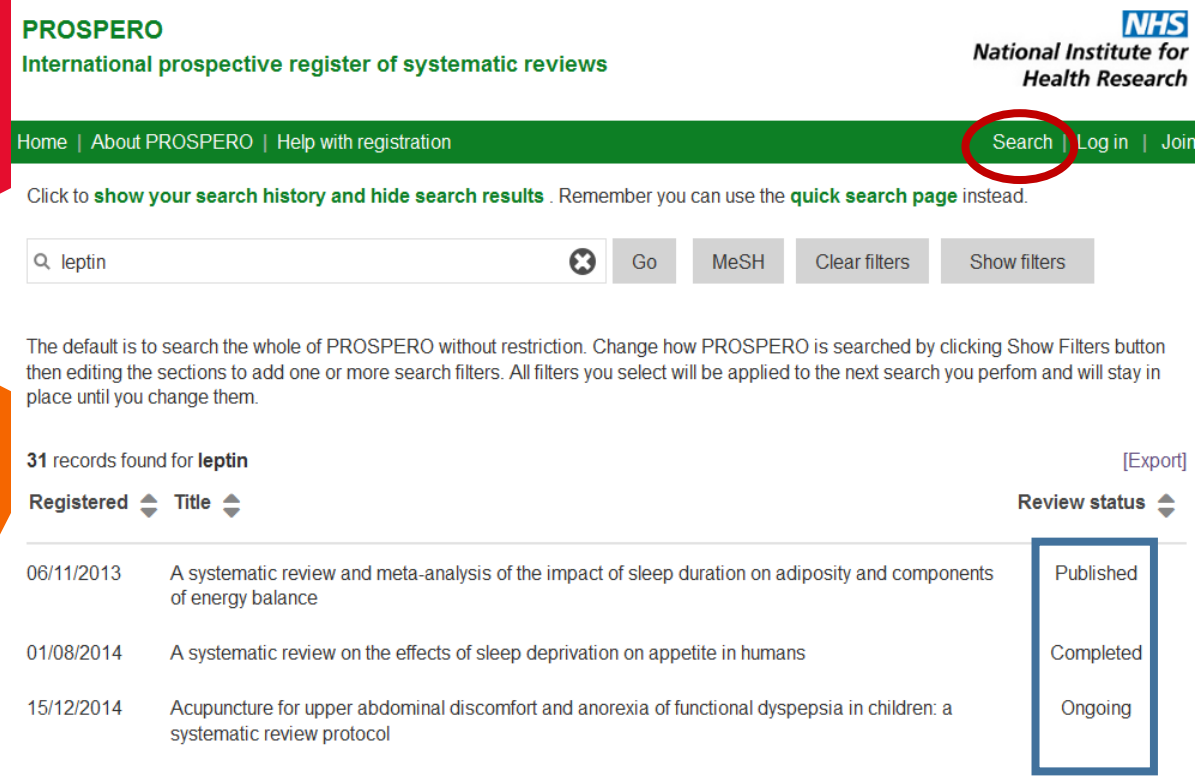
- **Do not register too early. Your systematic review protocol should be complete before you submit your registration request.**

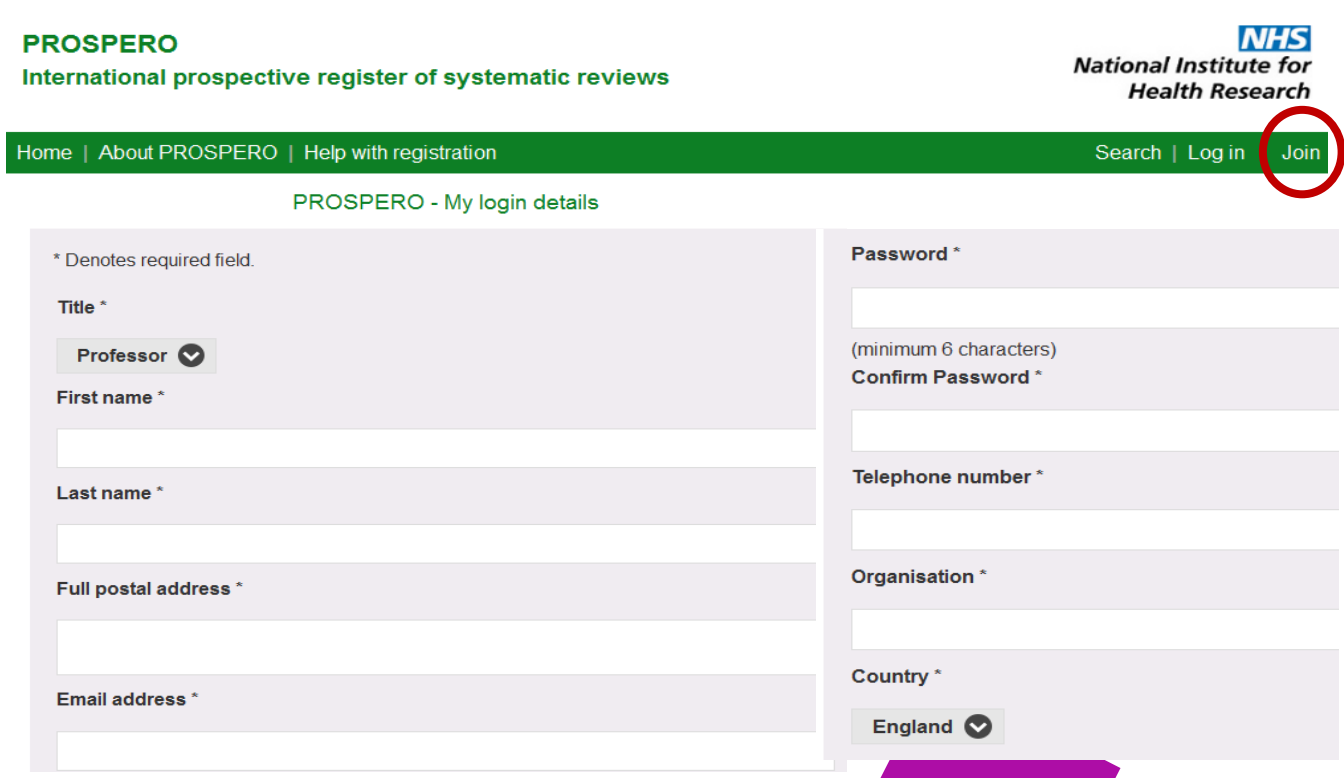
Step 3 and 4
Search PROSPERO

1. Search

2. Access

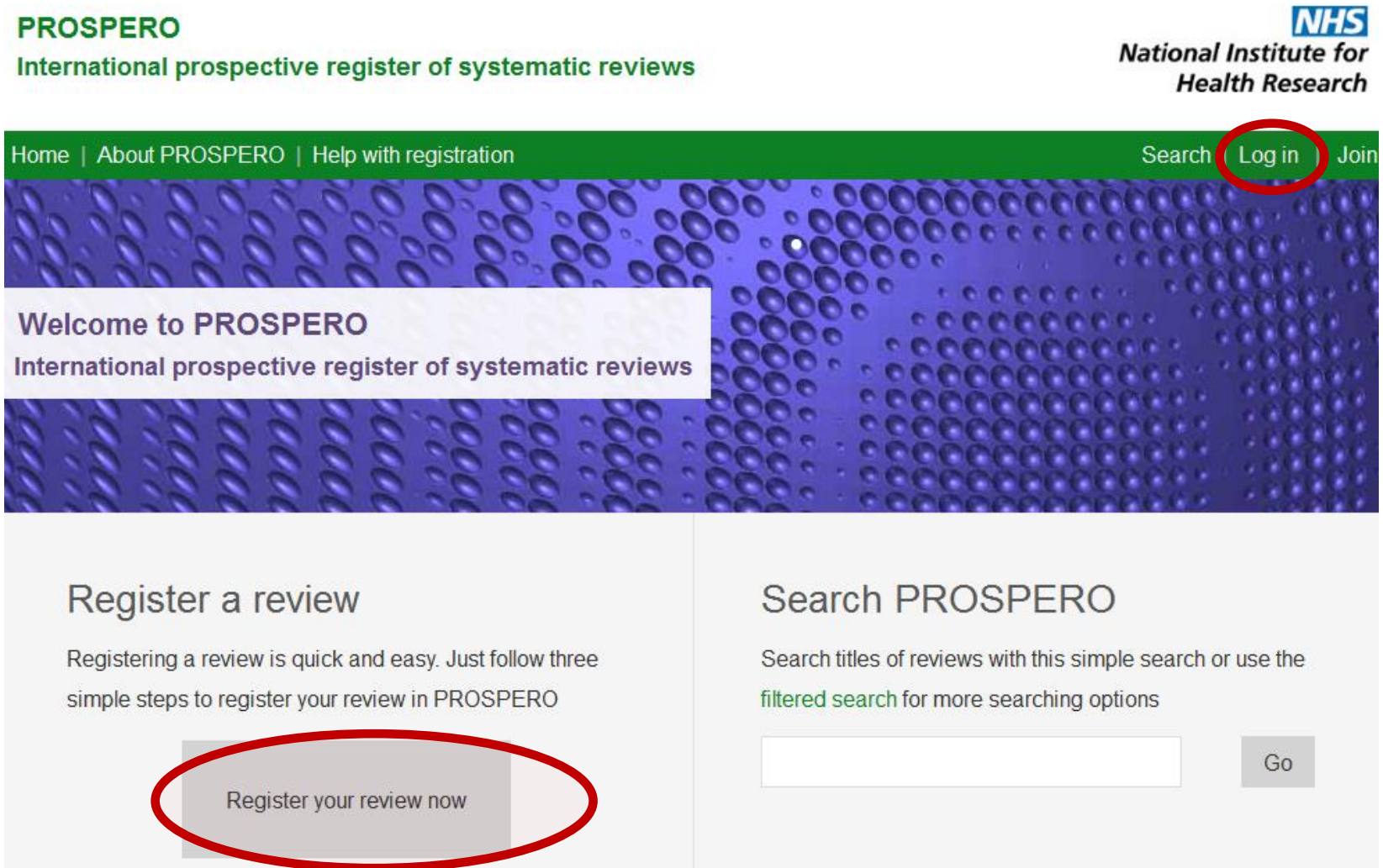
http://www.crd.york.ac.uk/PROSPERO/





Step 5 - register your protocol

3. Protocol registration



PROSPERO database
International prospective register of systematic reviews

PROSPERO registration fields (22*+18)

*** Mandatory fields**

1. **Review title** *
   Give the working title of the review according to PICO
   Study design has to be included.

2. Original language title

3. **Anticipated or actual start date** *
   After completion of a protocol, before screening of studies against eligibility criteria

4. **Anticipated completion date** * a whole year is usually enough
   When is the review expected to be completed?

PROSPERO database
International prospective register of systematic reviews

5. **Stage of review at time of registration** *

Example:

The review has not yet started [ ]

	Started	Completed
Preliminary searches	☑	☑
Piloting of the study selection process	☑	☐
Formal screening of search results against eligibility criteria	☐	☐
Data extraction	☐	☐
Risk of bias (quality) assessment	☐	☐
Data analysis	☐	☐

Green fields are optional, but if the red fields are labeled (checked), they reject your registration!

PROSPERO database

International prospective register of systematic reviews

6. Named contact * **lead reviewer or a representative of the review team**

7. Named contact email * **will be displayed in the public record**

8. Named contact address

9. Named contact phone number

10. Organizational affiliation of the review *

Example: University of Pécs, Medical School, Hungary

11. Review team members and their organisational affiliations

12. Funding sources/ sponsors * **individuals/organizations/legal entities who take responsibility for initiating managing sponsoring or financing- include identity number**

Example: NIHR HTA Program (Project ref 09/13/02). Funding provided by Merck.

PROSPERO database

International prospective register of systematic reviews

13. Conflicts of interest * **if any financial or personal relationships may influence or bias the results e.g. competing interests**

Example: None known

14. Collaborators

15. Review question(s) * **may be specific or broad**

Questions may be framed using PICO

16. Searches * **full search strategy is not required, but list all sources (databases, reference lists…) and restrictions (e.g. language)**

17. URL to search strategy

Consult with your junior mentor!

18. Condition or domain being studied * **give a short description of the disease, condition or healthcare domain being studied, this could include health and wellbeing outcomes.**

Example: Type 2 diabetes.

PROSPERO database

International prospective register of systematic reviews

19. Participants/ population * give summary criteria, preferred format includes details of both inclusion and exclusion criteria

20. Intervention(s), exposure(s) * detailed description is needed, ideally an intervention should be reported in enough detail that others could reproduce it or assess its applicability to their own settings

21. Comparator(s)/ control * details of both inclusion and exclusion criteria

22. Types of study to be included * Example: case- control studies, RCTs

Exact definition of your PICO and your outcomes is highly important.

If your PICO is not clear, it can lead to rejection of your protocol.

Maintain future tense throughout your sentences.

If you are unsure about your plans use phrase „we plan to…" instead of „we will do that…".

PROSPERO database

International prospective register of systematic reviews

23. Context

If the outcome is missing, they will reject your registration!

24. Primary outcome(s) *

give the pre-specified most important outcome and how the outcome is defined or measured

25. Secondary outcomes * **pre-specified additional outomes**

Example: None

26. Data extraction (selection and coding) **give the procedure, list the data to be extracted**

27. Risk of bias (quality) assessment *

Example: Cochrane risk of bias tool for RCTs, Newcastle-Ottawa Scale (NOS) for non-randomised studies

28. Strategy for data synthesis *

description of your statistical analysis

Consult with your statistitian!

29. Analysis of subgroups or subsets *

Subgroup analysis, detailes of categorisation, meta-regression etc.

PROSPERO database
International prospective register of systematic reviews

30. Type and method of review * - select it from the drop down lists

Example: Meta-analysis or Network meta-analysis, you may select more than one category

31. Language English

32. Country select the country in which the review is being carried out from the drop down list

33. Other registration details

34. Reference and/or URL for published protocol

35. Dissemination plans YES, in peer-reviewed journals

36. Keywords give words or phrases that best describe the review. This help users find your review in the Register.

37. Details of any existing review of the same topic by the same authors

PROSPERO database

International prospective register of systematic reviews

38. Review status *

Ongoing
Completed, but not published: *(Please provide anticipated publication date)*
Completed and published
Completed, published and being updated
Abandoned *(Please provide a brief reason)*

If it is not ongoing, they will reject your registration!

Review status should be updated when the review is completed and when it is published.

39. Any other information

40. Link to publication of final report

Before submission contact our PROSPERO coordinator:

margit.solymar@aok.pte.hu

What to publish? How to report your data?
Different types of reporting bias

TM TRANSLATIONAL MEDICINE

Depending on the nature and direction of the results

Publication bias The publication or non-publication of research findings

Time lag bias The rapid or delayed publication of research findings

Multiple (duplicate) publication bias The multiple or singular publication of research findings

Location bias The publication of research findings in journals with different ease of access or levels of indexing in standard databases, the accessibility of studies based on variable indexing in electronic databases

What to publish? How to report your data?
Different types of reporting bias

TRANSLATIONAL MEDICINE

Depending on the nature and direction of the results

Citation bias The citation or non-citation of research findings

Language bias The publication of research findings in a particular language

Outcome reporting bias The selective reporting of some outcomes but not others

Report all the outcomes that was planned to be measured in the protocol, irrespective of whether it is positive or negative.

PROSPERO database

International prospective register of systematic reviews

- **After submission you get a response within 20 working days.**
- **Changes can be made but a brief explanation of the reason should be given. Edits will appear in the public record – do your best first time**

Protocol registration

1. **No or delayed registration.**
2. **Poorly designed study protocol.**

Protocol registration

TAKE HOME MESSAGE

1. **Protocol registration is a „must-have”!**
2. **Plan your protocol carefully**

   (examples: Cochrane Reviews)!
3. **Publish everything what you planned to publish!**

Schedule for today

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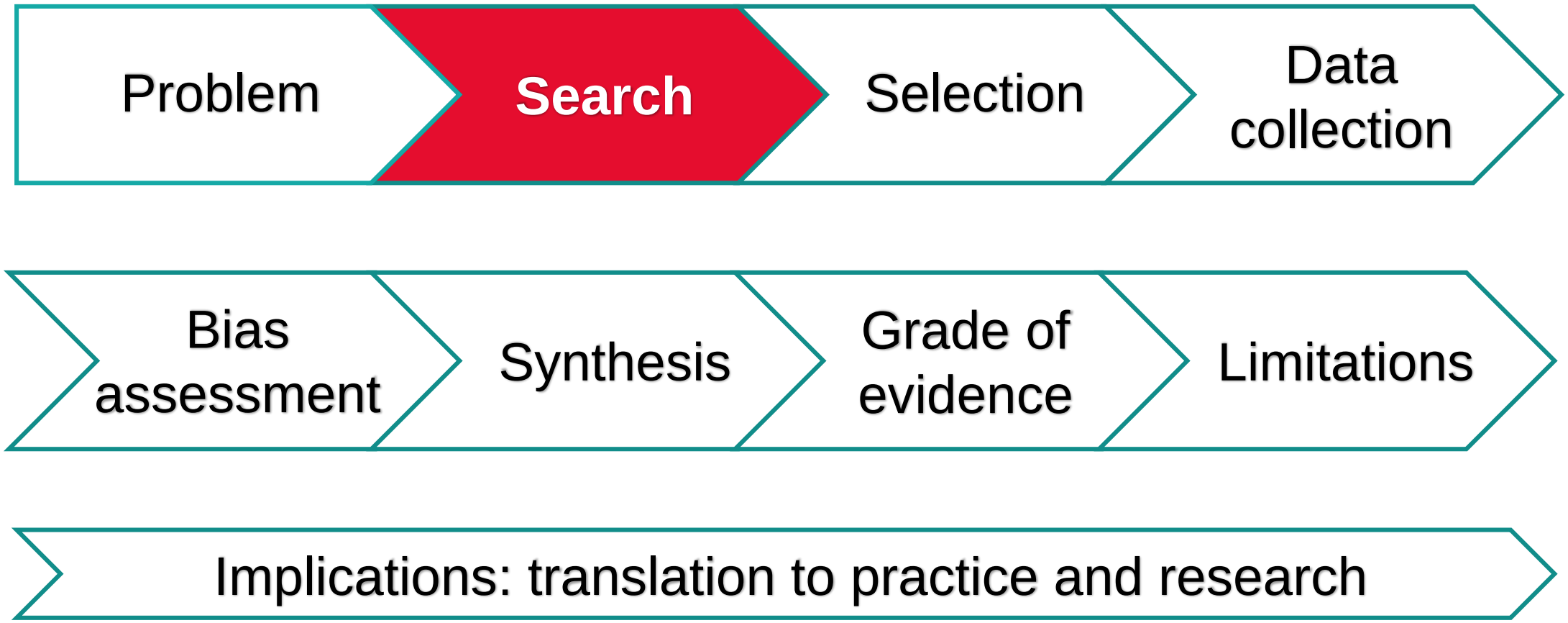
Flowchart


Problem
Search
Selection
Data collection
Bias assessment
Synthesis
Grade of evidence
Limitations
Implications: translation to practice and research

Terminology of search strategies

systematic vs. **non-systematic**

(non-selective) (selective, arbitrary)

Systematic search

Aim: to capture all the relevant articles published

Yield: records eligible for selection

Data sources

1. Search in electronic databases
2. Handsearch of printed material (journals)
3. Handsearch of reference lists (reviews, guidelines, included and excluded studies)
4. Handsearch of citing articles with Google Scholar

5. "Grey" literature
   - conference abstracts
   - unpublished and ongoing studies (trial registries)
   - original authors of the studies
   - non-indexed journals (?)

Electronic databases

Google Scholar

EMBASE

MEDLINE

TRIP

Cochrane TRIAL

Scopus

Grey literature (BIOSIS)

PsycINFO

ClinicalTrials.gov

Web of Science

WHO GLobal Health Library

Search in databases - key (query)

1. **Controlled vocabulary (thesaurus of terms)**
   - MEDLINE: MeSH
   - EMBASE: EMTREE

spark search ideas

2. **Free-text terms (what you write in the search bar)**
   - synonims (recovery vs. healing)
   - related words (head vs. brain)
   - variant spelling (tumor vs. tumour)
   - truncation (pharmaco*)

+automatic ‚explosion'

Example

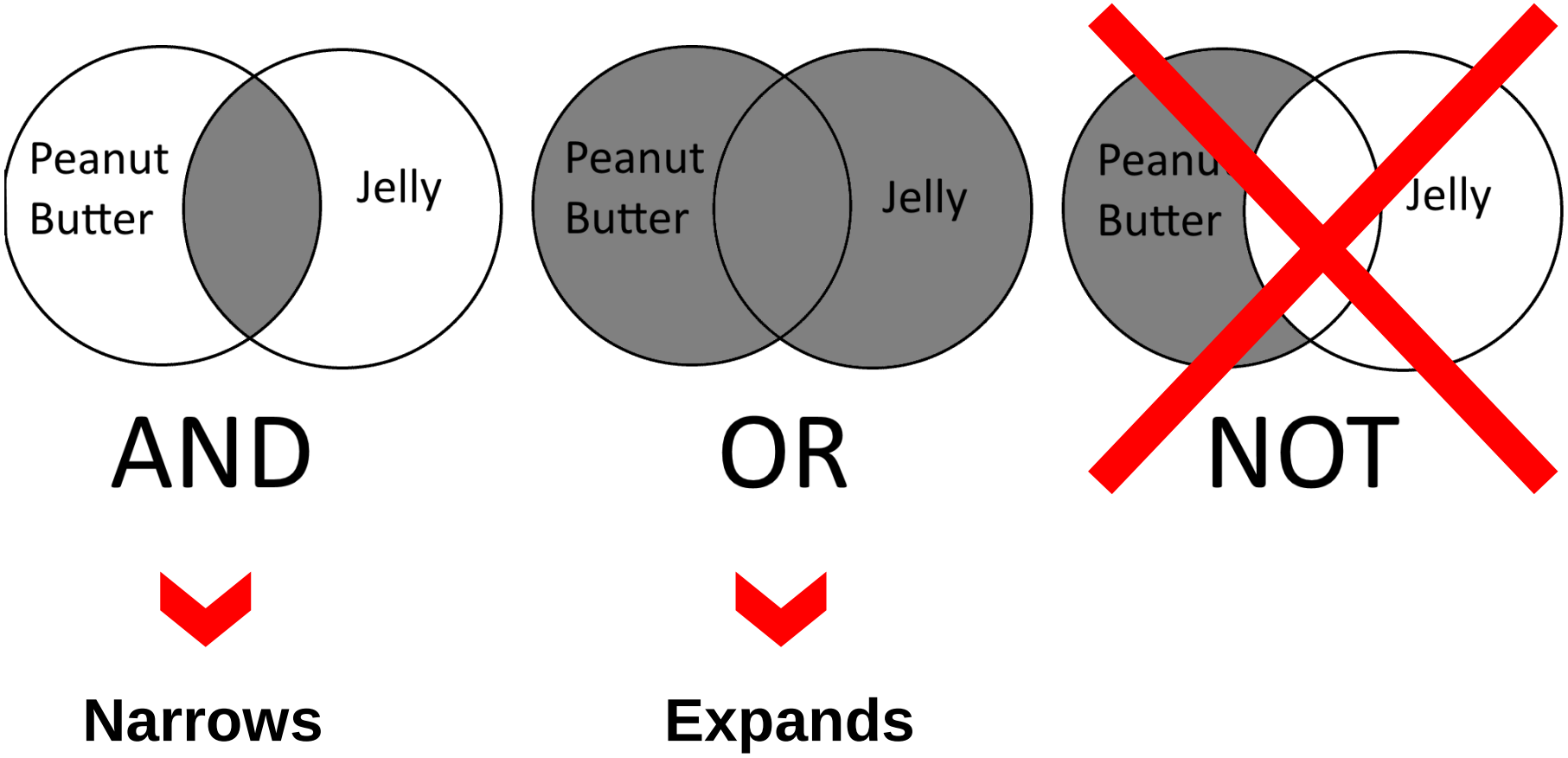
query

celiac AND disease AND ((mucosal AND healing) OR (mucosal AND recovery) OR (villous AND atrophy))

query transcript

celiac[All Fields] AND ("disease"[MeSH Terms] OR "disease"[All Fields]) AND ((("mucous membrane"[MeSH Terms] OR ("mucous"[All Fields] AND "membrane"[All Fields]) OR "mucous membrane"[All Fields] OR "mucosal"[All Fields]) AND (("wound healing"[MeSH Terms] OR ("wound"[All Fields] AND "healing"[All Fields]) OR "wound healing"[All Fields] OR "healing"[All Fields]) OR recovery[All Fields])) OR (villous[All Fields] AND ("atrophy"[MeSH Terms] OR "atrophy"[All Fields])))

Boolean operators



Source of figure: https://sru.libguides.com/c.php?g=531870&p=3883641

Boolean operators vs. quotation marks

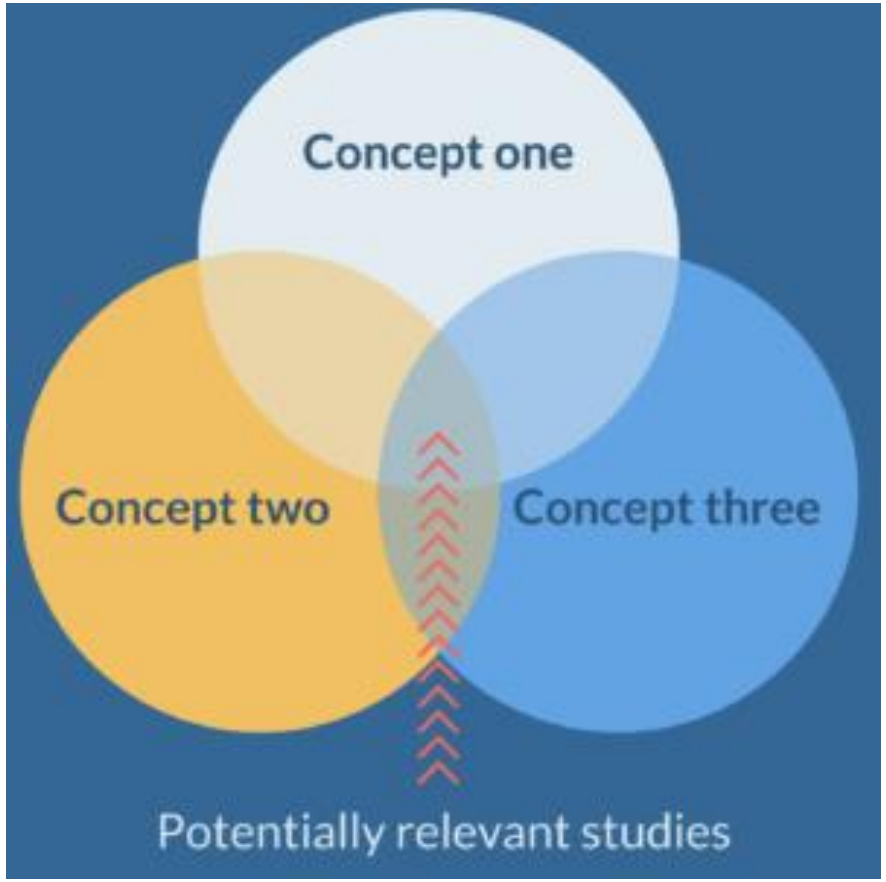
good AND clinical AND practice	**n=22 230**
vs.	
"good clinical practice"	**n=1 539**

Boolean operators and the concepts

P: chronic myeloid leukemia

IC: tyrosine-kinase inhibitors

O: pregnancy outcomes



Boolean operators and the concepts

P: chronic myeloid leukemia

IC: tyrosine-kinase inhibitors

O: pregnancy outcomes

{ (chronic AND (myeloid OR myelogenous) AND (leukemia OR leukaemia))
AND
("tyrosine kinase inhibitor*" OR imatinib OR "152459-95-5" OR nilotinib OR "641571-10-0" OR dasatinib OR "302962-49-8" OR bosutinib OR "380843-75-4" OR ponatinib OR "943319-70-8")
AND
(pregnan* OR gestation OR conception OR fertil* OR inseminat* OR childbearing OR embryotoxic* OR genotoxic* OR teratogenic*)

A common mistake

celiac AND disease AND ((mucosal AND healing) OR (mucosal AND recovery) OR (villous AND atrophy))

n=1358

celiac AND disease AND (mucosal AND healing) OR (mucosal AND recovery) OR (villous AND atrophy))

n=6112

Mind the order of operations!

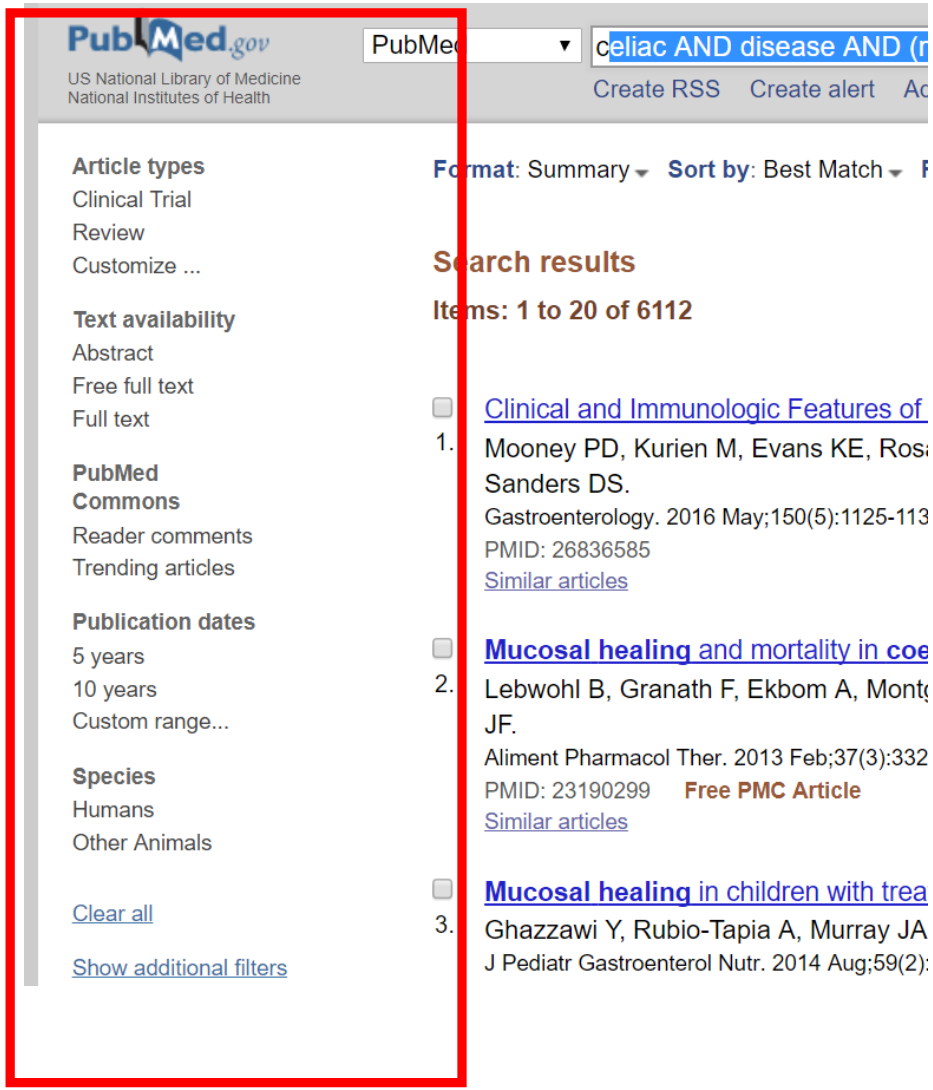
Restriction of search

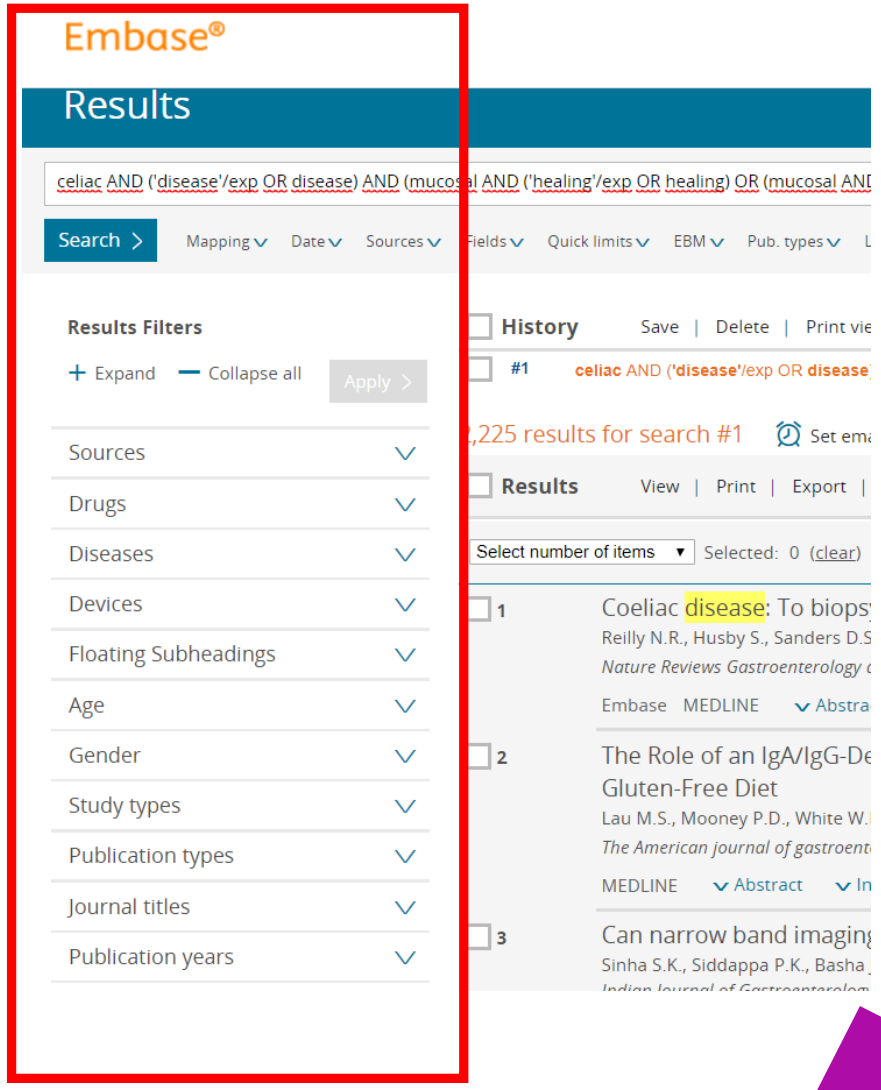
Filters:

- English language records
- humans
- trials/RCTs
- time frames

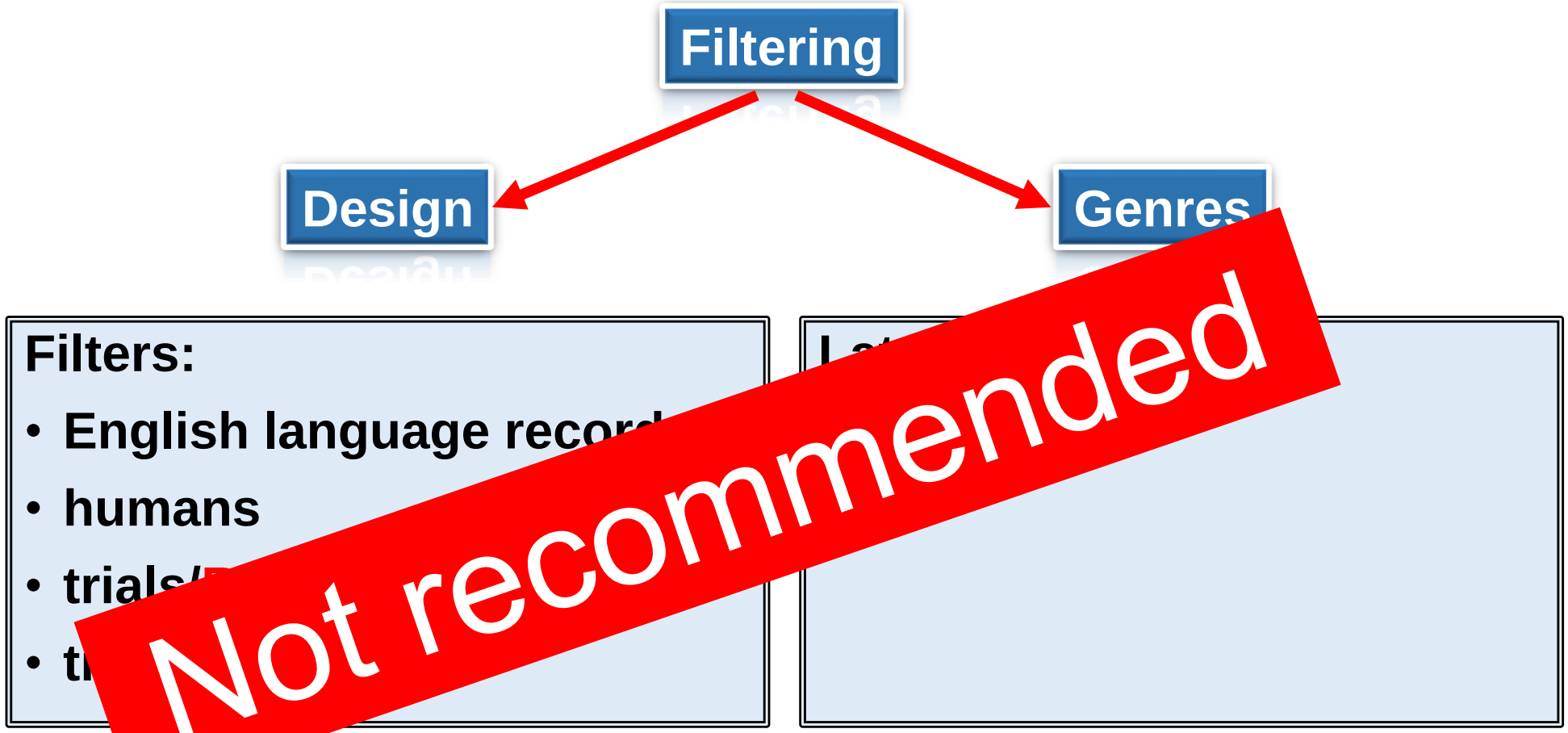
Later…

Restriction of search





Restriction of search



How many records should a search yield?

Database	Raw search
Embase	3914
PubMed	2848
Cochrane Trials	128
Web of Science	2266
Scopus	2437
ClinicalTrials.gov	45
WHO Global Health Libary	2432
∑	14071

No rules!!!

(magnitude: 100-1000)

Save time!

Sensitivity versus precision?

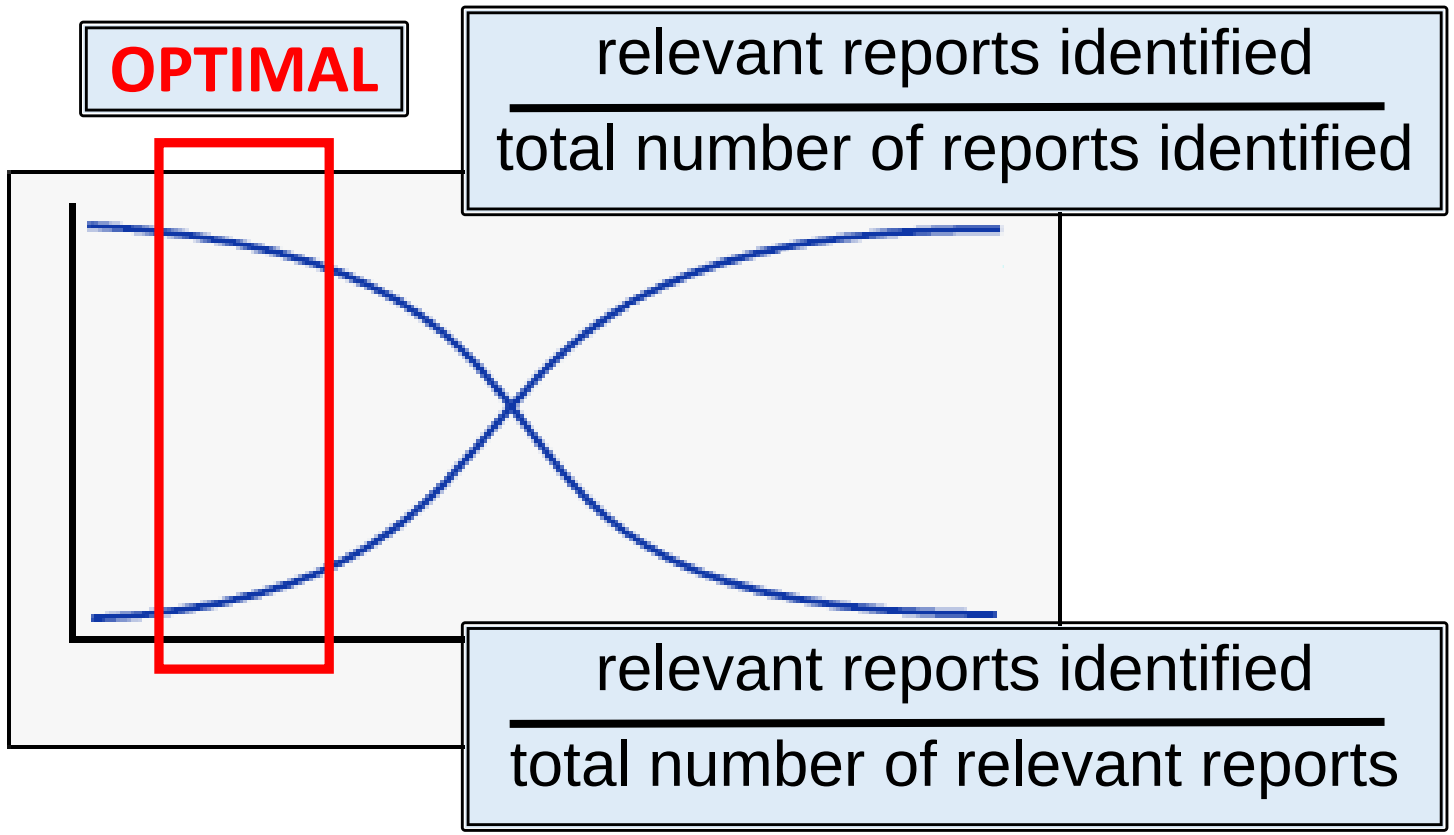
$$\frac{\text{relevant reports identified}}{\text{total number of relevant reports}}$$

$$\frac{\text{relevant reports identified}}{\text{total number of reports identified}}$$

Save time!

2 abstracts in a minute › **120** abstracts in an hour › **about 1000** abstracts in an 8-hour shift

How many records should a search yield?



Yield		Relevant
10	›	2/20
50	›	6/20
100	›	12/20
500	›	14/20
1000	›	16/20
5000	›	17/20
10000	›	18/20

How to design good search strategies?

1. Design a preliminary search key without using filters based on the medical terminology you know
2. Start selecting and pick a few key articles
3. Review these articles thoroughly and identify key terms (words, phrases, concepts)
4. Pick previous reviews through the preliminary search and identify key terms (words, phrases, concepts)
5. Design the final query
6. Test the query whether it identifies the key articles you had found previously

Systematic search

COMMON MISTAKE

1. The search is not comprehensive => missing records
2. Application of filters => missing records
3. Insufficient databases => missing records
4. Skipping preliminary search => poorly designed final search

Systematic search

TAKE HOME MESSAGE

1. Design your search strategy with caution
2. Do not underestimate the yield of preliminary search

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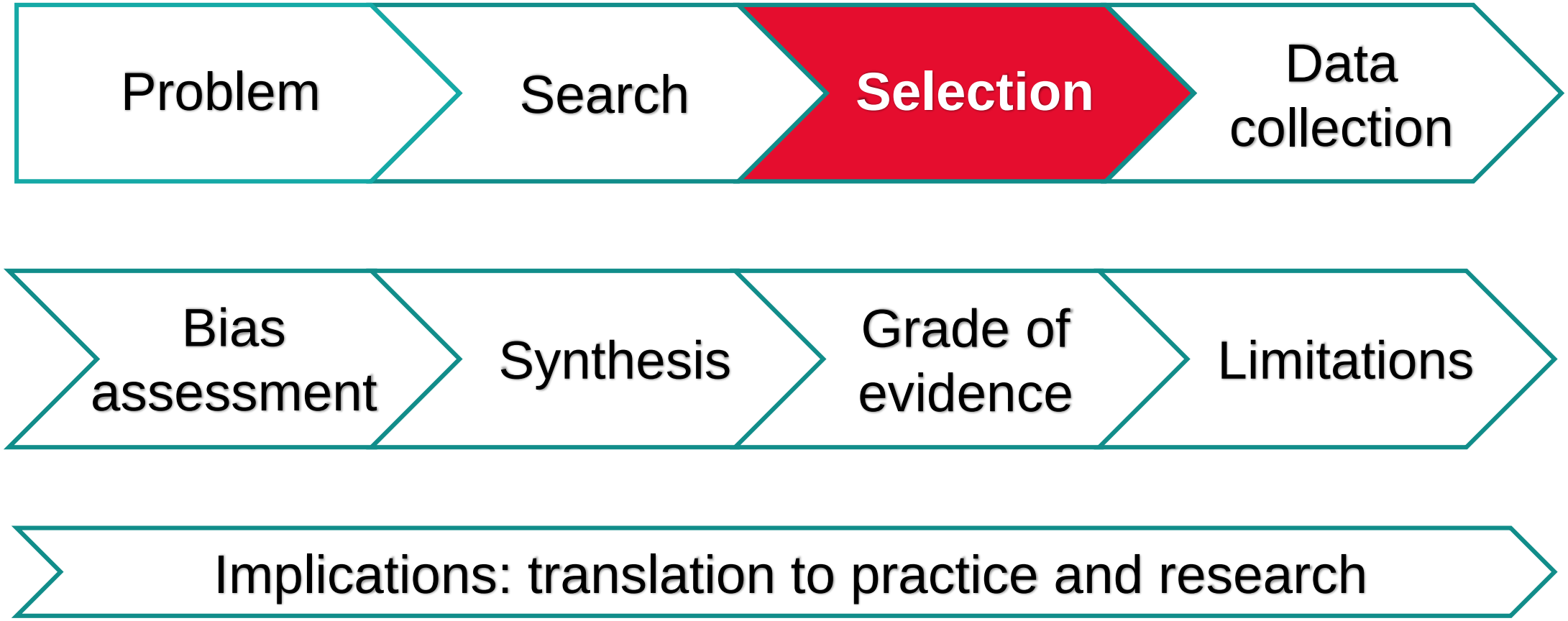
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Search
Selection
Data collection
Bias assessment
Synthesis
Grade of evidence
Limitations
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Selection

Aim: to select the relevant records from a large pool

Benefit: all records eligible for data collection

Selection

Needle in the haystack….

Steps of selection

Removal of overlapping database content and duplicates

3-step selection

Removal of overlapping study populations

Steps of selection

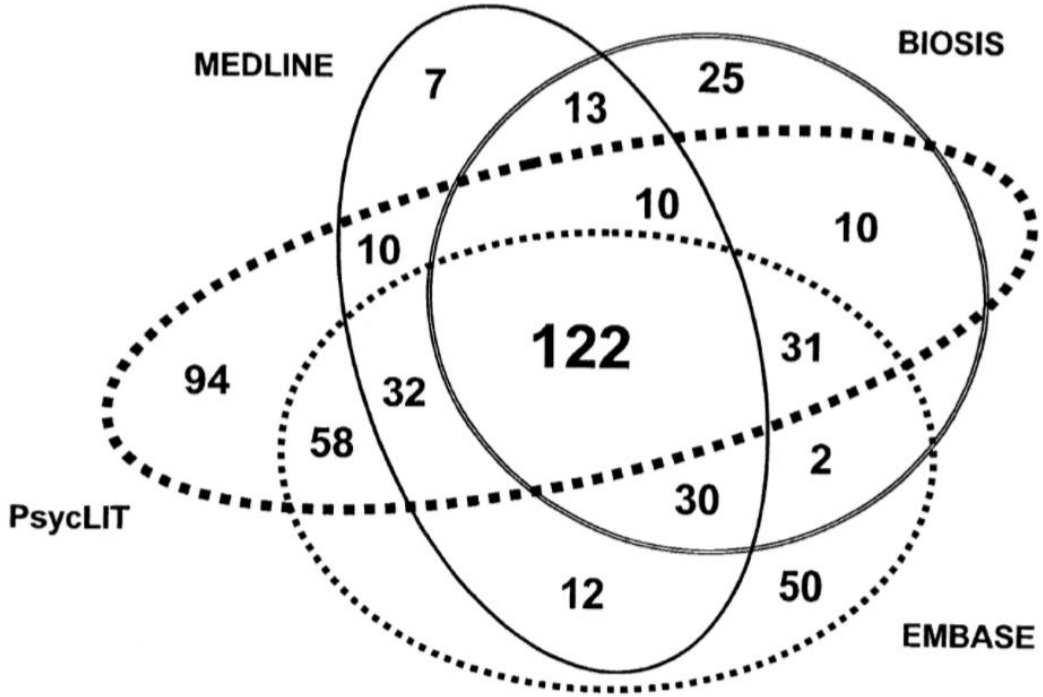
Removal of overlapping database content and duplicates

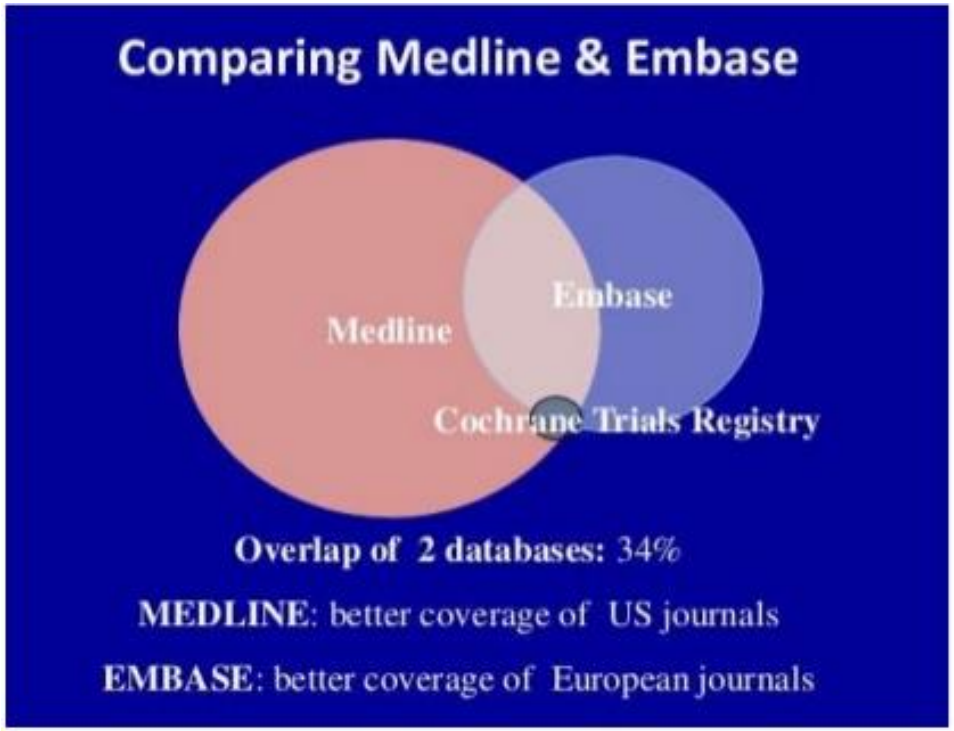
3-step selection

Removal of overlapping study populations

Overlapping database content

Papers are uploaded to multiple databases





McDonald S, Taylor L, Adams C. Searching the right database. A comparison of four databases for psychiatry journals. Health Libr Rev. 1999; 16: 151-156., Smith BJ, Darzins PJ, Quinn M, et al. Modern methods of searching the medical literature. Med J Aust. 1992; 157: 603-611.

Duplicate references

Exactly the same papers published in more than one journal

Setting	No. of Systematic Reviews	Total No.		Main Reports		Duplicate Reports	
		Reports	Subjects	No.	No. of Subjects	No. (% of Total)	No. of Subjects (% of Total)
Postoperative nausea and vomiting*	13	306	46 769	286	40 014	20 (6.5)	6755 (14.4)
Albumin	9	113	6944	96	6229	17 (15.0)	715 (10.3)
Oral analgesics	7	134	25 011	126	23 810	8 (6.0)	1201 (4.8)
Epidural for surgery	5	170	11 741	145	10 151	25 (14.7)	1590 (13.5)
Transfusion	5	139	17 048	131	16 529	8 (5.8)	519 (3.0)
Epidural for labor	3	21	4115	17	3739	4 (19.0)	376 (9.1)
Intra-articular morphine	2	37	2096	34	1950	3 (8.1)	146 (7.0)
Endarterectomy†	2	18	4118	17	4043	1 (5.6)	75 (1.8)
Miscellaneous‡	10	296	24 084	279	22 872	17 (5.7)	1212 (5.0)
Total	**56**	**1234**	**141 926**	**1131**	**129 337**	**103** (8.3)	**12 589** (8.9)

*The quantitative impact of duplicates of ondansetron trials on meta-analysis has been previously analyzed.[4]
†Local anesthetic vs general anesthesia.
‡Prevention of postoperative pulmonary complications; epidural analgesics; cerebrospinal fluid drainage; preoperative tests; morphine for postoperative pain; prev
pain with propofol; recovery from general anesthesia; premedication for anxiety; postoperative delirium; and spinal hematoma.

Source: von Elm E, Poglia G, Walder B, et al. Different patterns of duplicate publication: an analysis of articles used in systematic reviews. Jama. 2004; 291: 974-980.

How to deal with duplicates and overlapping database content?

…with a reference manager software (e.g., EndNote)

Step 1.

- Import the yield of the search **from each database**

Aim: to build up a single pool from databases

Download a 30-day trial from http://endnote.com/downloads/30-day-trial

How to deal with duplicates and overlapping database content?

…with a reference manager software

Step 2.

- Use the ‚Find duplicates' function of the software and eliminate them

Aim: to gain a near duplicate-free pool of records

Download a 30-day trial from http://endnote.com/downloads/30-day-trial

How to deal with duplicates and overlapping database content?

…with a reference manager software

Step 3.

- Check the duplicates manually as well!

Aim: to gain a duplicate-free pool of records

Download a 30-day trial from http://endnote.com/downloads/30-day-trial

For further assistance see:

https://tm-centre.org/download/article-realated/114/selection-with-endnote-0809084855.pdf

Why is important to remove duplicates and overlapping database content?

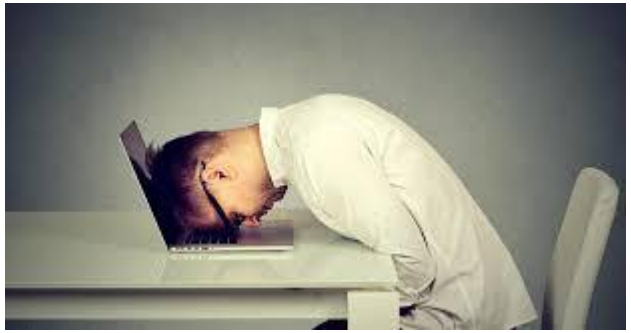
Database	Raw search
Embase	3914
PubMed	2848
Cochrane Trials	128
Web of Science	2266
Scopus	2437
ClinicalTrials.gov	45
WHO Global Health Libary	2432
∑	14071

Preliminary search and planning of the searchkey:
days!!!!

Build up an EndNote pool:
15 min

Removing overlaps:
30 min

After removing them:
3254 records



Steps of selection

Removal of overlapping database content and duplicates

3-step selection

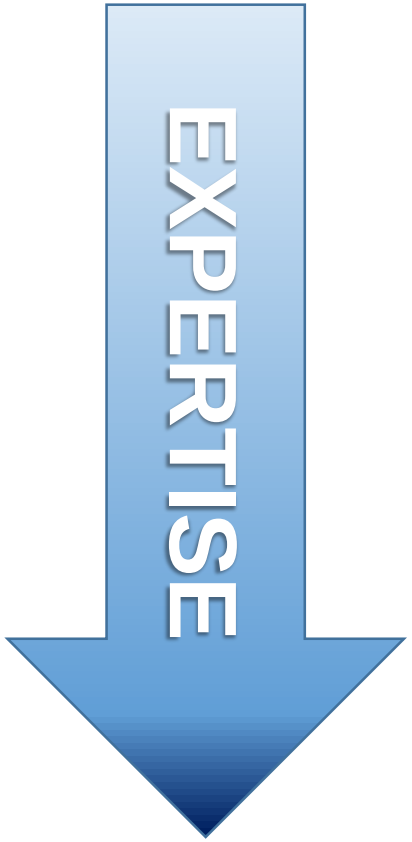
Removal of overlapping study populations

Selection

You need…

- a strategy (e.g., EndNote)
- labor force (at least two review authors) with at least basic English language skills
- pre-defined selection criteria
- a decision making strategy
- time, patience, and stamina…
- expertise?

Classical 3-step selection

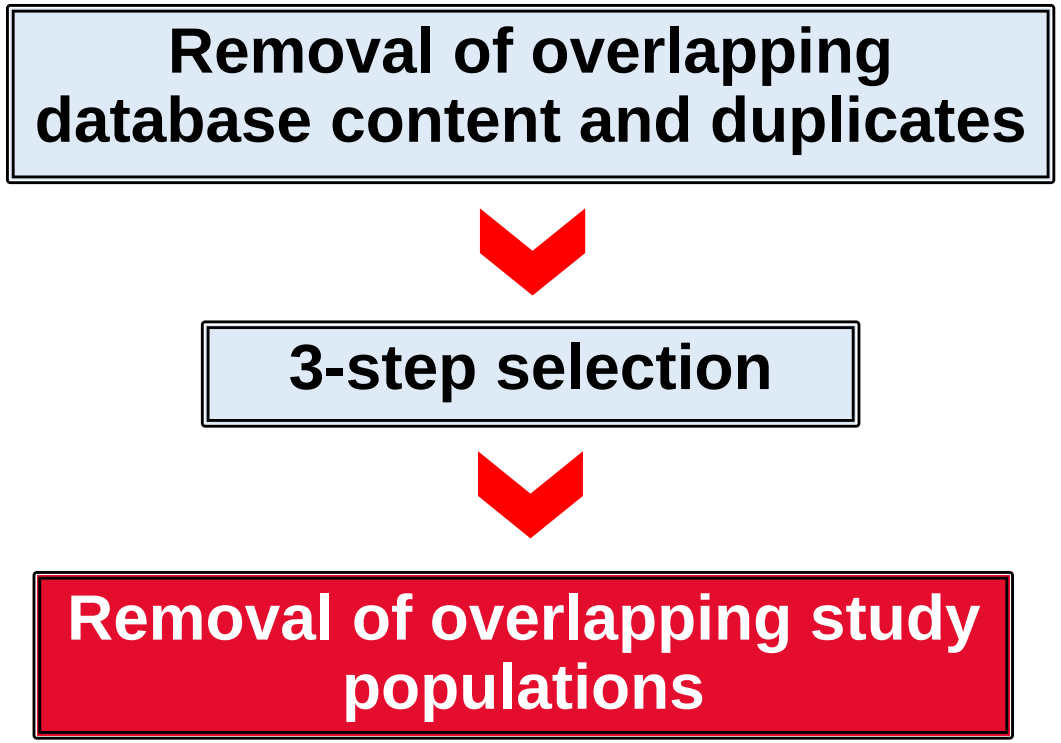


Selection by title

Selection by abstract

Selection by full-text

Steps of selection



Overlapping study populations

Multiple publications from the same study population which are different in some way

↓

Overrepresentation of some patients in analyses

↓

To exclude these and leave only one copy by checking **authors, sites and period of recruitment, and the data**

How to carry out selection?

1. Plan your eligibility criteria before you start selecting!

Example: Does follow-up biopsy predict long-term outcomes in celiac disease?

Inclusion criteria (by scientific content) - PICO!!!

1. **diagnosed celiac disease**
2. **adherence to gluten-free diet**
3. **at least one follow-up biopsy with available histological results (recovery vs. atrophy)**
4. **outcomes reported by histology separately**

How to carry out selection?

1. Plan your eligibility criteria before you start selecting!

Example: Does follow-up biopsy predict long-term outcomes in celiac disease?

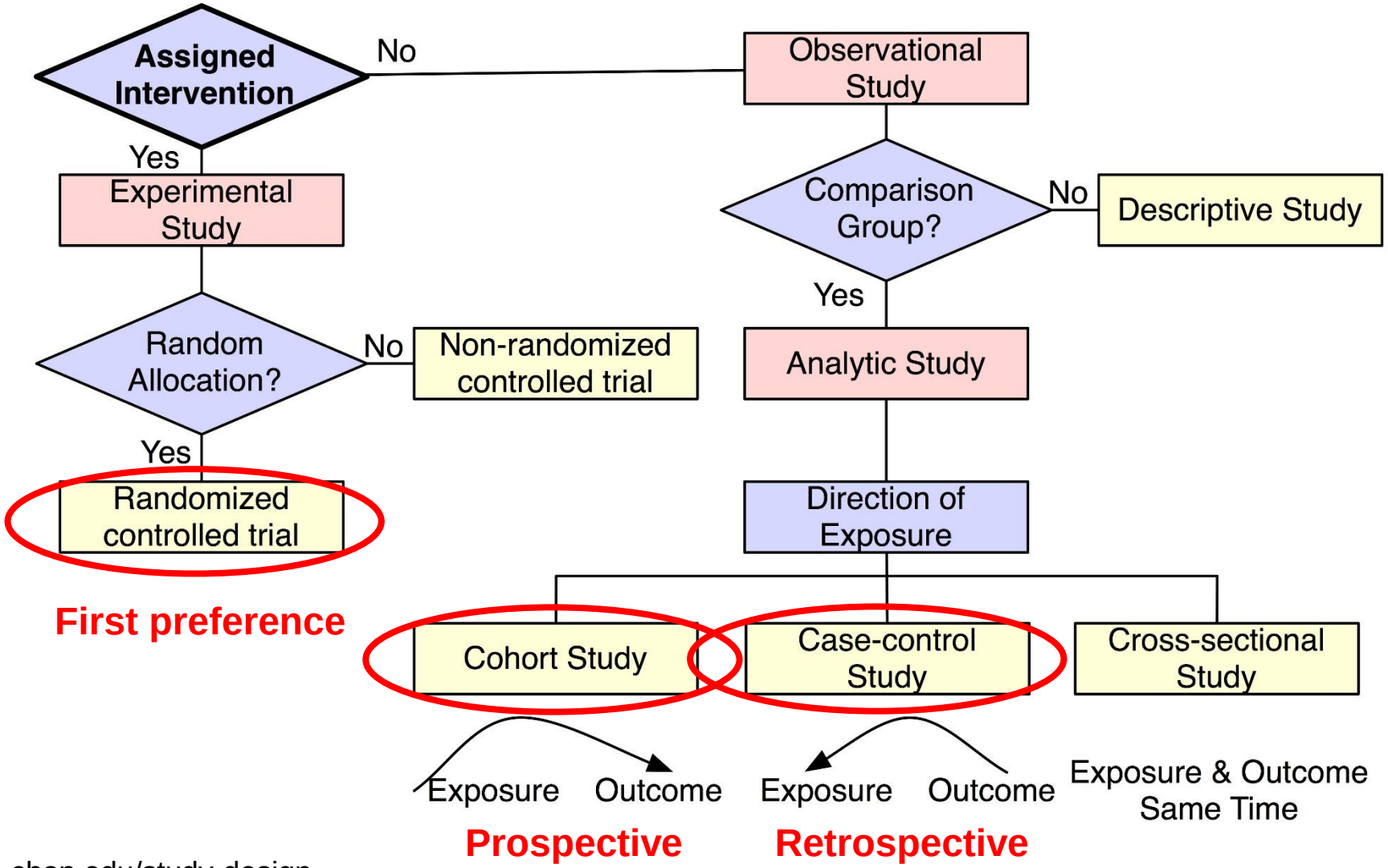
Inclusion criteria (by study design):

1. observational studies

Exclusion criteria (by study design)

1. case studies, case series
2. conference abstracts

Study designs - decision-making strategy



https://irb.research.chop.edu/study-design

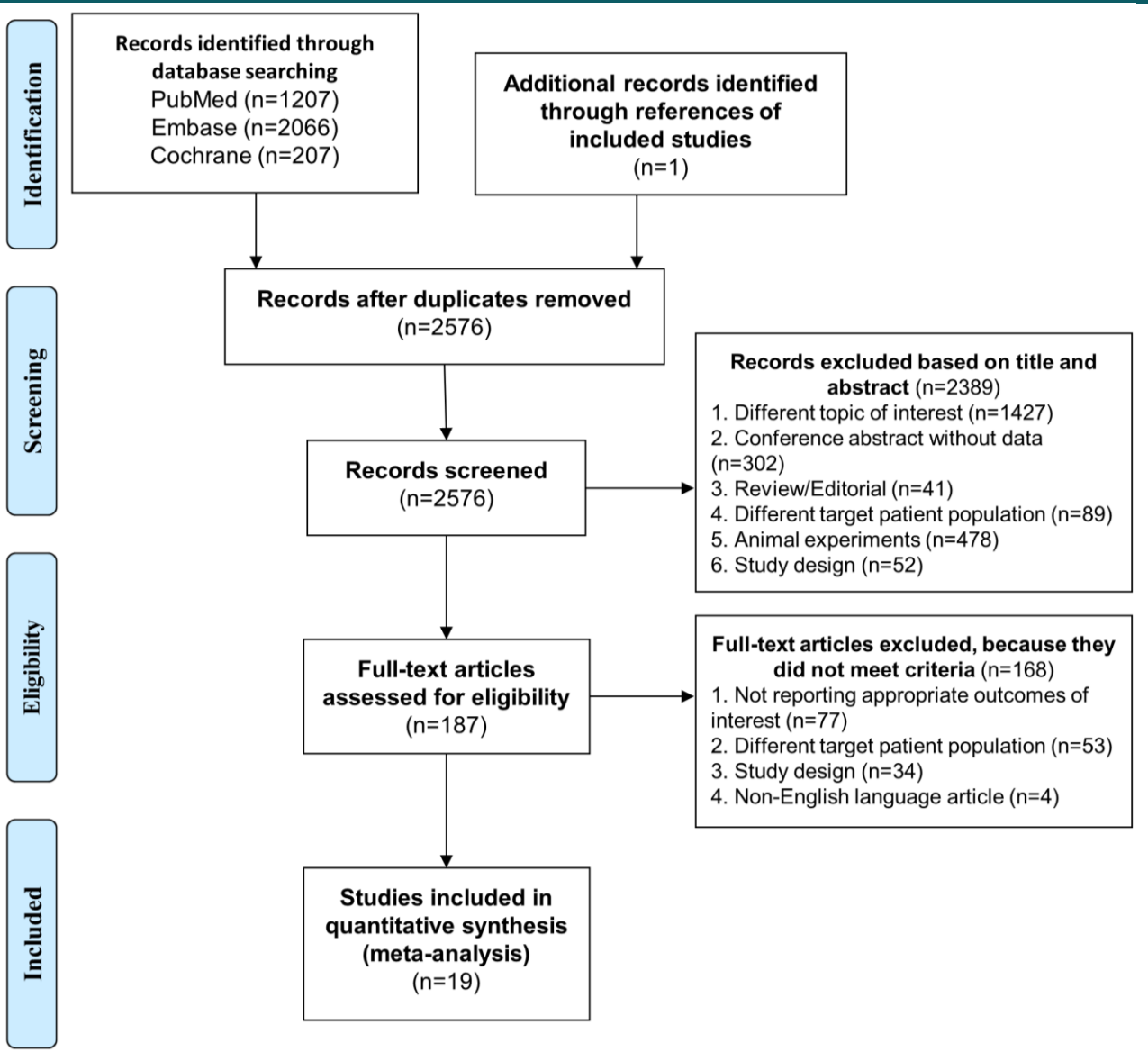
How to carry out selection?

1. Plan your eligibility criteria before you start selecting!

2. Make the selection process transparent and reproducible!

- Date of search, databases, keywords, filters should be accurately documented!
- Flow chart is mandatory (PRISMA)!
- List of articles excluded on full-text assessment with reasons (xlsx file uploaded as supporting information)!

Flowchart


Identification
Screening
Eligibility
Included
Records identified through database searching
PubMed (n=1207)
Embase (n=2066)
Cochrane (n=207)
Additional records identified through references of included studies
(n=1)
Records after duplicates removed
(n=2576)
Records screened
(n=2576)
Records excluded based on title and abstract (n=2389)
1. Different topic of interest (n=1427)
2. Conference abstract without data (n=302)
3. Review/Editorial (n=41)
4. Different target patient population (n=89)
5. Animal experiments (n=478)
6. Study design (n=52)
Full-text articles assessed for eligibility
(n=187)
Full-text articles excluded, because they did not meet criteria (n=168)
1. Not reporting appropriate outcomes of interest (n=77)
2. Different target patient population (n=53)
3. Study design (n=34)
4. Non-English language article (n=4)
Studies included in quantitative synthesis (meta-analysis)
(n=19)

How to carry out selection?

1. Plan your eligibility criteria before you start selecting!

2. Make the selection process transparent and reproducible!

3. Two review authors should select the records in duplicate to reduce the number of false positives and false negatives!

Calculate Cohen's Kappa to measure inter-rater agreement!

https://www.statisticshowto.datasciencecentral.com/cohens-kappa-statistic/

Selection

1. Plan your eligibility criteria before you start selecting!

2. Make the selection process transparent and reproducible!

3. Two review authors should select the records in duplicate to reduce the number of false positives and false negatives!

4. Describe how discrepancies were resolved between the review authors

- Third party arbitration (expert in the field)
- Committee concensus (experts in the field)

Selection

COMMON MISTAKE

1. Lack of transparency
2. Insufficient laborforce (not done in duplicate)
3. Failure to check overlapping study populations

Selection

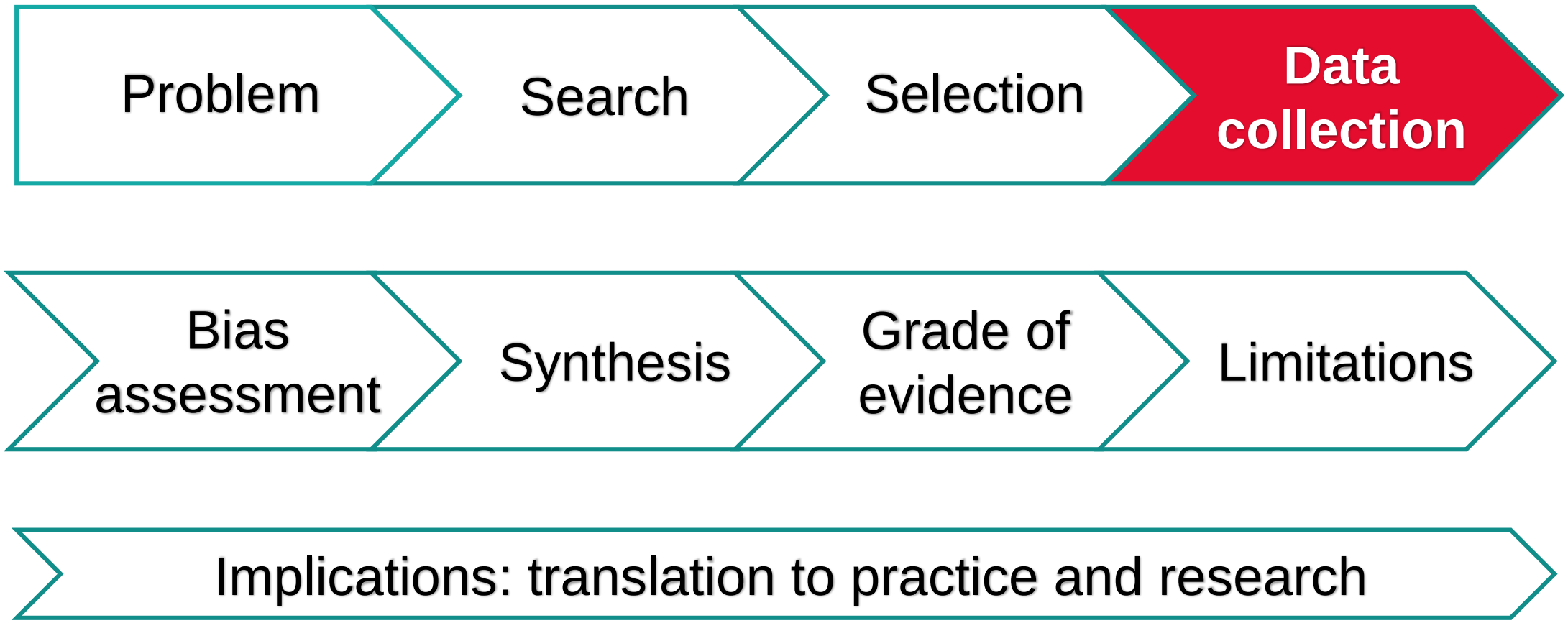
TAKE HOME MESSAGE

1. **Selection process:** remove duplicates => do 3-step selection by title, abstract, and full-text => remove overlapping populations
2. **Document everything (with rationales)**

Schedule for today

1.	Erőss Bálint	**Voting,** The role of meta-analyses in translational medicine
2.	Mikó Alexandra	Questions and hypotheses
3.	Márta Katalin	Meta-analysis guidelines
4.	Solymár Margit	Protocols and reporting bias
5.	Pécsi Dániel	Systematic search
		Break
6.	Balaskó Márta	Selection of records
7.	Hanák Lilla	Data collection - statistical aspects
8.	Erőss Bálint	Data collection - practical aspects
9.	Szakács Zsolt	Bias
		Break
10.	Soós Alexandra	Statistics of meta-analyses
11.	Szakács Zsolt	Grade of evidence
12.	Szakács Zsolt	Limitations and implications
13.	Szakács Zsolt	Future perspectives, **voting**

Flowchart


Problem
Search
Selection
Data collection
Bias assessment
Synthesis
Grade of evidence
Limitations
Implications: translation to practice and research

The process

WHAT WE HAVE

data in the script

WHAT WE DO

correct data collection

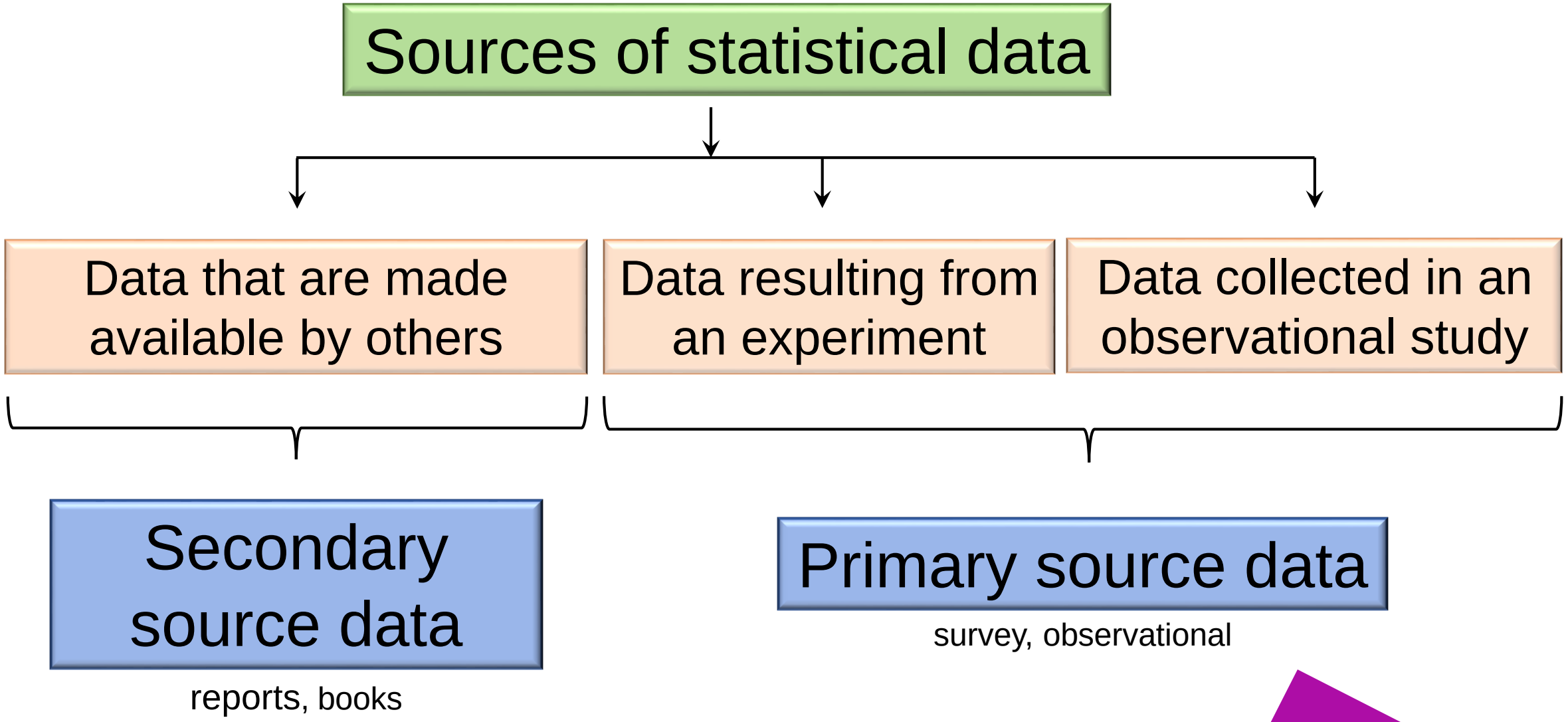
WHAT WE WANT

perfect database

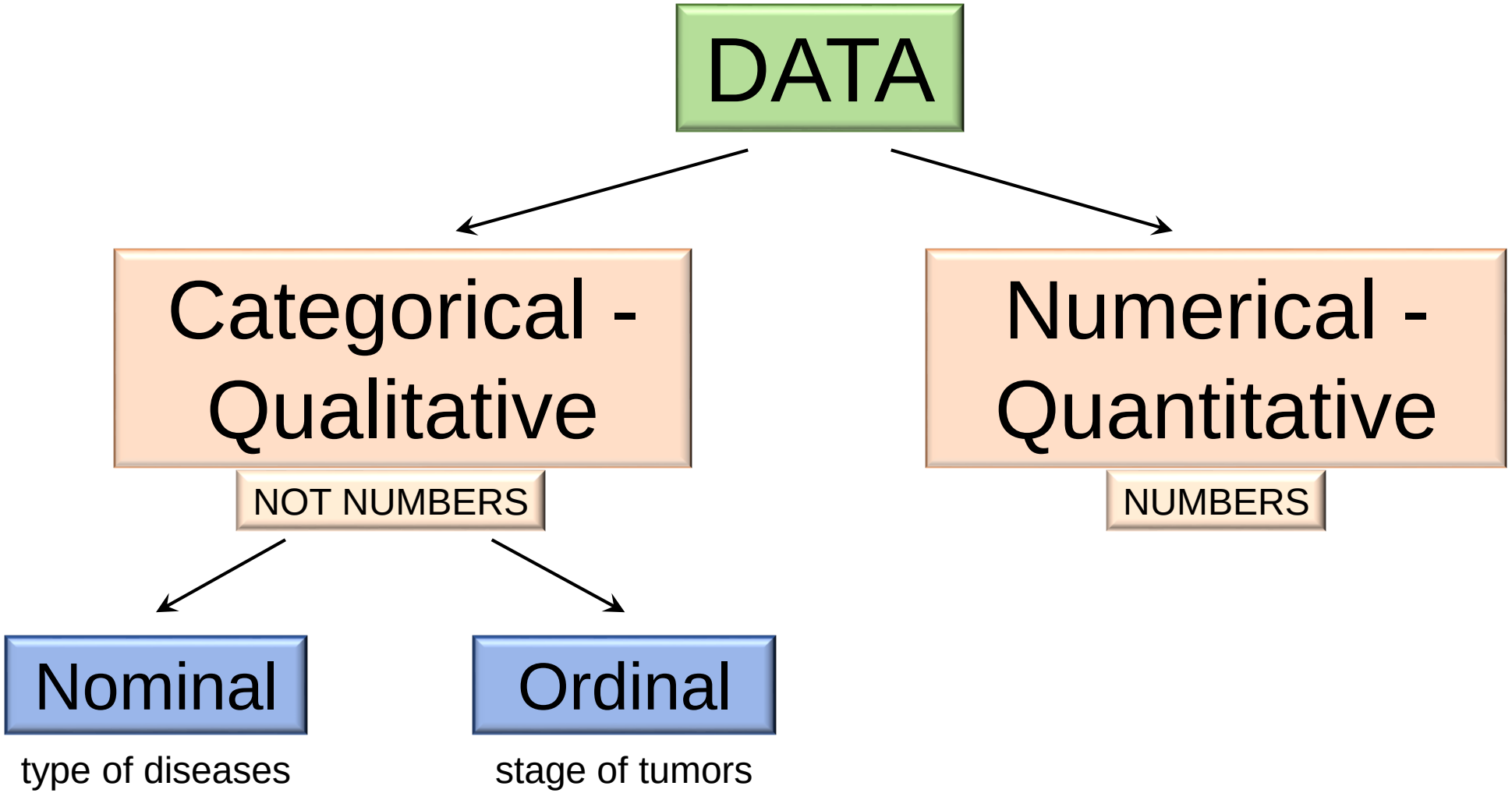
Definition of data

- Collection of information
- Understanding the nature of data is the most **fundamental part**

Sources of data



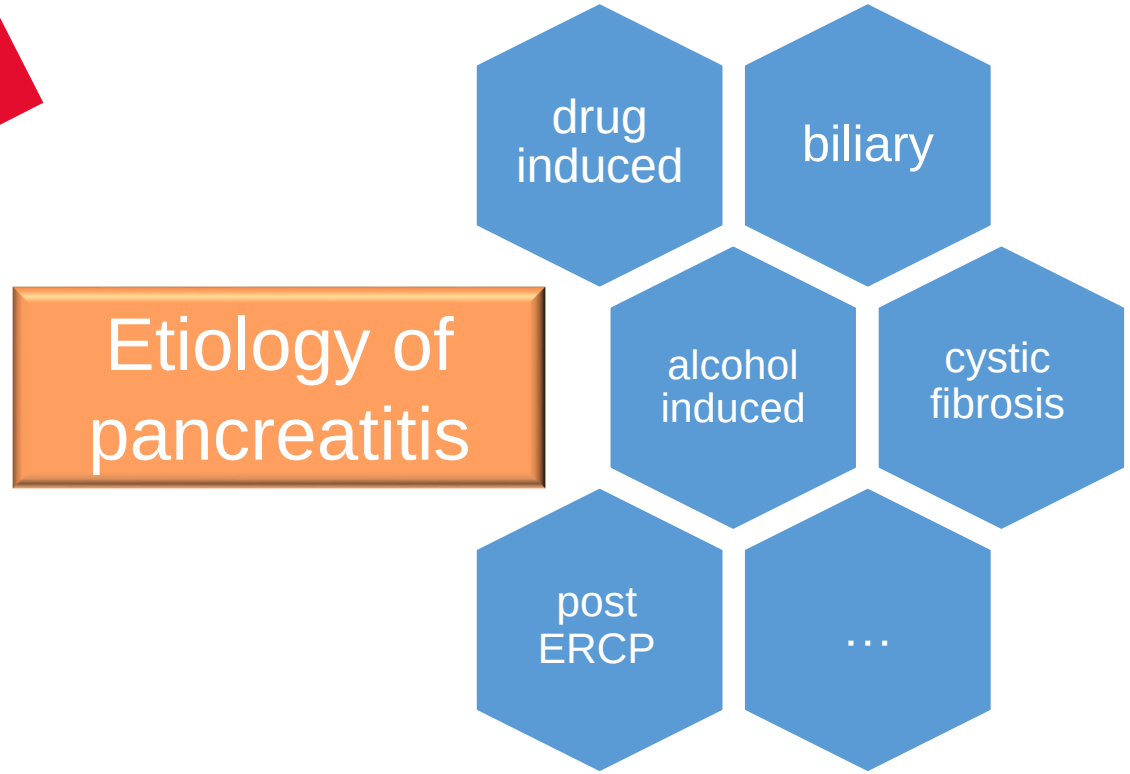
Data types


DATA
Categorical - Qualitative
NOT NUMBERS
Numerical - Quantitative
NUMBERS
Nominal
type of diseases
Ordinal
stage of tumors

Categorical data - examples

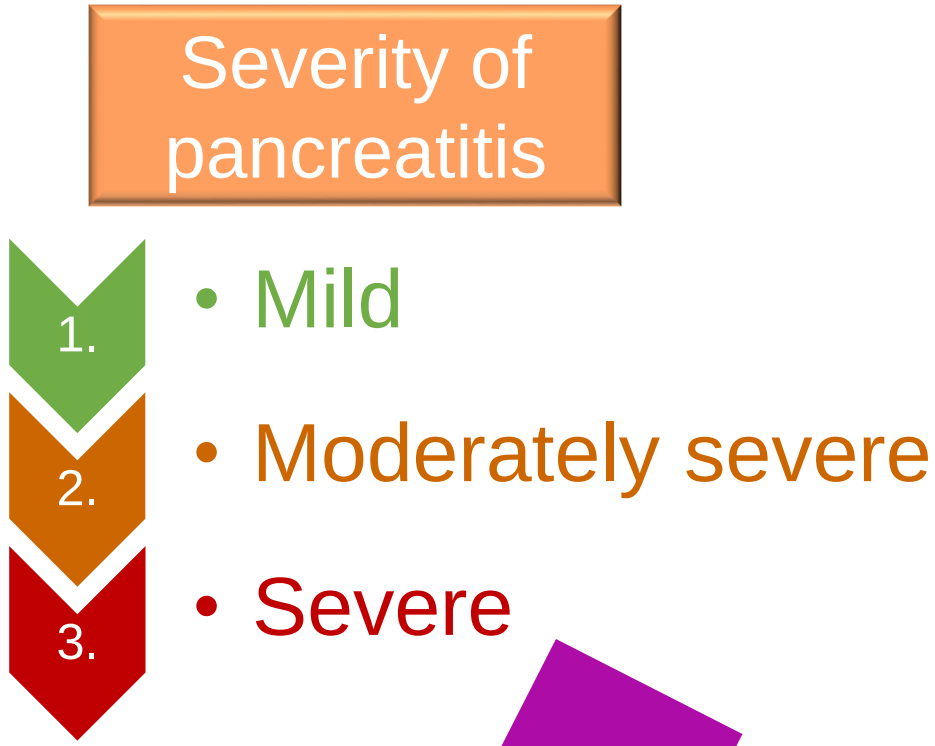
Nominal data

categories without order or direction



Ordinal data

categories with rank or order

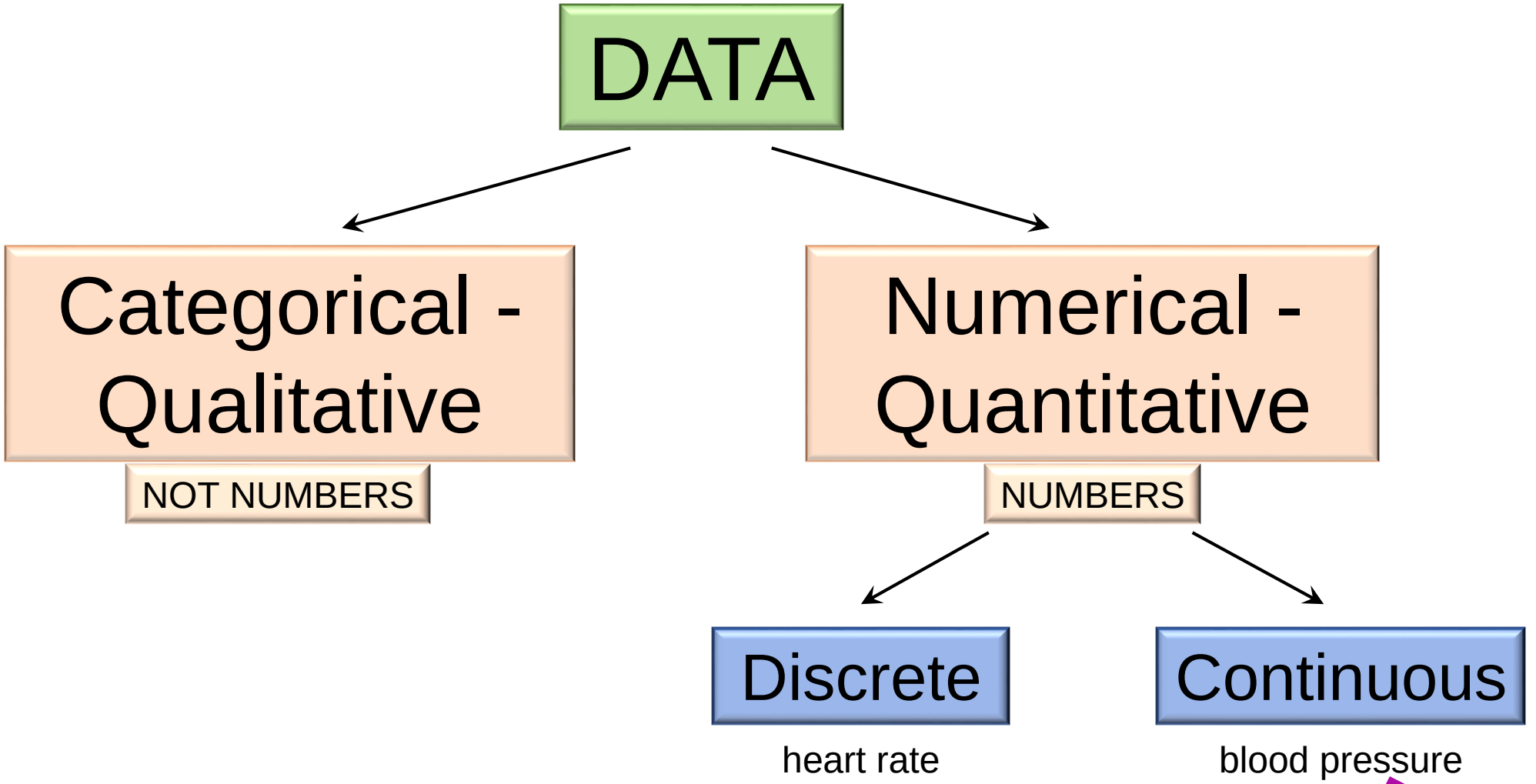


Categorical data collection

First Author	Year of publication	Gender	
		Female	Male
Abrar-Ahmad	2014	21	7
Ben-Skowronek	2013	240	221
Betterle	2001	165	82
Choudhuri	2005	34	7
Cruz	2007	203	51
Handa	2003	357	268
Horie	2012	121	76
Karagüzel	2008	28	29
Karavanaki	2009	69	15
Kondonouri	2002	8951	8798
Renzullo	2013	95	20

First Author	Year of publication	Result after irrigation	
		Positive	Negative
Ercan	2004	3	12
Kuruvilla	1998	5	5
Rôças	2016	10	15
Vianna	2006	8	8
Xavier	2013	7	5
Zandi	2016	12	17

Data types


DATA
Categorical - Qualitative
NOT NUMBERS
Numerical - Quantitative
NUMBERS
Discrete
heart rate
Continuous
blood pressure

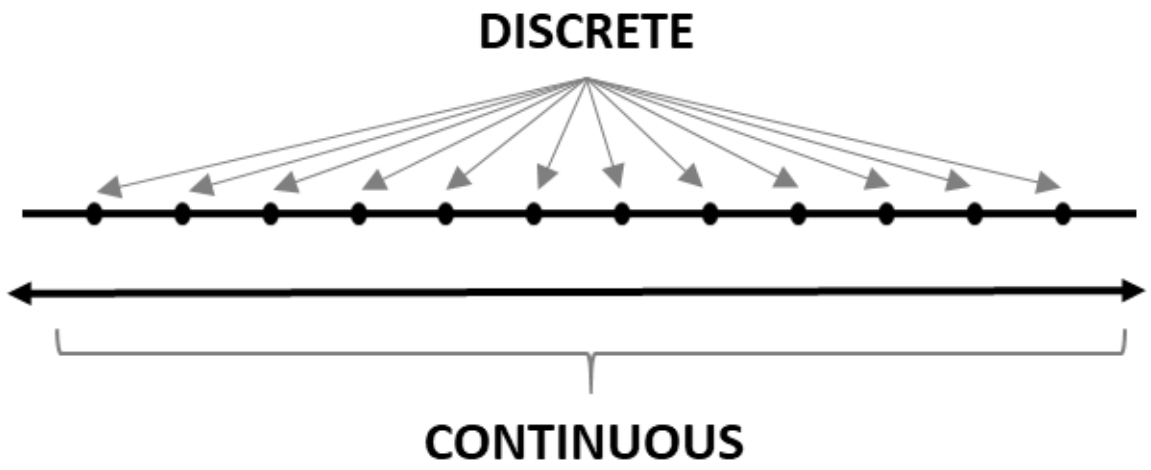
Numerical data - examples

Discrete data

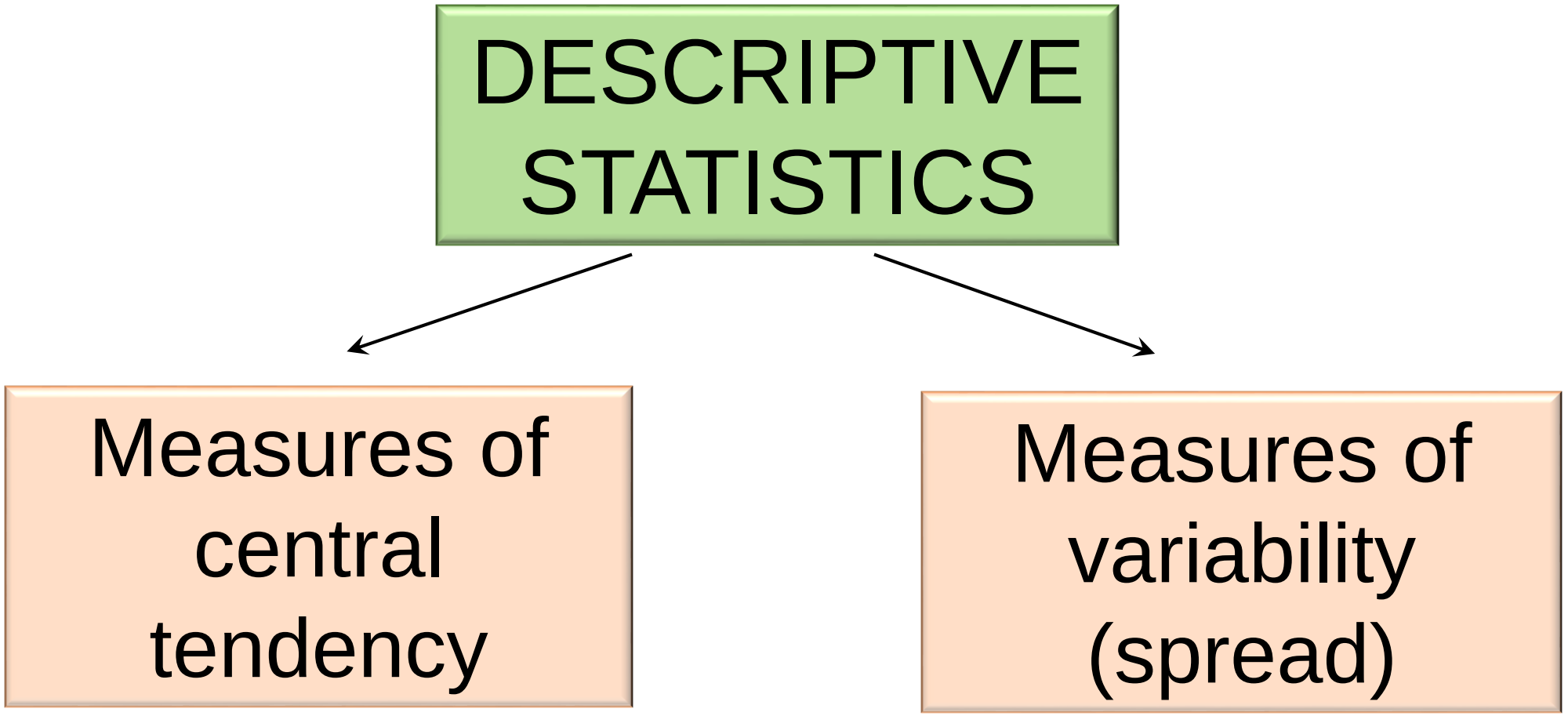
- can take only finite numbers
- for example **number of interventions** (1, 2, 3…) or **heart rate**

Continuous data

- can take any numerical values
- infinite number of opportunities
- for example **CRP level** or **WBC count**



Numerical data collection I.



Numerical data collection II.

Central tendency	Variability (spread)
mean	standard error (SE)
	standard deviation (SD)
median	range (min, max)
	quartiles (Q1, Q3, IQR)

Special cases I.

Changes of fertility parameters (for example testosterone level) using vitamin D

Study	Year	Intervention	Number of patients	Testosterone level				p-value
				Before intervention (pre)		After intervention (post)		
				Mean	SD	Mean	SD	
Soma Saha et al.	2017	Vitamin D	41	22.2	5.3	20.5	6	
Stefan Pilz et al.	2010	Vitamin D	31	10.7	3.9	13.4	4.7	0.001
Elisabeth Lerchbaum et al.	2017	Vitamin D	50	18.7	4.73	18.2	3.58	
Armin Zittermann et al.	2018	Vitamin D	71	11.2	1.92	10	1.58	0.082

Special cases II.

BAVENO VI recommendations for ruling out varices needing treatment against variceal screening endoscopy to reduce unnecessary endoscopies

Study	Year	Number of patients	HREV			
			True Positive	False Positive	False Negative	True Negative
Bellan et al.	2018	147	16	97	1	33
Cales et al.	2017	158			0	29
Llop et al.	2017	161			0	54
Maurice et al.	2016	310	13	195	2	100
Sousa et al.	2017	104	9	47	0	48

Final database

MAIN RULES

- **one type of data into one cell**
- use labels to name every column (number of patients, age…)
- raw data (not interested in percentages)
- **one measure of variability for one measure of central tendency:**
    - mean with standard error (SE) or standard deviation (SD)
    - median with range (min, max) or interquartiles (IQR)

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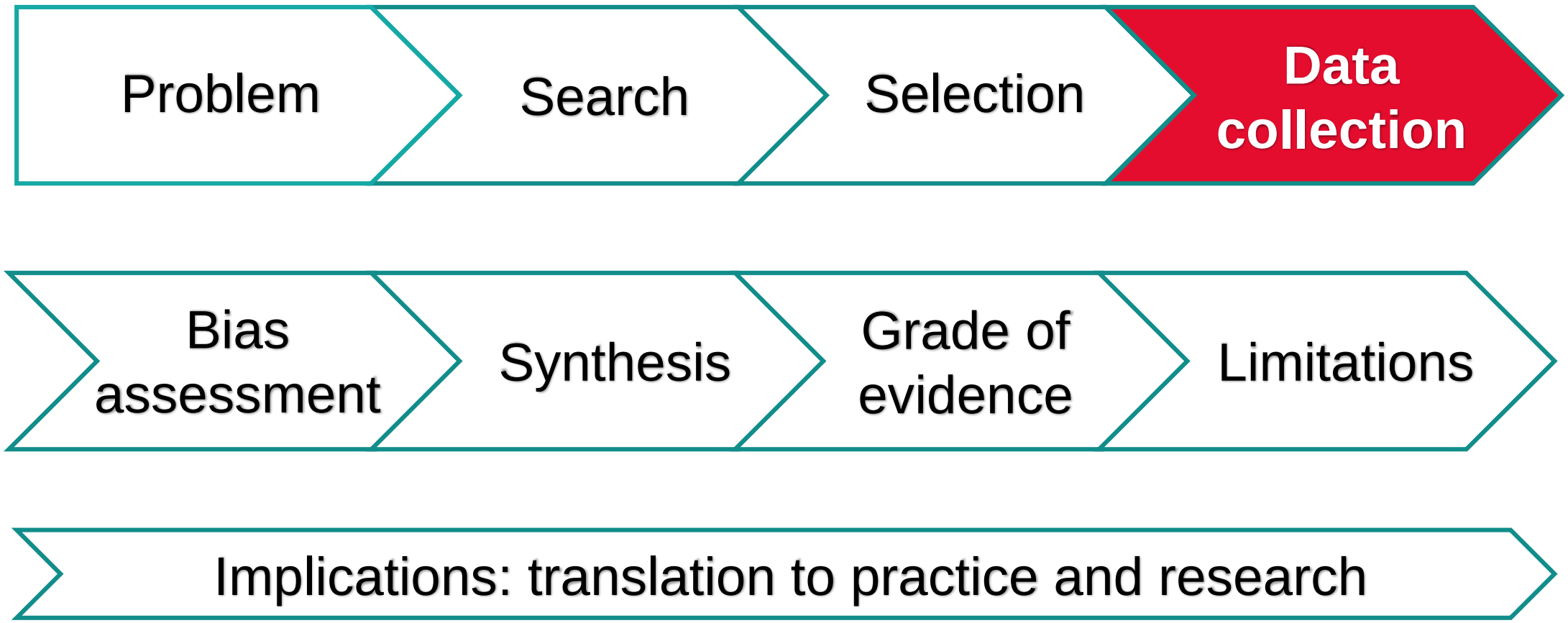
Flowchart


Problem
Search
Selection
Data collection
Bias assessment
Synthesis
Grade of evidence
Limitations
Implications: translation to practice and research

DATA EXTRACTION

Aim: to extract raw data accurately and efficiently

Yield: records eligible for data extraction

EXTRACTING DATA FROM REPORTS

Cochrane Handbook for Systematic Reviews of Interventions

Version 5.1.0
[updated March 2011]
Editors: Julian PT Higgins and Sally Green

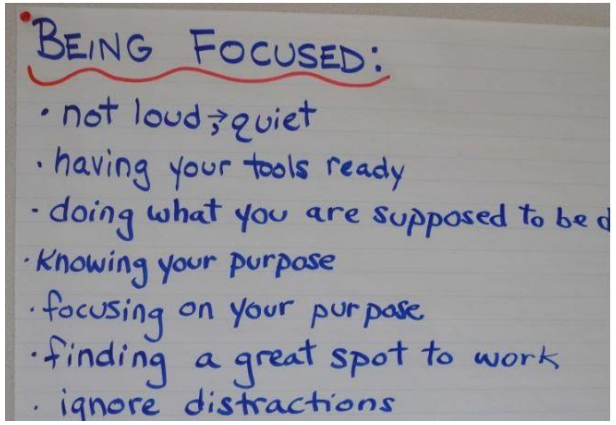
Part 2, Chapter 7, Subchapter 7.6

URL:

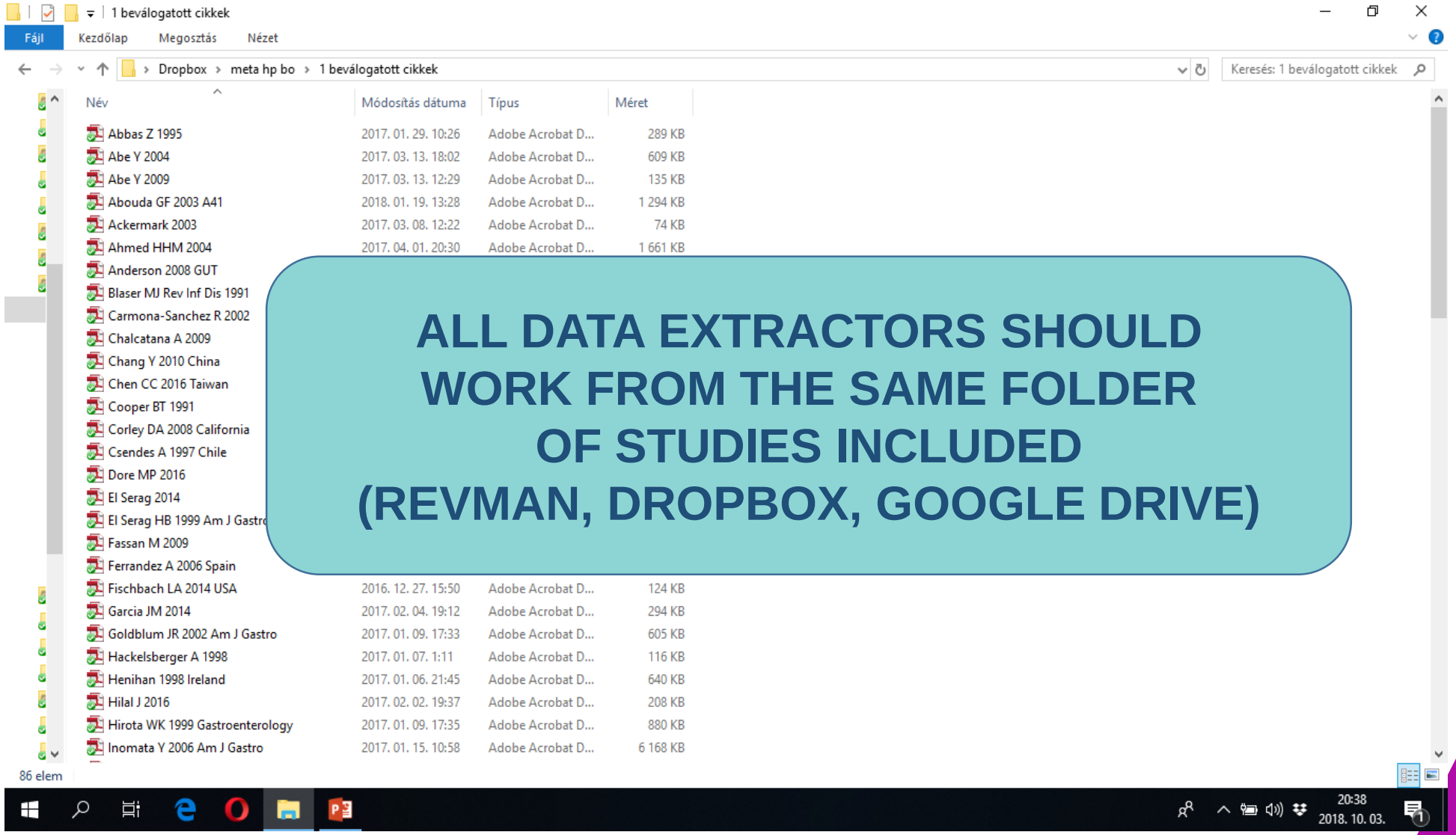
https://handbook-5-1.cochrane.org/chapter_7/7_6_extracting_data_from_reports.htm

INTRODUCTION

- In meta-analyses, the primary sources of information are published reports of studies, usually **journal articles**.
- One of **the most important and time-consuming** part of a meta-analysis is data extraction.
- The **data collection form .xls table** needs to be designed with data extraction in mind.



INTRODUCTION



ALL DATA EXTRACTORS SHOULD WORK FROM THE SAME FOLDER OF STUDIES INCLUDED (REVMAN, DROPBOX, GOOGLE DRIVE)

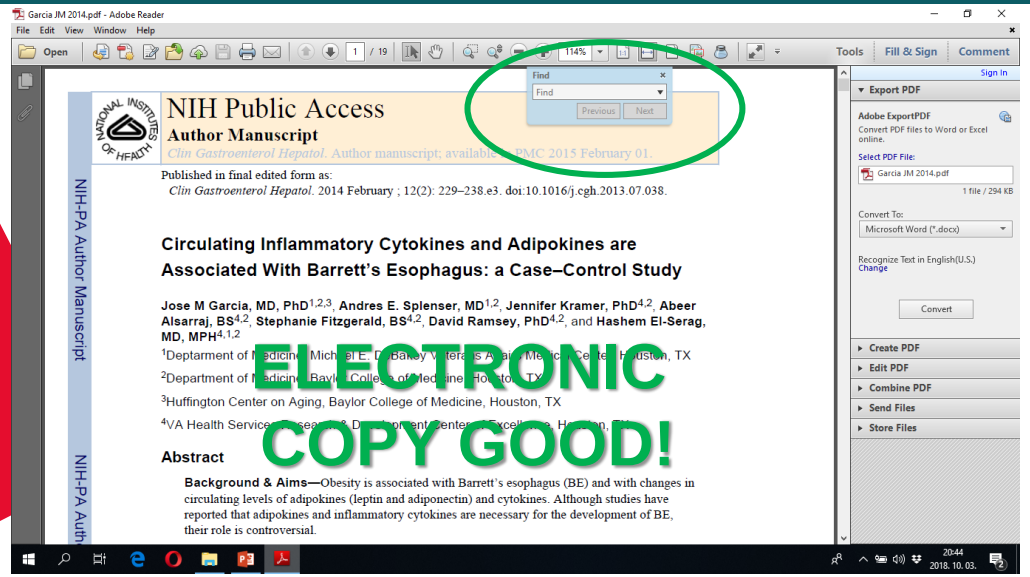
INTRODUCTION

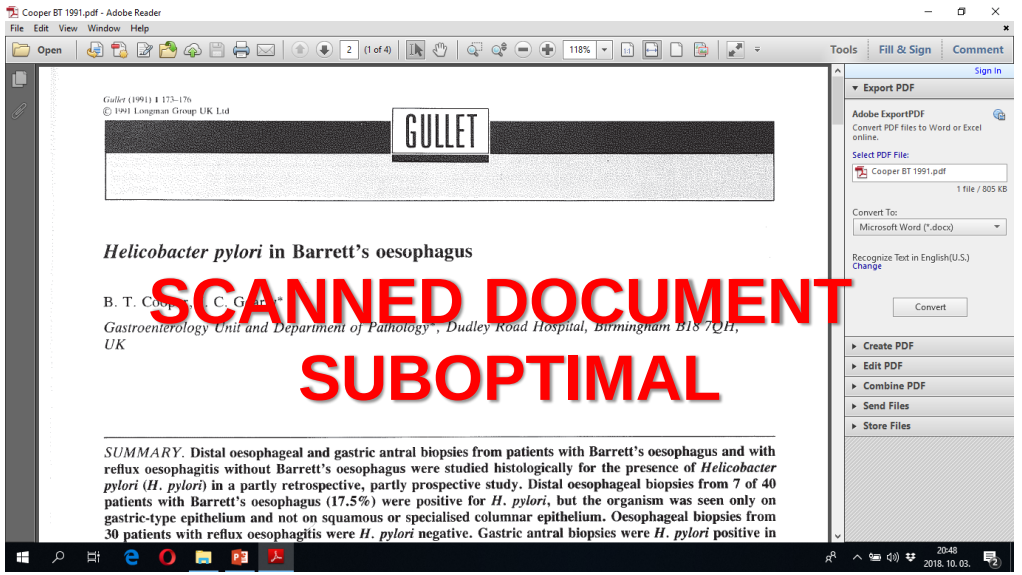
- **Electronic searches** for text can provide a useful aid to locating information within a report, for example using search facilities in PDF viewers.

- **Text searching should not be considered a replacement for reading the report.**

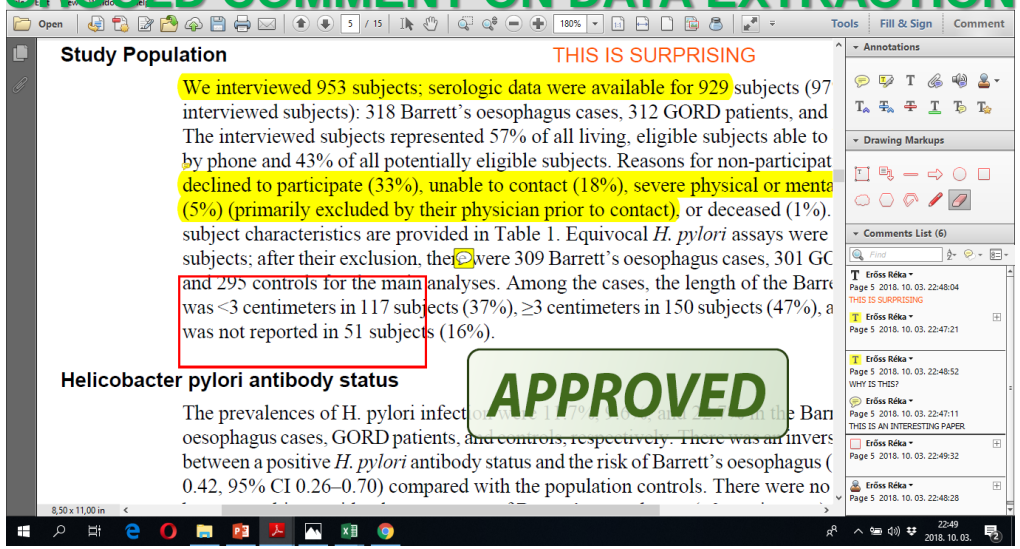
INTRODUCTION

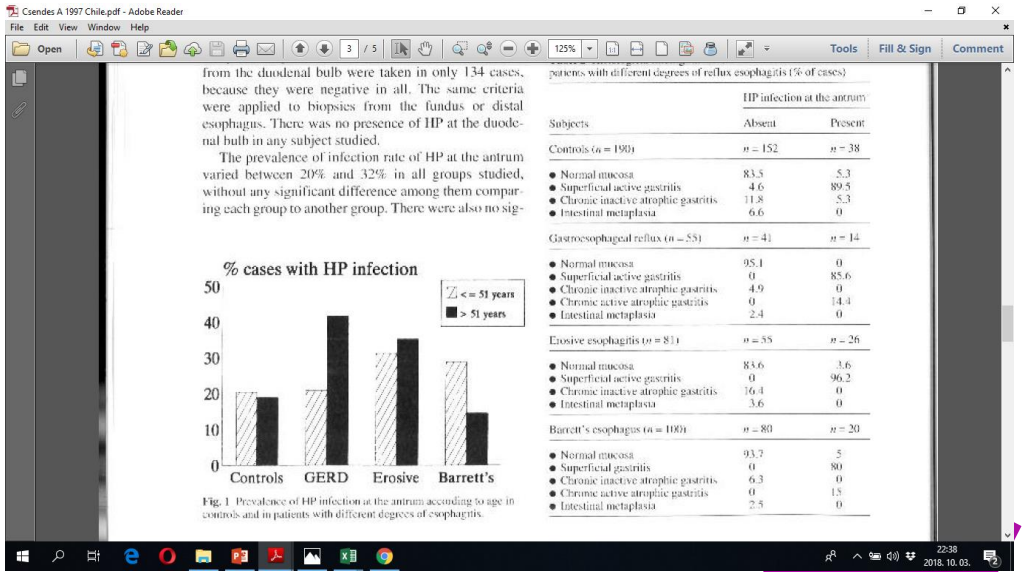
TRANSLATIONAL MEDICINE





SHOULD COMMENT ON DATA EXTRACTION





WHO SHOULD EXTRACT DATA?

- It is strongly recommended that **more than one person extract data** from every report (to minimize errors and reduce potential biases).
- Information that is **critical** to the interpretation should be **extracted independently by at least two people**.
- It is desirable that data extractors are from **complementary disciplines.**
- It is important that everyone involved in data extraction has **practice using the form.**
- If the form was designed by someone else, the data extractor **receives appropriate training.**

Important information

WHO SHOULD EXTRACT DATA?

TRANSLATIONAL MEDICINE

Carmona-Sanchez R 2002.pdf - Adobe Reader

sin regurgitaciones ni esofagitis, lo que no mostró diferencia significativa entre los grupos (65% casos *vs.* 66% controles, p = 0.98, RR 1.00 [IC 95% 0.81-1.24]).

Al analizar la relación entre el grado de esofagitis y la prevalencia de infección por Hp se observó que la bacteria fue detectada en 91 de 143 pacientes con esofagitis leve (grados A-B de Los Angeles), en 41 de los 59 pacientes con esofagitis grave (grados C-D) y en 15 de los 24 con esófago de Barrett. Así, la proporción de pacientes infectados por la bacteria fue similar entre los diferentes estadios de gravedad de la esofagitis (grado A-B, 64%; grado C-D, 69%; Barrett, 63%; p = NS) como se muestra en la *figura 1*.

un estudio de prevalencia h
ción por Hp puede causar E

La atención de la mayor p
se ha centrado en el potenci
contra el desarrollo de ERGE
favor de dicho papel protecto
gitis luego de su erradicación
lógicos[14,16,21,22,26,27] han demos
entre ambos padecimientos y
ción por Hp es un factor prot

En contraste con estos res
los estudios epidemiológicos
no han encontrado relación al

Corley DA 2008 California.pdf - Adobe Reader

Study Population

We interviewed 953 subjects; serologic data were available for 929 subjects (97% of interviewed subjects): 318 Barrett's oesophagus cases, 312 GORD patients, and 299 controls. The interviewed subjects represented 57% of all living, eligible subjects able to be contacted by phone and 43% of all potentially eligible subjects. Reasons for non-participation included: declined to participate (33%), unable to contact (18%), severe physical or mental disorders (5%) (primarily excluded by their physician prior to contact), or deceased (1%). The general subject characteristics are provided in Table 1. Equivocal *H. pylori* assays were found in 24 subjects; after their exclusion, there were 309 Barrett's oesophagus cases, 301 GORD patients, and 295 controls for the main analyses. Among the cases, the length of the Barrett's segment was <3 centimeters in 117 subjects (37%), ≥3 centimeters in 150 subjects (47%), and the length was not reported in 51 subjects (16%).

Helicobacter pylori antibody status

The prevalences of H. pylori infection were 11.7%, 9.6%, and 22.7% in the Barrett's oesophagus cases, GORD patients, and controls, respectively. There was an inverse association between a positive *H. pylori* antibody status and the risk of Barrett's oesophagus (Table 2) (OR 0.42, 95% CI 0.26–0.70) compared with the population controls. There were no differences

CRITICAL DATA CAN BE GIVEN IN VERY DIFFERENT WAYS

Abouda

151 **PREVALENCE OF *HELICOBACTER PYLORI* VIRULENCE FACTORS IN PATIENTS WITH REFLUX OESOPHAGITIS AND BARRETT'S OESOPHAGUS**

G.F. Abouda, J.C. Cotton, J.F. Dillon. *Department of Molecular and Cellular Pathology, Ninewells Hospital, University of Dundee, UK*

Background: *Helicobacter pylori* (Hp) is a microaerophilic spiral rod, which is associated with gastritis, duodenitis and gastric carcinoma. Its role in GORD is unclear, recent studies have suggested a protective role of a virulent strain against the development of GORD.

Aim of work: To evaluate the prevalence of this virulence factor in

Method: 67 patients with reflux oesophagitis, 60 patients with Barrett's oesophagus, and 25 non reflux patients (control group) underwent upper GIT endoscopy. 4 biopsies were taken from each

1 from the antrum. Clo test, ELISA for Hp IgG, Western Blot for Cag, Vac, and HSP 60 of Hp, and histopathological grading of the severity, was performed on each patient.

Results: 21(31.3%) of reflux patients were CLO positive, 18(30%) of Barrett's patients were Clo positive, and 5 (20%) of the control group were CLO positive. The Cag and Vac strain was +ve in 22

25 (37%) patients with reflux oesophagitis and 19 patients with Barrett's. 4 patients exhibited high grade dysplasia, and were negative for all strains except HSP60. IgG ELISA was positive in 35 (52.2%) of

greater for SSB than for segments >3 ≤6cm in length, risk is for length >6cm (Pearson χ^2 p=0.02). Whilst d tors have previously shown an influence on the risks of there is little correlation with the length of segment wh

153 **NOVEL MECHANISM OF NITROSATIVE S DIETARY NITRATE RELEVANT TO GASTRO JUNCTION CANCER**

K. Iijima[1], J. Grant, K. McElroy, S. Anderson, V. Fyfe, S. ton, K.E.L. McColl. [1]*Dept of Gastroenterology, Tohoku Un School of Medicine, Sendai, Miyagi, Japan; Dept Therapeutics, Western Infirmary, Glasgow, UK*

Abstract: High concentrations of nitric oxide are g gastro-oesophageal (GO) junction due to the reduc nitrite to nitric oxide by acidic gastric juice containin Salivary nitrite is derived from the enterosalivary dietary nitrate.

Aims: To determine whether nitric oxide generat way will exert nitrosative stress on the adjacent epith

Methods: A benchtop model was constructed chemistry occurring at the GO junction and incorporat compartment maintained at pH 7.4 separated from thin hydrophobic barrier. The secondary amine added to each compartment and *N*-nitrosomorpholine min measured.

Table 2. Demographic and Clinical Characteristics of Patients With Different Grades of Erosive Esophagitis and Barrett's Esophagus

Characteristic	Grade A (1)	Grade B (2)	Grade C (3)	Grade D (4)	Barrett's Esophagus (5)	*P* value
No. of patients	40	40	40	40	33	
Age of men, mean (SD), years	51.23 (14.2)	49.78 (12.9)	53.39 (9.4)	58.48 (13.3)	63.0 (11.25)	$P_{2\text{ vs. }4,5}<0.01$ $P_{5\text{ vs. }1,3}<0.05$
Age of women, mean (SD), years	55.75 (11.5)	61.35 (10.2)	62.09 (12.0)	55.8 (11.62)	62.0 (13.24)	$P_{2\text{ vs. }3,5}<0.05$
Age of all patients, mean (SD), years	54.98 (12.3)	54.7 (13.05)	56.21 (10.9)	57.36 (12.6)	62.67 (11.8)	$P_{5\text{ vs. }1,2,3}<0.05$
BMI, mean (SD), kg/m²	27.54 (3.52)	28.67 (3.87)	28.26 (2.67)	28.88 (3.06)	29.33 (3.75)	$P_{1\text{ vs. }5}=0.039$
Smokers, n (%)	17 (42.5)	15 (37.5)	18 (52.9)	19 (52.8)	18 (54.5)	>0.05
Hiatal hernia, n (%)	31 (77.5)	33 (82.5)	40 (100)	38 (95)	33 (100)	*P* <0.05
Positive for *H. pylori*, n (%)	31 (77.5)	26 (65)	19 (47.5)	18 (45)	12 (36.7)	$P_{1,2\text{ vs. }3,4,5}<0.01$

Medicina (Kaunas) 2011;47(8)

WHO SHOULD EXTRACT DATA?

- One study observed that independent data extraction by two authors resulted in **fewer errors** than a data extraction by a single author followed by verification by a second (Buscemi 2006).

- A **high prevalence of data extraction errors** (**errors in 20 out of 34 reviews**) were observed (Jones 2005).

- A further study found that a minimum of **seven out of 27** reviews had **substantial errors** (Gøtzsche 2007).

PREPARING FOR DATA EXTRACTION

DON’T DO IT!

DESIGNING THE DATA EXTRACTION TABLE

- **A STATISTICIAN MUST**
- **ALL DATA EXTRACTORS AND REVIEWERS SHOULD**

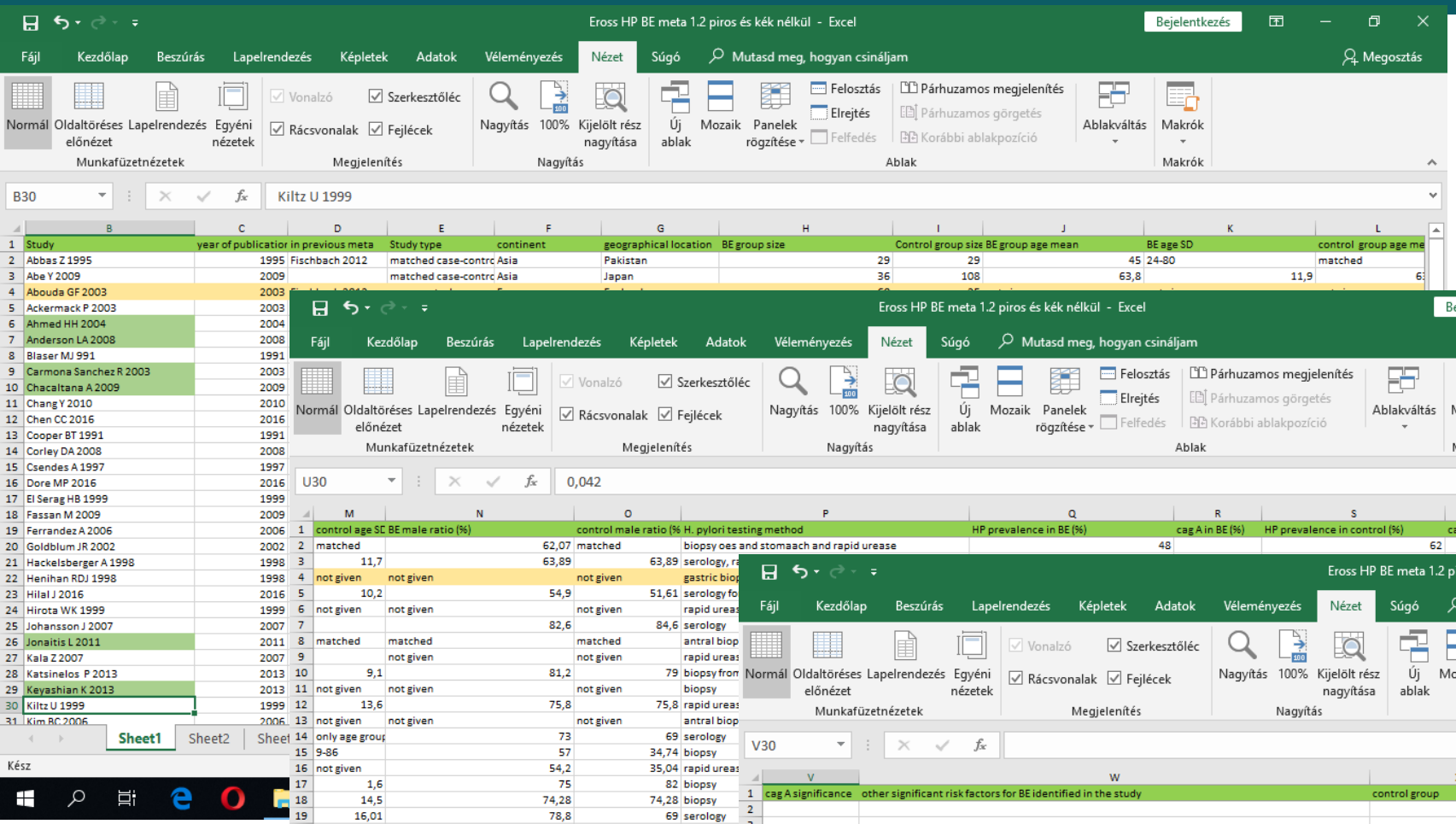
BE INVOLVED IN THE DESIGN OF THE DATA EXTRACTION SHEET.

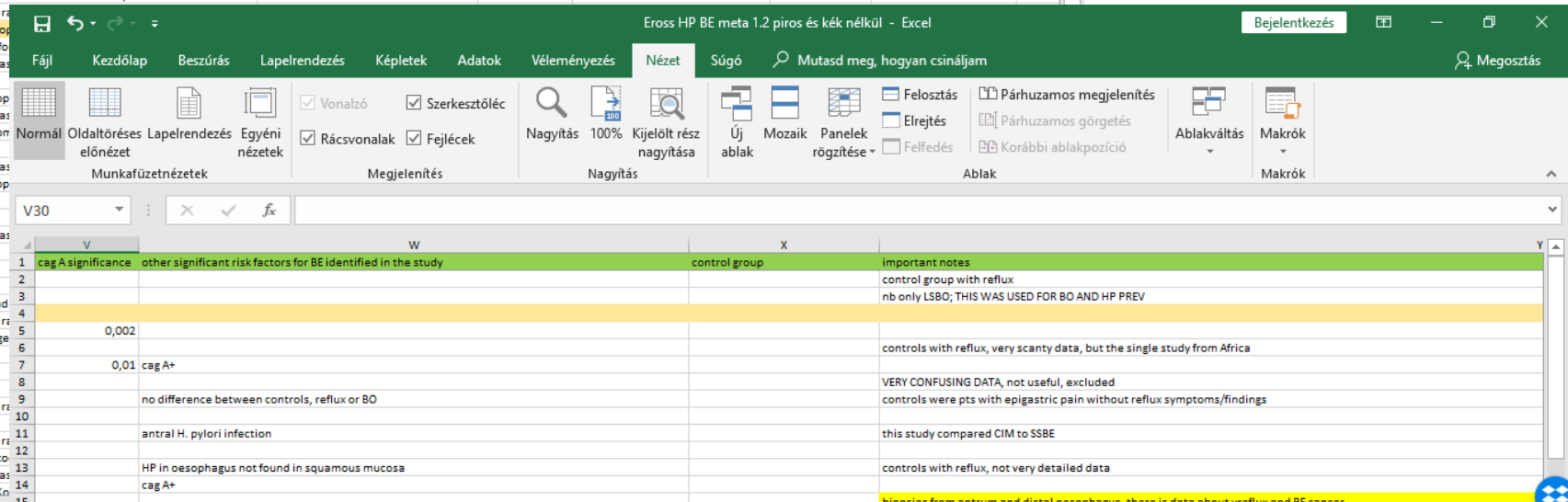
PREPARING FOR DATA EXTRACTION

TRANSLATIONAL MEDICINE

COLUMNS:
CHARACTERISTICS OF STUDIES

ROWS:
STUDIES INCLUDED





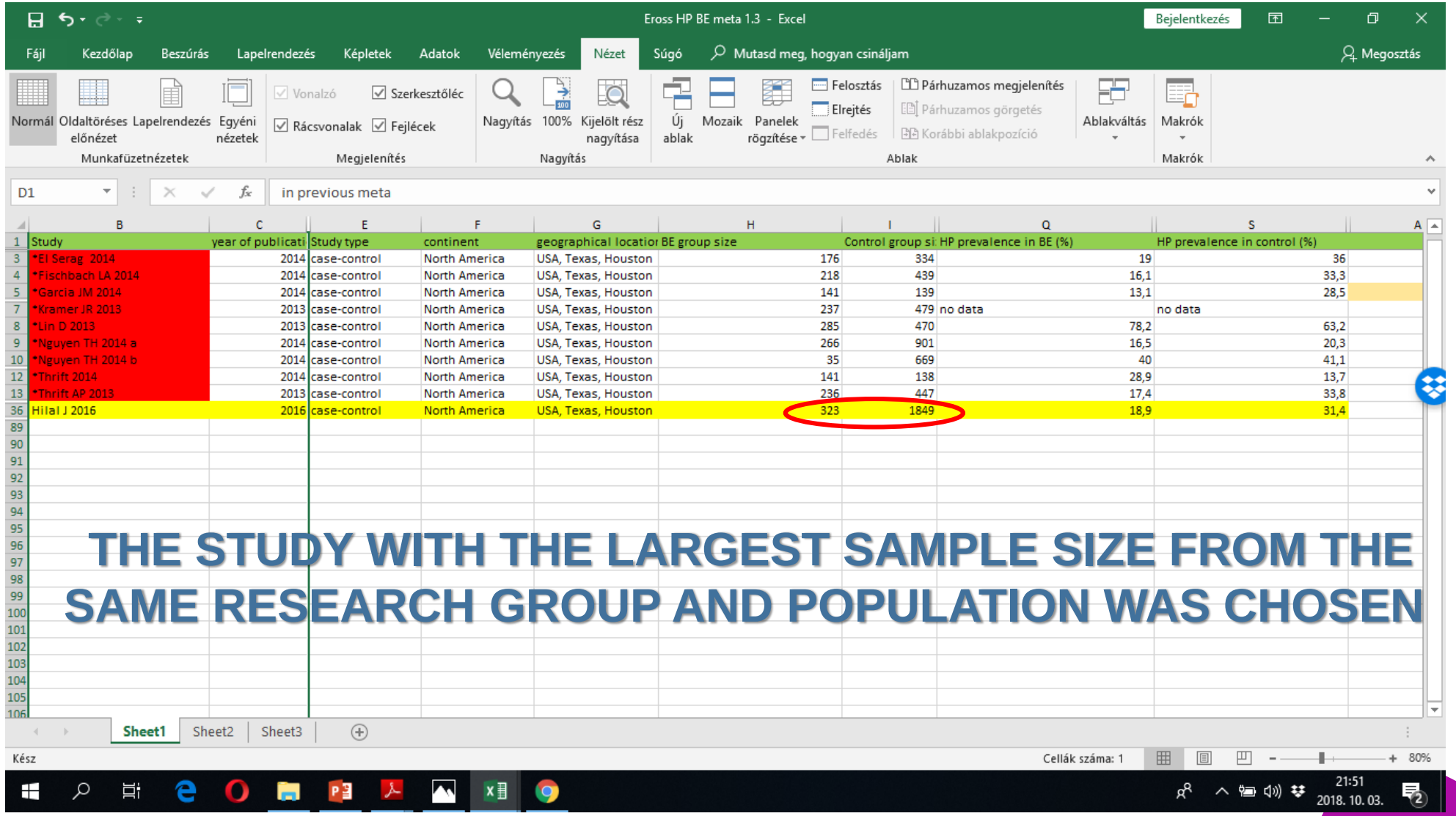
EXTRACTING DATA FROM MULTIPLE REPORTS OF THE SAME STUDY

- Studies are frequently reported in **more than one publication** (Tramèr 1997, von Elm 2004).

- Review authors will need to decide between two strategies:
  - Extract data from each report separately, then combine information across multiple data collection forms.
  - Extract data from all reports directly into a single data collection form.

EXTRACTING DATA FROM MULTIPLE REPORTS OF THE SAME STUDY

TRANSLATIONAL MEDICINE



THE STUDY WITH THE LARGEST SAMPLE SIZE FROM THE SAME RESEARCH GROUP AND POPULATION WAS CHOSEN

IMPORTANCE OF DISAGREEMENT

- When more than one author extracts data from the same reports, there is **potential for disagreement.**
- An explicit **procedure or decision rule** should be identified in the protocol for identifying and resolving disagreements.
- Any disagreements that cannot be resolved should be addressed by **contacting the study authors**; if this is unsuccessful, the disagreement **should be reported** in the review.

COMMON MISTAKES

- Insufficient, inaccurate data are extracted.
- Data extraction form is not planned and piloted well.
- Data extraction needs to be done multiple times.

TAKE HOME MESSAGE

- A statistician must be involved in the planning!
- Plan and pilot the data extraction sheet and process!
- Do it in pairs!
- Identify and resolve disagreements!

Schedule for today

1.	Erőss Bálint	**Voting,** The role of meta-analyses in translational medicine
2.	Mikó Alexandra	Questions and hypotheses
3.	Márta Katalin	Meta-analysis guidelines
4.	Solymár Margit	Protocols and reporting bias
5.	Pécsi Dániel	Systematic search **Break**
6.	Balaskó Márta	Selection of records
7.	Hanák Lilla	Data collection - statistical aspects
8.	Erőss Bálint	Data collection - practical aspects
9.	Szakács Zsolt	Bias **Break**
10.	Soós Alexandra	Statistics of meta-analyses
11.	Szakács Zsolt	Grade of evidence
12.	Szakács Zsolt	Limitations and implications
13.	Szakács Zsolt	Future perspectives, **voting**

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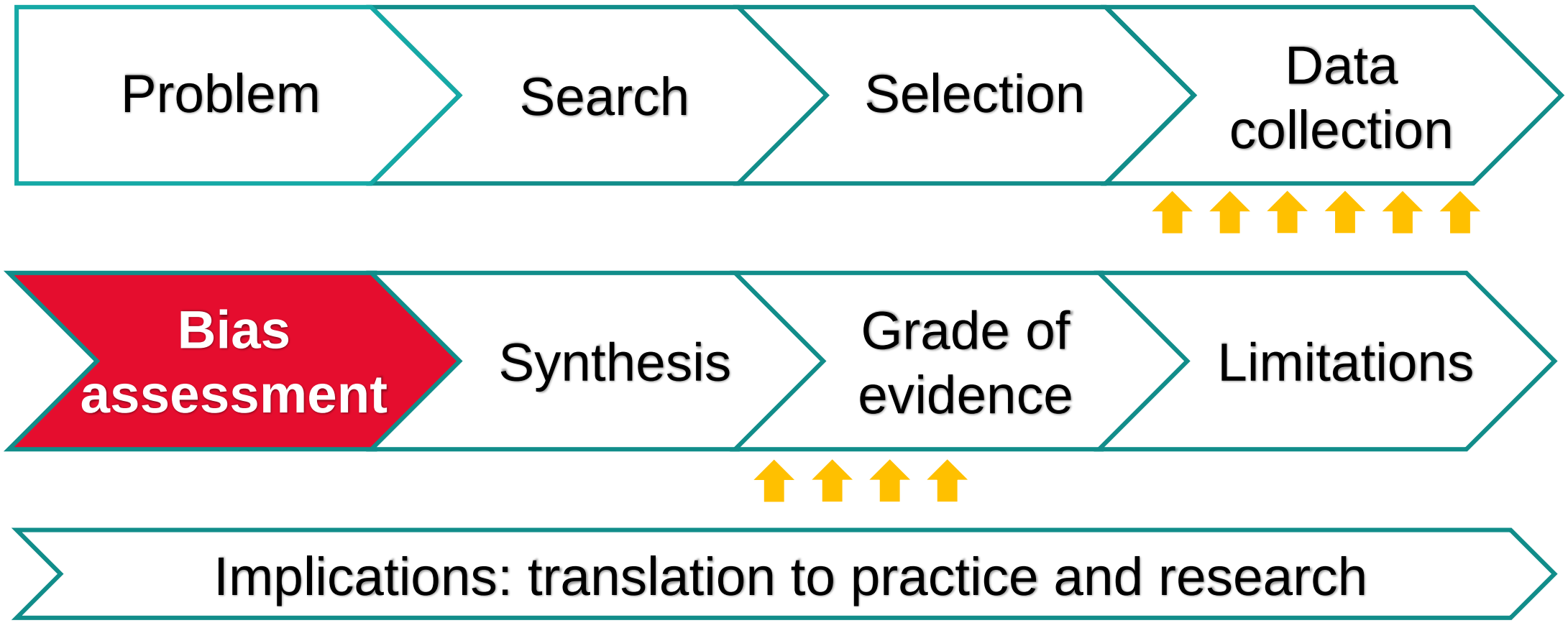
Break

Break

Flowchart

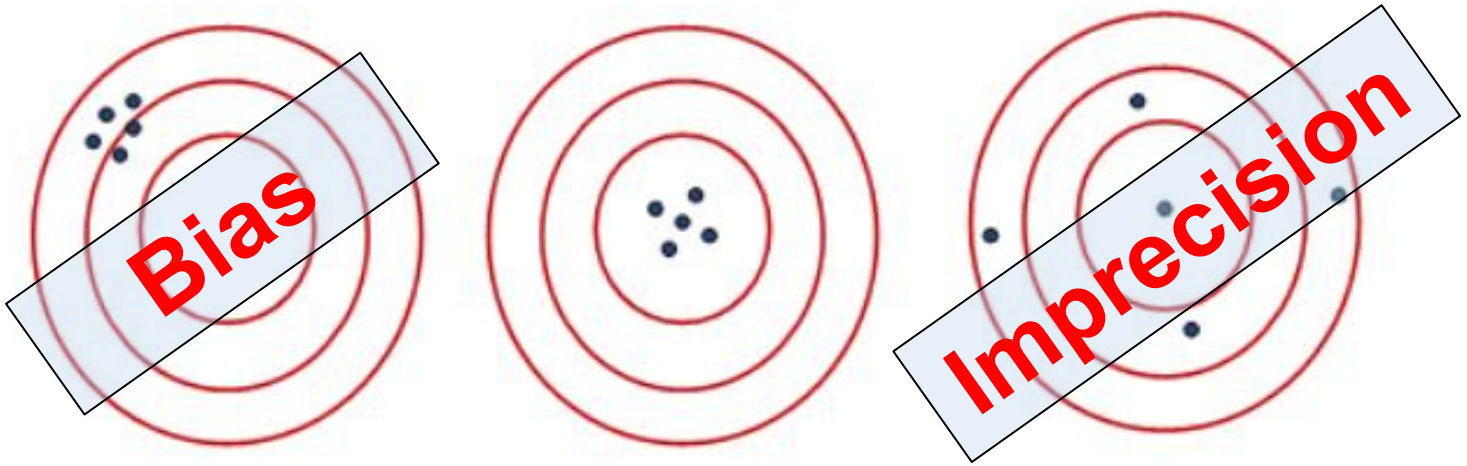

Problem
Search
Selection
Data collection
Bias assessment
Synthesis
Grade of evidence
Limitations
Implications: translation to practice and research

Risk of bias assessment

Aim: to explore potential factors in included studies leading to false associatons

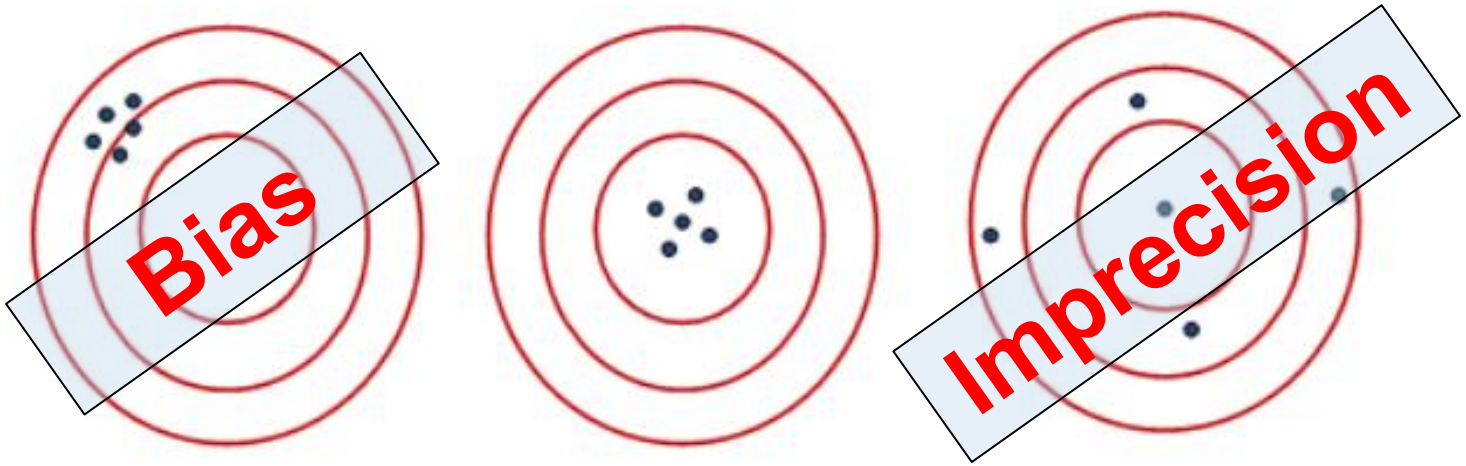
Benefit: the internal validity of the conclusions can be secured

Errors in epidemiological studies



Valid?	✗	✓	✓
Precise?	✓	✓	✗

Errors in epidemiological studies



Systematic error

Sample size ↑ Risk –

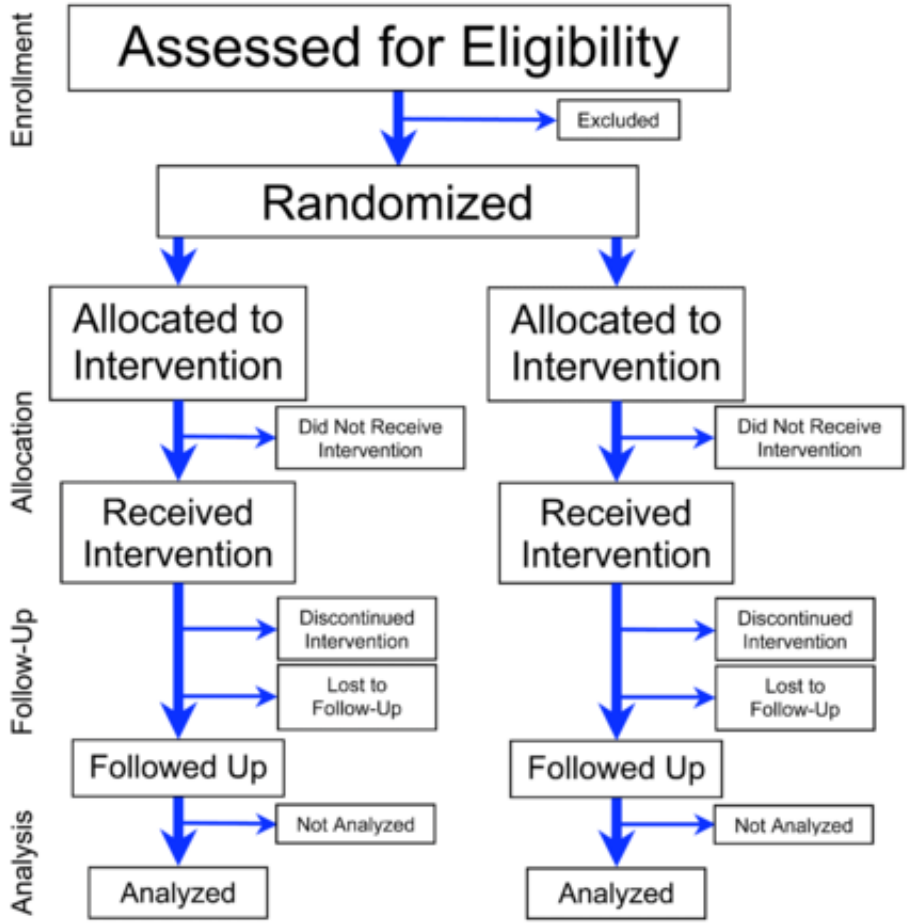
Random error

Sample size ↑ Risk ↓

What is bias?

Bias is the deviation from the truth

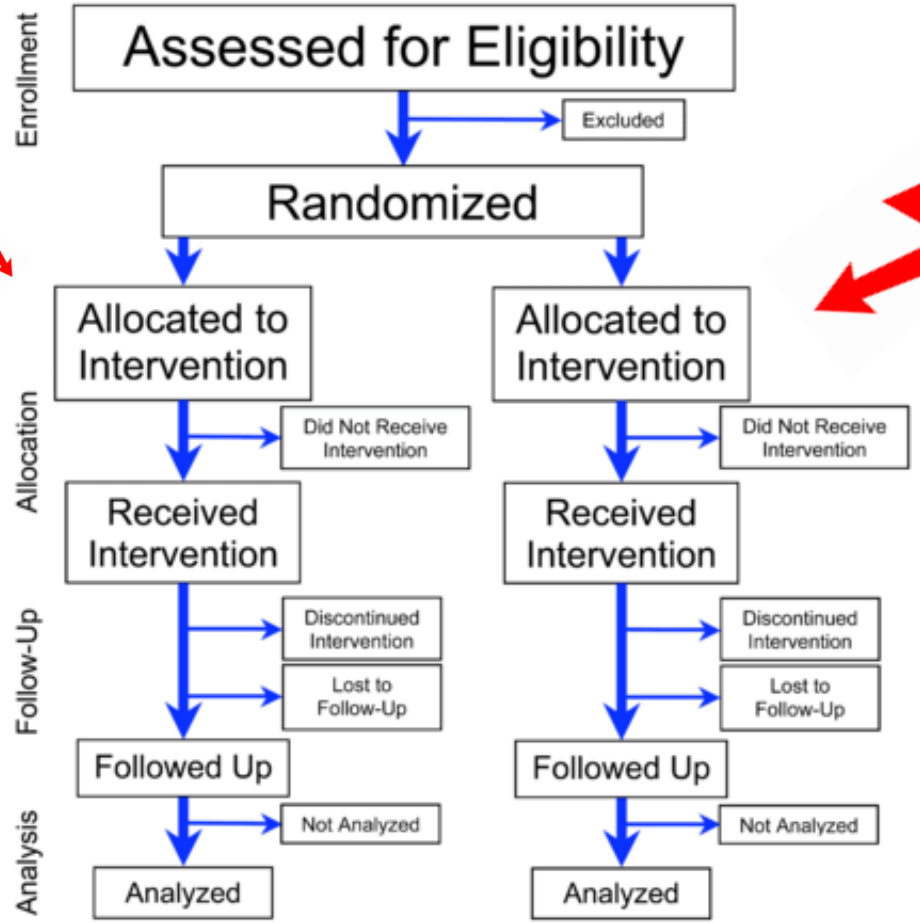
An ideal setting…



Only the treatment is different

Difference in outcomes is caused by treatment

A biased setting…



Not only the treatment is different

Difference in outcomes may be caused by treatment or other factors

What is bias?

Bias is the deviation from the truth

- **Overestimation**
- **Underestimation**

False negative/positive conclusions

Example for overestimation of the effect

Let's compare a new drug to the old one…

Design: experimental, parallel (2 arms), non-randomized.

The new drug reduces mortality by 20% (95% CI: 15-25%).

But…

Mean age of groups are 74±8 y (old drug) and 61±2 y (new drug) (p<0.001)

Biased!

Where should we seek for biases?

In the studies included in the analysis!

Threaten internal validity!

What type of biases should we seek for?

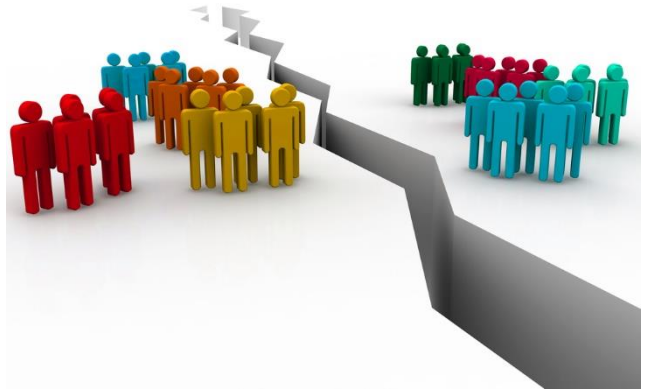
Terminology: vague

- **Selection bias**
- **Performance bias**
- **Detection bias**
- **Attrition bias**
- **Reporting bias**

Types of bias

Selection bias

Definition: differences between baseline characteristics of groups compared



Examples for selection bias

Let's compare a new drug to the old one…

Design: experimental, parallel (2 arms), non-randomized.

The new drug reduces mortality by 20% (95% CI: 15-25%).

But…

Mean age of groups are 74±8 y (old drug) and 61±2 y (new drug) (p<0.001)

Others: gender, stage of disease, severity of disease, comorbidities…

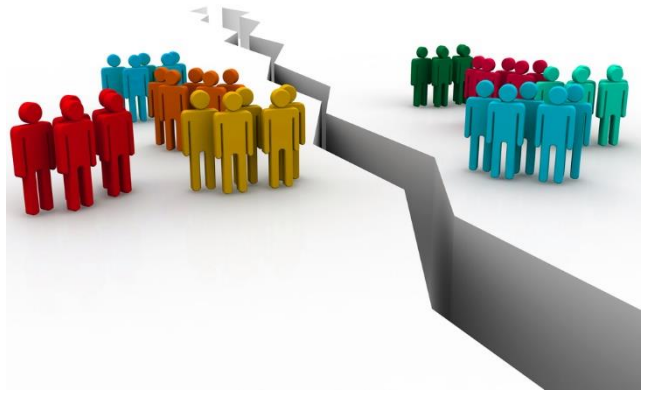
Types of bias

Selection bias

Definition: differences between baseline characteristics of groups compared

How can you prevent it from occurring?

Randomization



What to assess?

Random sequence generation

Allocation concealment

Types of bias

Performance bias

Definition: differences in care or exposure to factors (other than the intervention) between groups

Examples for performance bias

Let's compare a new drug to the old one…

Design: experimental, parallel (2 arms), randomized, open-label.

The new drug reduces thrombosis rate by 20% (95% CI: 15-25%).

But doctors do not trust the new drug…

20% of patient (old drug) and 85% of patients (new drug) were prescribed additional anticoagulants.

Any treatment distrubuting unequally between groups

Types of bias

Performance bias

Definition: differences in care or exposure to factors (other than the intervention) between groups

How can you prevent it from occurring?

Blinding

What to assess?

Blinding (participants and personnel)

Types of bias

Detection bias

Definition: differences in how outcomes were assessed between groups

Examples for detection bias

Let's compare a new drug to the old one…

Design: experimental, parallel (2 arms), randomized, open-label.

The new drug reduces pneumonia rate by 20% (95% CI: 15-25%).

But doctors do not trust the new drug…

20% of patient (old drug) and 85% of patients (new drug) were ordered chest X-ray (p<0.001)

Any diagnostic modality distrubuting unequally between groups

Types of bias

Detection bias

Definition: differences in how outcomes were determined between groups

How can you prevent it from occurring?

Blinding

What to assess?

Blinding (outcome assessment)

Types of bias

Attrition bias or follow-up bias (drop-outs)

Definition: differences in withdrawals between groups

Examples for attrition bias

Let's compare a new drug to the old one…

Design: experimental, parallel (2 arms), randomized, double-blind

The new drug reduces 1-y mortality by 20% (95% CI: 15-25%) in those completed the whole follow-up period (per protocol).

But had severe side effects in women (dysmenorrhea).

Withdrawal rate: 20% (50% women) with the old drug, 40% (90% women with the new drug (p<0.001)

In the disease: females' mortality is higher than that of males

Imbalanced drop-out

Types of bias

Attrition bias or follow-up bias (drop-outs)

Definition: differences in withdrawals between groups

How can you minimize it?

Intention-to-treat analysis (imputations)

What to assess?

Incomplete outcome data

Types of bias

Reporting bias

Definition: differences between reported and unreported findings

Odds ratios for reporting significant results:
efficacy: OR=2.4 (95%CI: 1.4-4.0)
harms: OR=4.7 (95%CI: 1.8-12.0)

Chan AW, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA*2004; 291: 2457-2465.

Examples for detection bias

Let's compare a new drug to the old one…

Design: experimental, parallel (2 arms), randomized, double-blind

Results:

- **mortality reduced by 2% (95% CI: 1.5-2.5%)**
- **organ failure rate reduced by 1.0% (95% CI: 0.8-1.2%)**
- **short-term (1-month) neurological deficit did not change**

Picking of the desired results

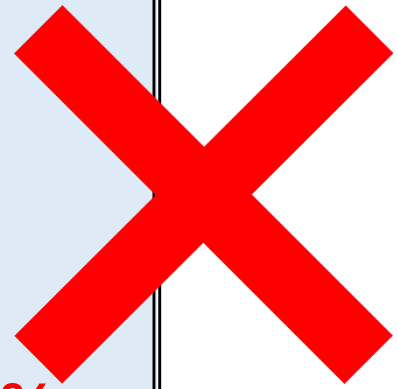
Examples for detection bias

Let's compare a new drug to the old one…

Design: experimental, parallel (2 arms), randomized, double-blind

Results:

- **mortality reduced by 2% (95% CI: 1.5-2.5%)**
- **organ failure rate reduced by 1.0% (95% CI: 0.8-1.2%)**
- **short-term (1-month) neurological deficit did not change**
- **long-term (1-year) neurological deficit increased by 40% (95% CI: 34-60%)**



Picking of the desired results

Types of bias

Reporting bias

Definition: differences between reported and unreported findings

How can you prevent it from occurring?

Complete reporting

Assessment in Cochrane Tool?

Incomplete outcome data

Tools for risk of bias assessment

Randomized	Cochrane Risk of Bias Tool
Non-randomized	
Experimental interventional	ROBINS-1
Observational interventional	Newcastle-Ottawa Scale
Diagnostic	QUADAS-2
Prognostic	QUIPS and PROBAST

Steps of risk of bias assessment

Identify the design of the included studies

Lancet Epidmioilogy Series 2002

Chose the proper RoB assessment tool

Or multiple if needed

Tailor the tool according to your needs

By the requirements of the tool

Steps of risk of bias assessment

Make a plan! (trial and error…test and modify)

Risk of bias should be assessed by two review authors in duplicate! Resolve discrepancies!

- Reaching concensus
- Third party arbitration (expert in the field)
- Committee (experts in the field)

Results of tools are non-summative!

Supplementary Appendix 10. Results of risk of bias assessment

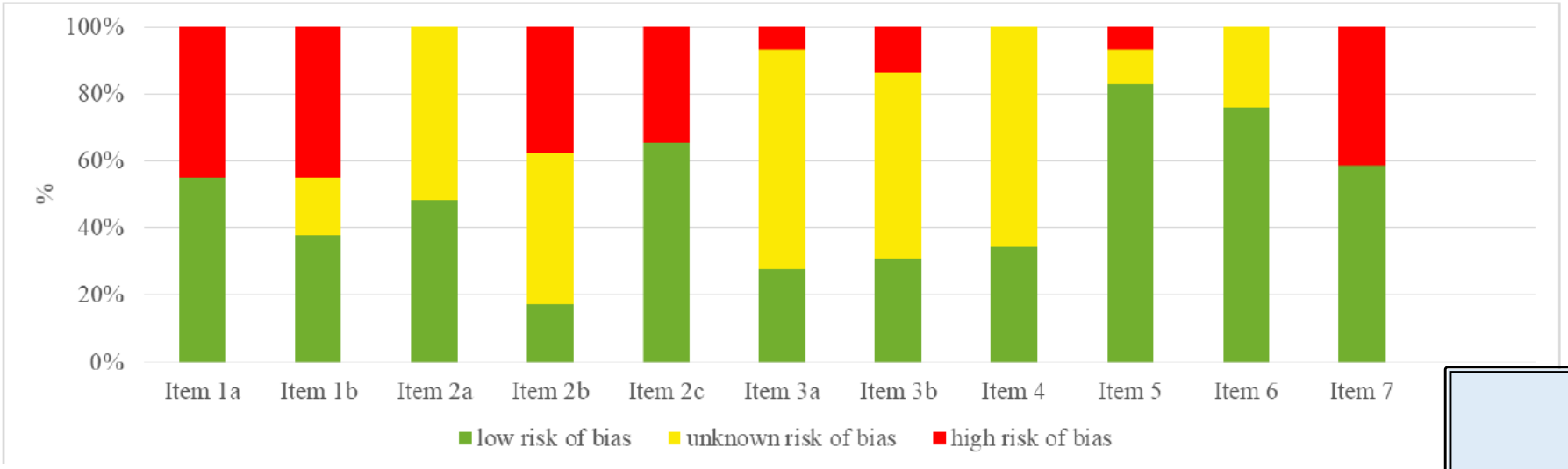
Supplementary Table 13. Quality of each included study.

	Item 1		Item 2			Item 3		Item 4	Item 5	Item 6	Item 7
	a	b	a	b	c	a	b				
Bardella 2007	✗	✗	✓	✓	✓	?	?	?	✓	✓	✗
Biagi 2014	✓	✓	?	✗	✗	?	?	?	✓	✓	✗
Cammarota 2007	✗	✗	?	?	✗	?	?	✓	✓	✓	✗
Carroccio 2008	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Ciacci 2002	✓	✓	✓	✗	✓	?	✗	?	✓	✓	✓
Cornell 2016	✗	✗	?	?	✗	?	?	✓	✓	✓	✗
Dickey 2008	✗	✗	✓	✓	✓	?	✓	?	✓	✓	✓
Fang 2017	✗	✗	?	✓	✓	✓	✓	?	✓	✓	✗
Ghazzawi 2014	✓	✓	?	✗	✓	?	?	?	✓	✓	✗
Haere 2016	✓	?	✓	✗	✓	?	✓	✓	✓	?	✗
Kaukinen 2007	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Kemppainen 1998	✓	?	✓	?	✓	?	?	✓	✓	✓	✓
Koskinen 2010	✗	✗	?	?	✓	?	?	✓	✓	?	✗
Lebwohl 2013a	✗	✗	?	?	✗	?	?	?	✓	✓	✓
Lebwohl 2013b	✗	✗	?	?	✗	?	?	?	✓	✓	✓
Lebwohl 2014	✗	✗	?	?	✗	?	?	?	✓	✓	✓
Lebwohl 2015a	✗	✗	?	?	✗	?	?	?	✓	✓	✓
Lebwohl 2015b	✓	✓	?	?	✗	✓	?	?	✓	✓	✓
Leonard 2017	✓	✓	✓	✗	✓	✓	✓	?	✓	✓	✗
Mahadev 2017	✗	✗	?	?	✓	✗	?	✓	✓	✓	✓
Pekki 2015	✓	?	✓	✗	✓	✓	✗	?	✓	?	✓
Pekki 2017	✓	?	✓	✗	✓	?	✓	?	?	?	✓
Rubio-Tapia 2010	✓	✓	✓	✗	✗	?	✗	?	✓	✓	✓
Selby 1999	✓	✓	✓	?	✗	✗	✓	✓	✓	✓	✗
Souroujon 1982	✓	?	?	?	✓	?	?	?	?	?	✗
Thornquist 1992	✗	✗	✓	✗	✓	?	?	?	✗	?	✗
Tuire 2012	✓	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓
Valdimarsson 1994	✓	✓	?	✗	✓	✓	✗	?	✗	✓	✓
Walters 1995	✗	✗	?	?	✓	?	?	?	?	?	✓

Instead the scores…

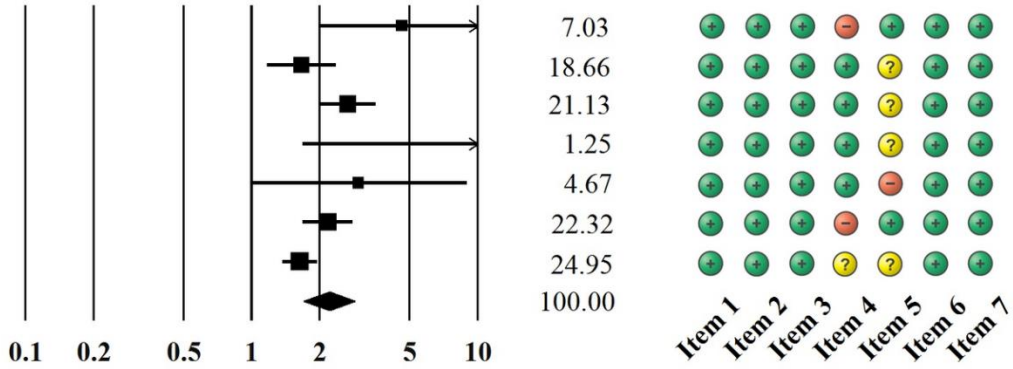
Use tables…

Supplementary Figure 6. Risk of bias assessment graph.



…or graphs!

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Weight (%)
de Fonseka et al., 2015	4.623	1.978	10.804	<0.001	7.03
Nguyen et al., 2014, A	1.660	1.171	2.353	0.004	18.66
Nguyen et al., 2014, B	2.660	2.007	3.525	<0.001	21.13
Singh et al., 2015	16.403	1.684	159.750	0.016	1.25
Végh et al., 2014	2.970	0.989	8.915	0.052	4.67
Wallaert et al., 2015	2.170	1.691	2.785	<0.001	22.32
Wilson et al., 2015	1.630	1.370	1.940	<0.001	24.95
Total	2.202	1.698	2.856	<0.001	100.00



Steps of risk of bias assessment

Incorporate risk of bias assessment in each section of your manuscript!

- **Methods:** give a description of the tool
- **Results:** give a brief description, a table and a graph, you may perform additional analysis based on risk of bias
- **Discussion:** integrate it into the interpretation (limitations and GRADE approach)

Bias is observational studies?

Inherent…

Risk of bias assessment

COMMON MISTAKE

1. Not understanding the concept of bias
2. Missing using risk of bias assessment tools
3. Failure to integrate the results of assessment into the sections of the manuscript (GRADE appraoch!)

Risk of bias assessment

TAKE HOME MESSAGE

1. Assess risk of bias
2. Integrate the results of risk of bias assessment

Schedule for today

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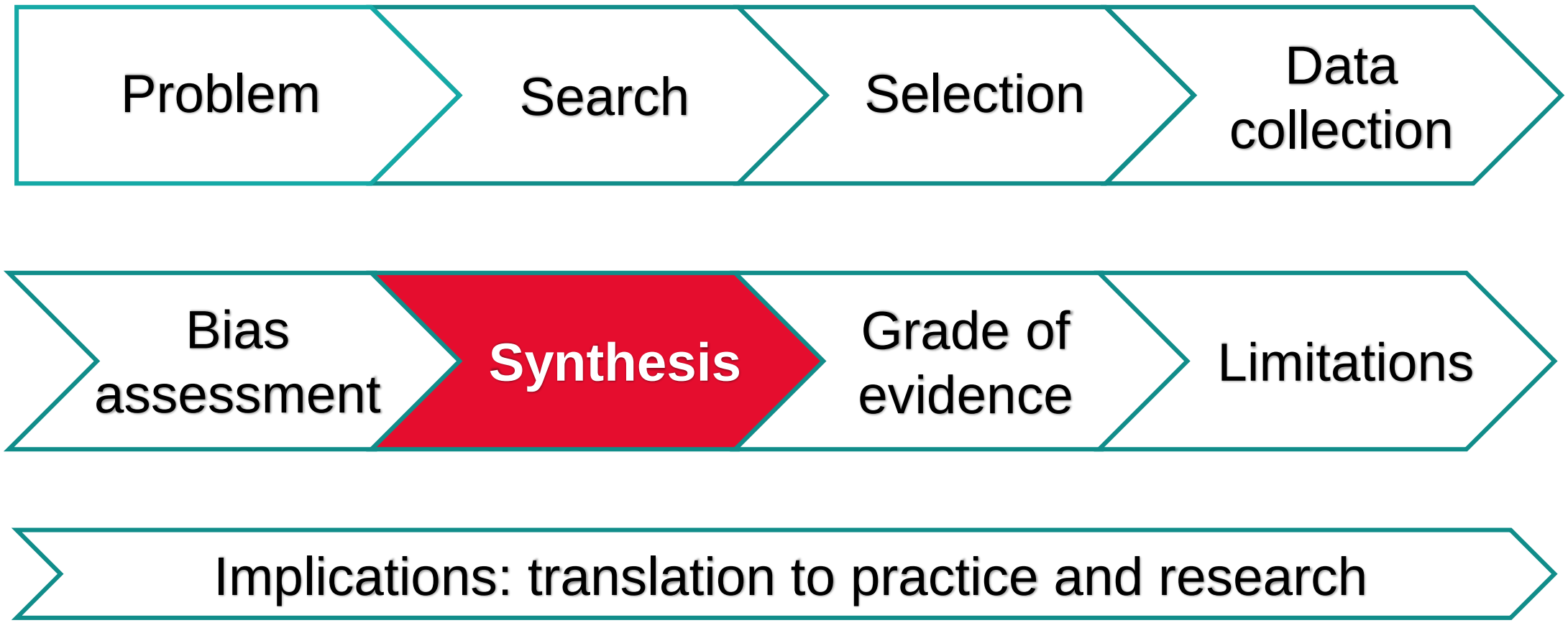
Flowchart


Problem
Search
Selection
Data collection
Bias assessment
Synthesis
Grade of evidence
Limitations
Implications: translation to practice and research

Narrative review

No statistics

Statistics

Meta-analysis

Hypothesis Generation

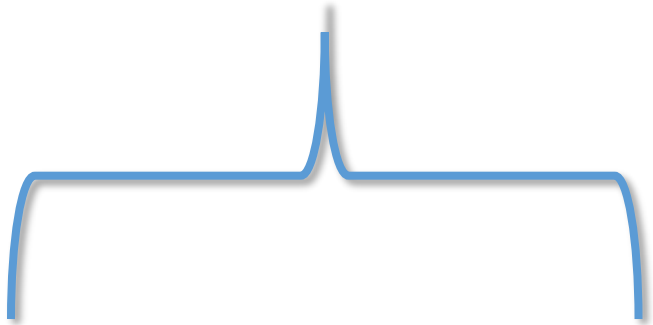
- PICO

- The hypo

g a hypothesis

Outcome types I.

From continuous variables



Mean difference, smd

Paired mean difference

From discrete variables

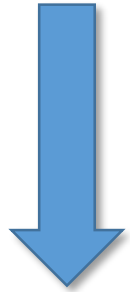
	Disease	**No Disease**	
Exposed	Exposed Cases	Exposed Non-Cases	Total exposed
Not Exposed	Non-Exposed Cases	Non-Exposed Non-Cases	Total non-exposed
	Total cases	Total non-cases	Total number

Outcome types II.

From two continuous variables

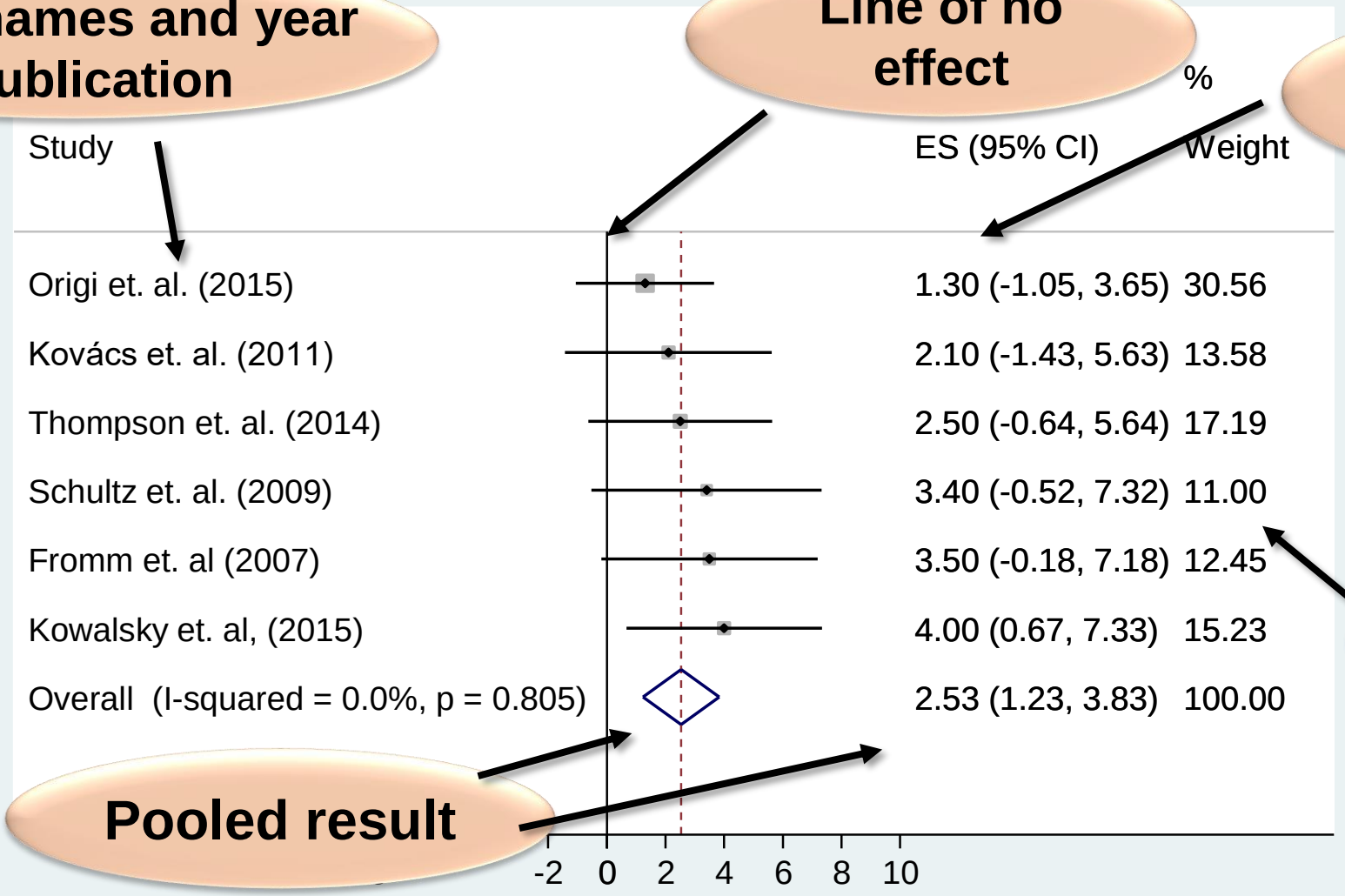
Correlation

From number of events

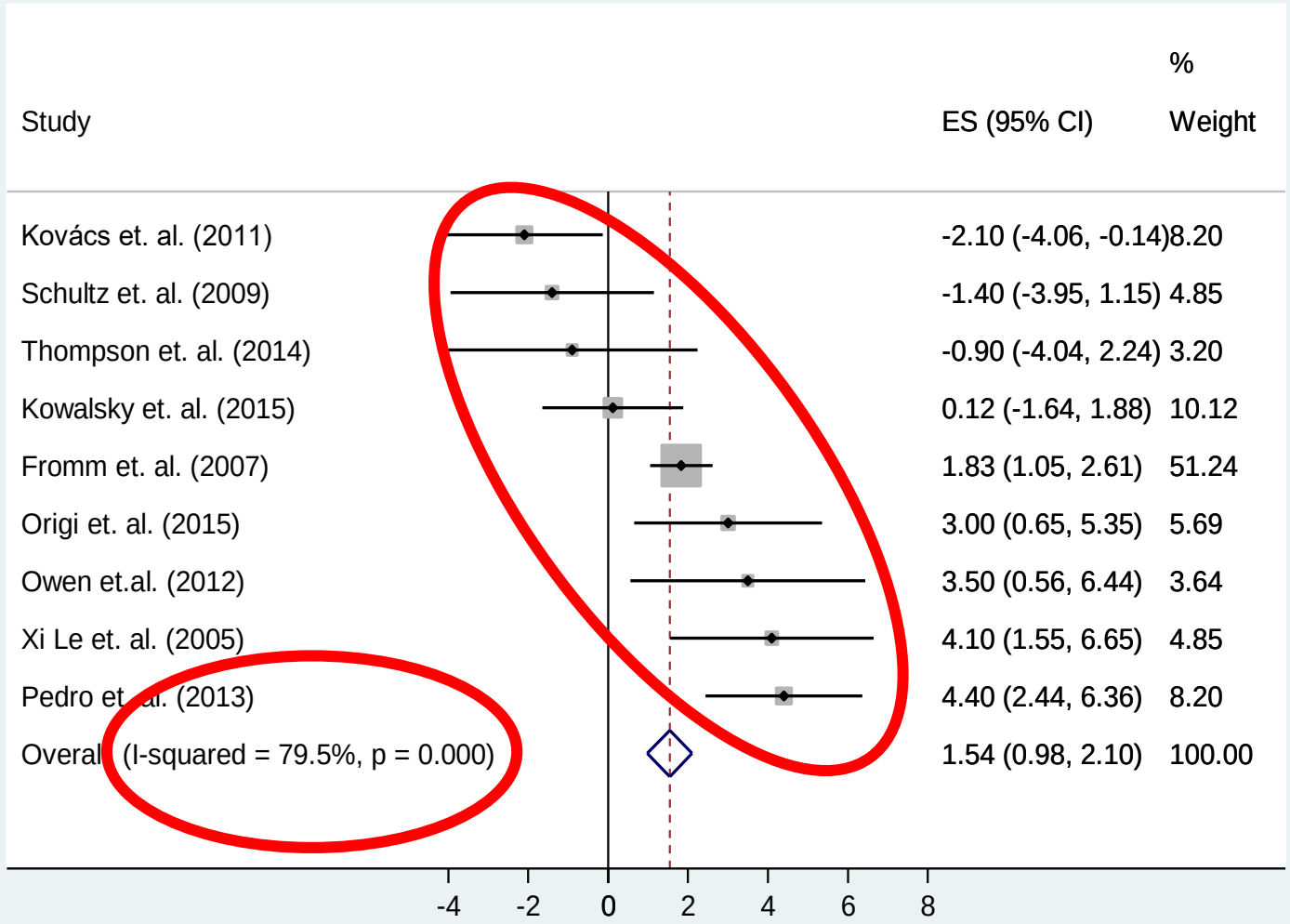


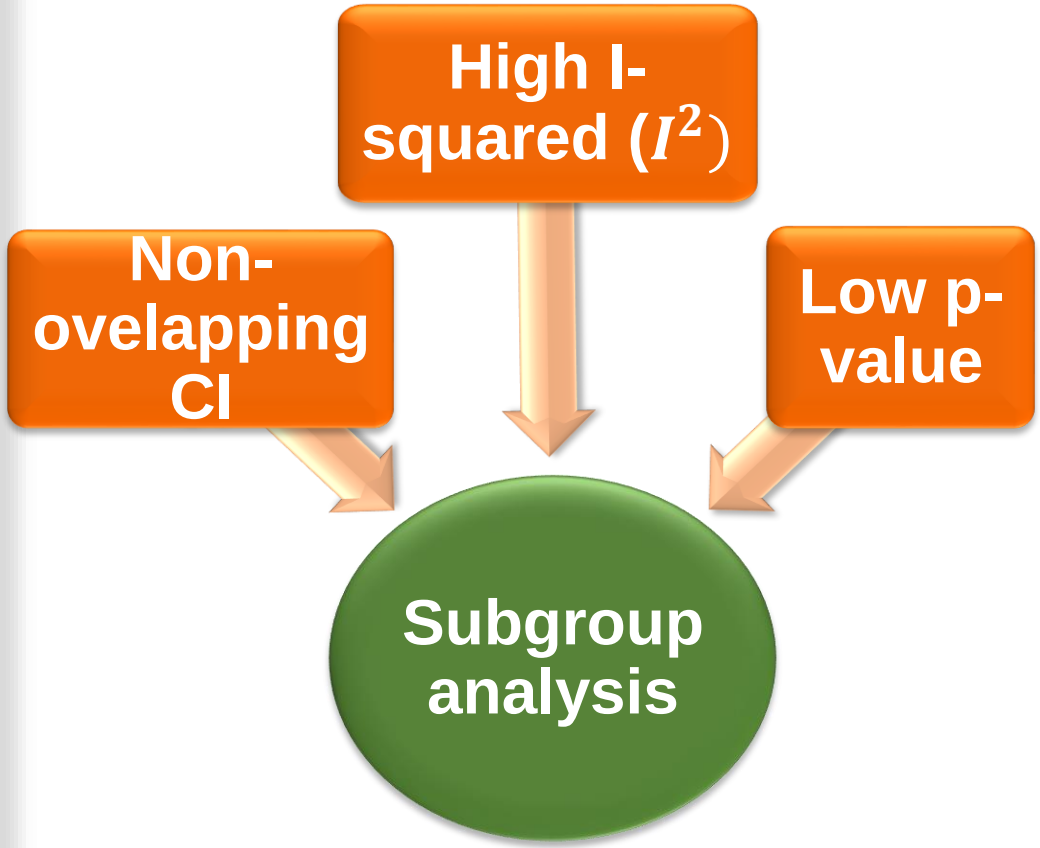
Event rate

Forest plot

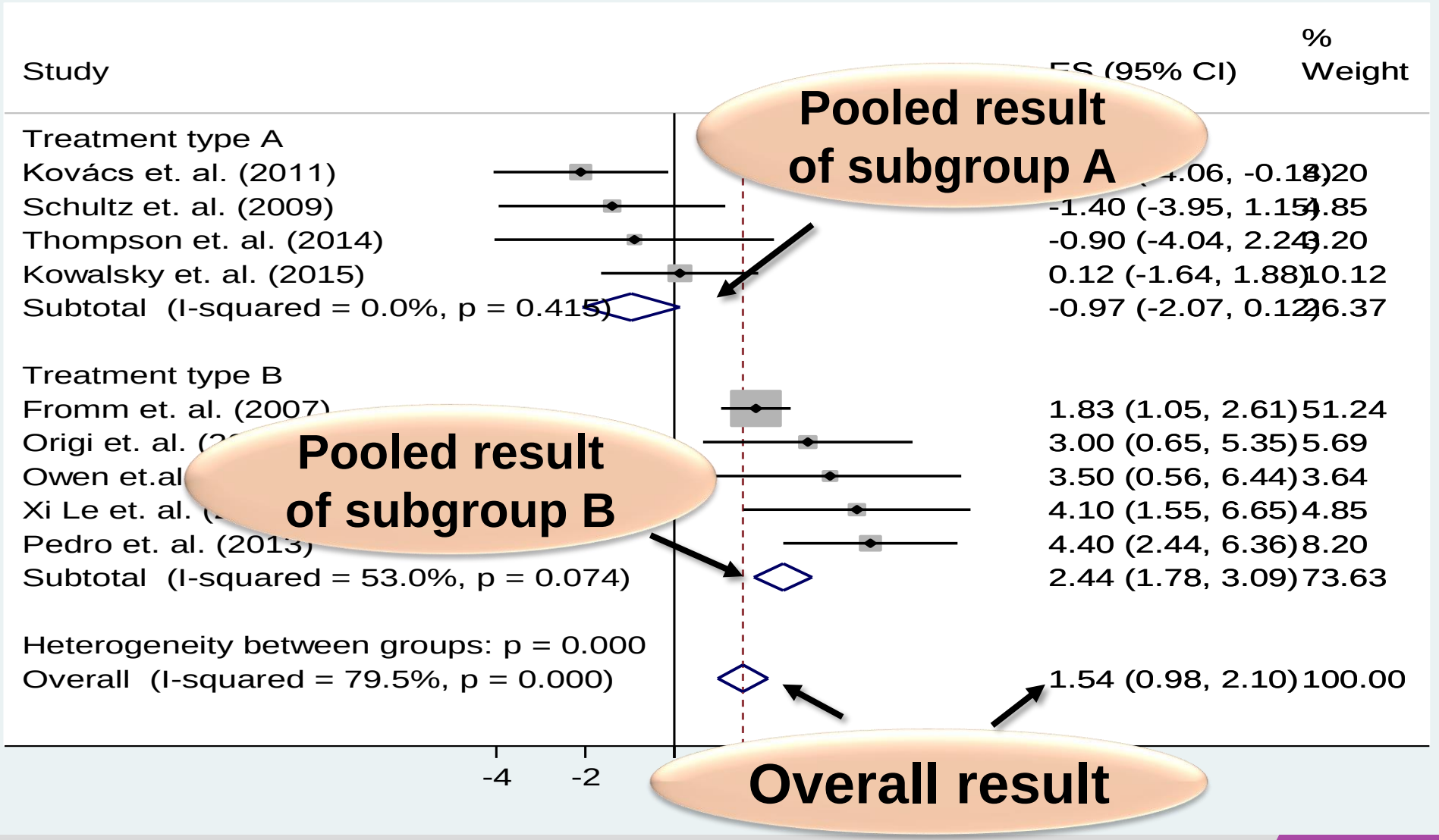

Studies names and year of publication
Line of no effect
Effect size & 95%CI
Weight of the studies
Pooled result
Study
ES (95% CI)
%
Weight
Origi et. al. (2015)
1.30 (-1.05, 3.65) 30.56
Kovács et. al. (2011)
2.10 (-1.43, 5.63) 13.58
Thompson et. al. (2014)
2.50 (-0.64, 5.64) 17.19
Schultz et. al. (2009)
3.40 (-0.52, 7.32) 11.00
Fromm et. al (2007)
3.50 (-0.18, 7.18) 12.45
Kowalsky et. al, (2015)
4.00 (0.67, 7.33) 15.23
Overall (I-squared = 0.0%, p = 0.805)
2.53 (1.23, 3.83) 100.00
-2
0
2
4
6
8
10

Forest plot of heterogeneous studies

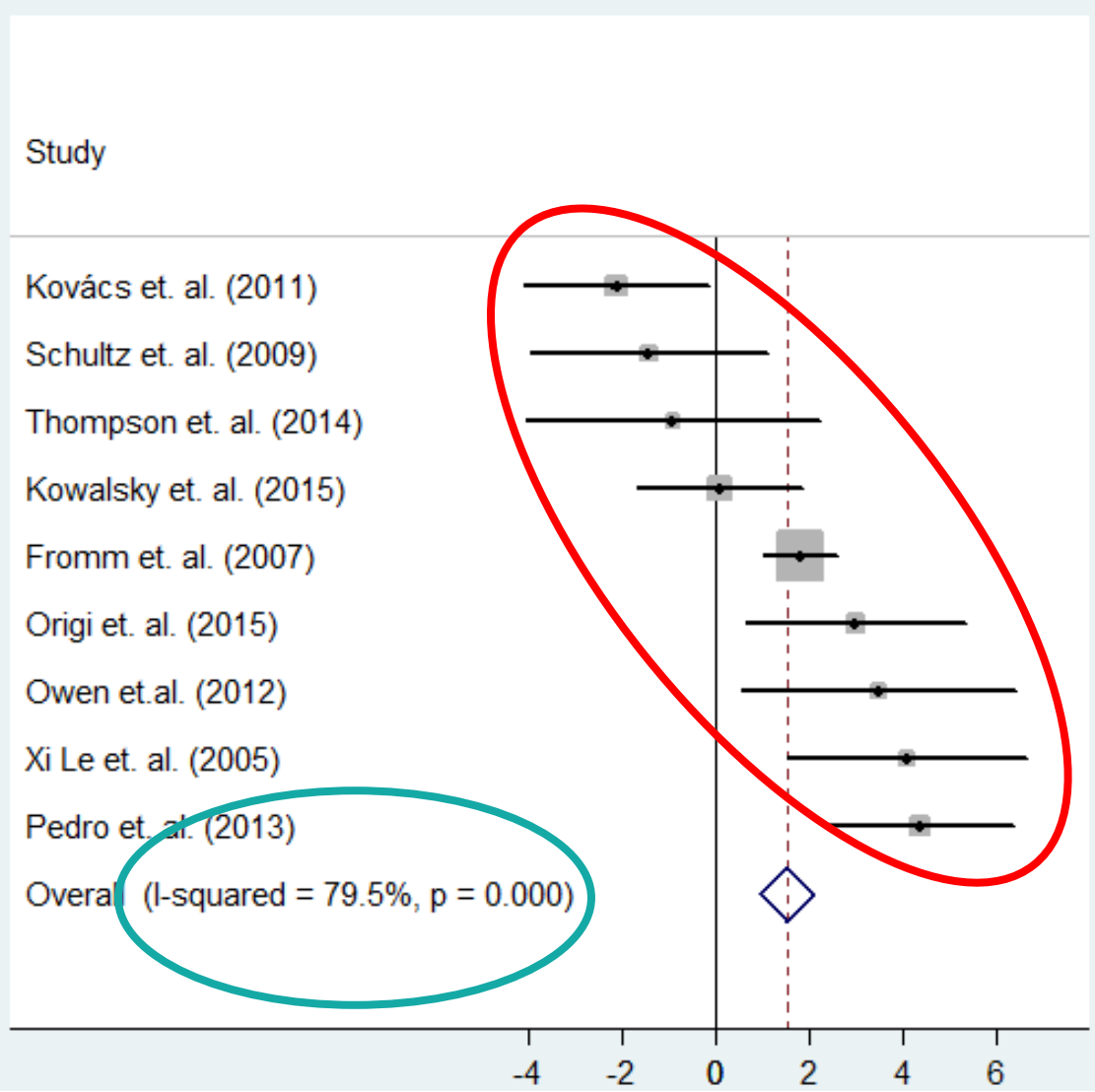


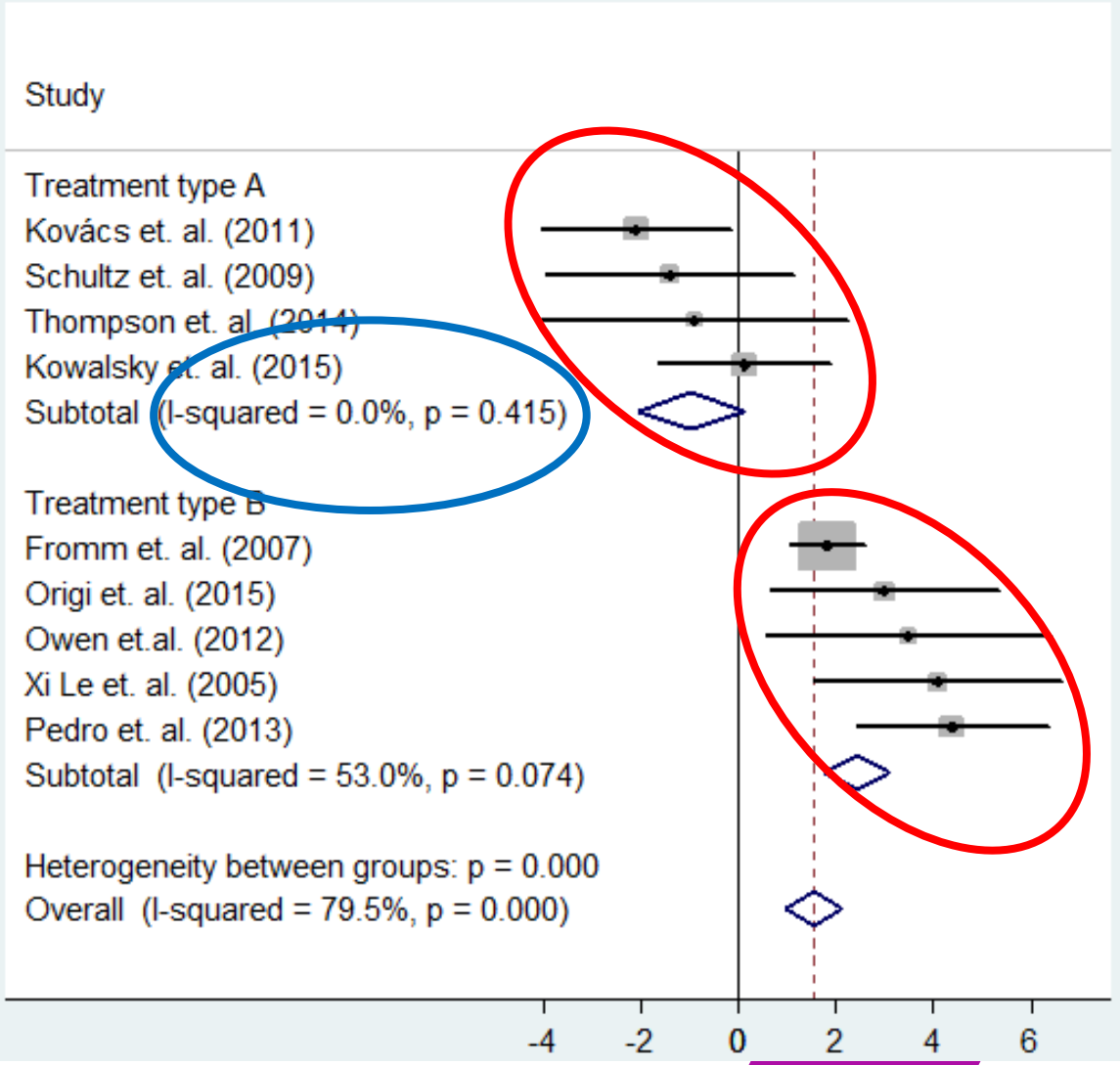


Subgroup analysis

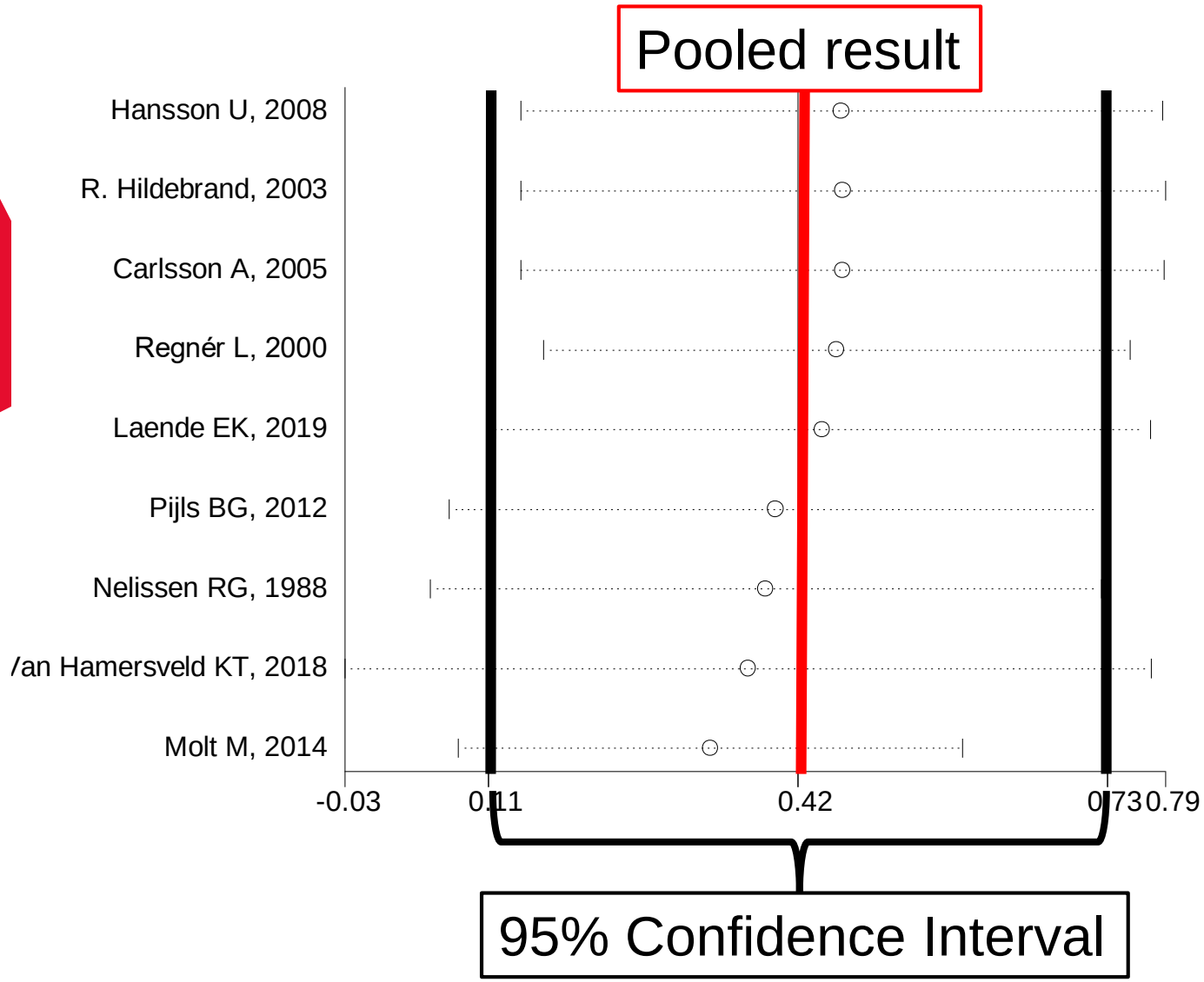


Heterogeneity

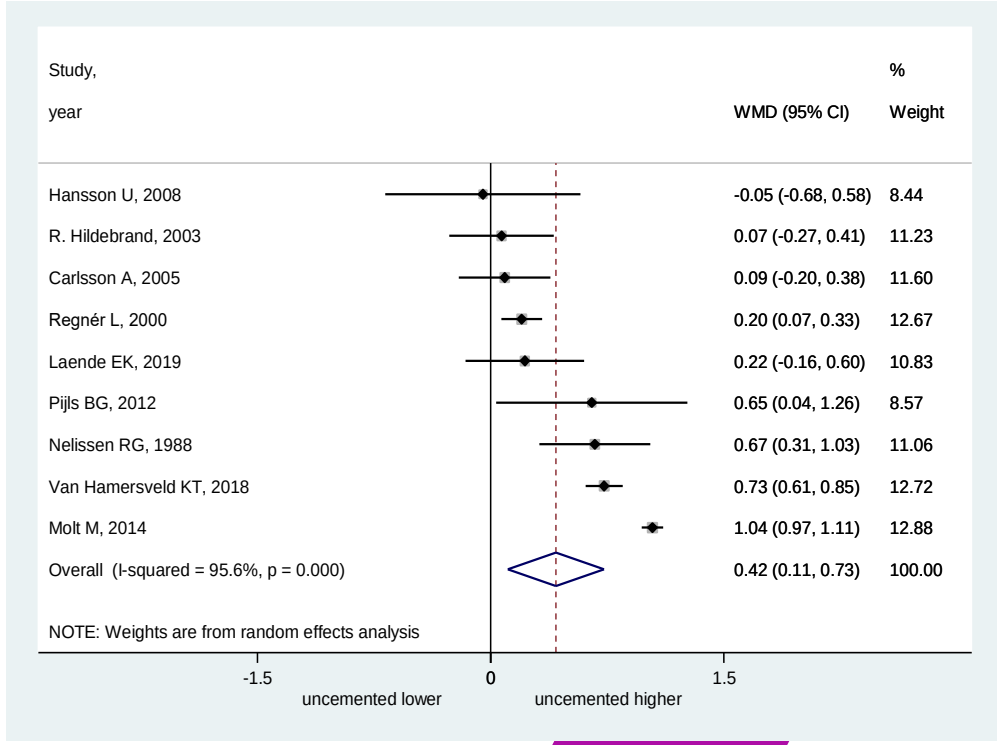




Sensitivity analysis



It helps to identify studies which have high impact on the pooled result.



Summary

Two main things we need to assess when reading a meta analysis

- Pooled result – 95% CI
- Heterogeneity – I^2 and p-value

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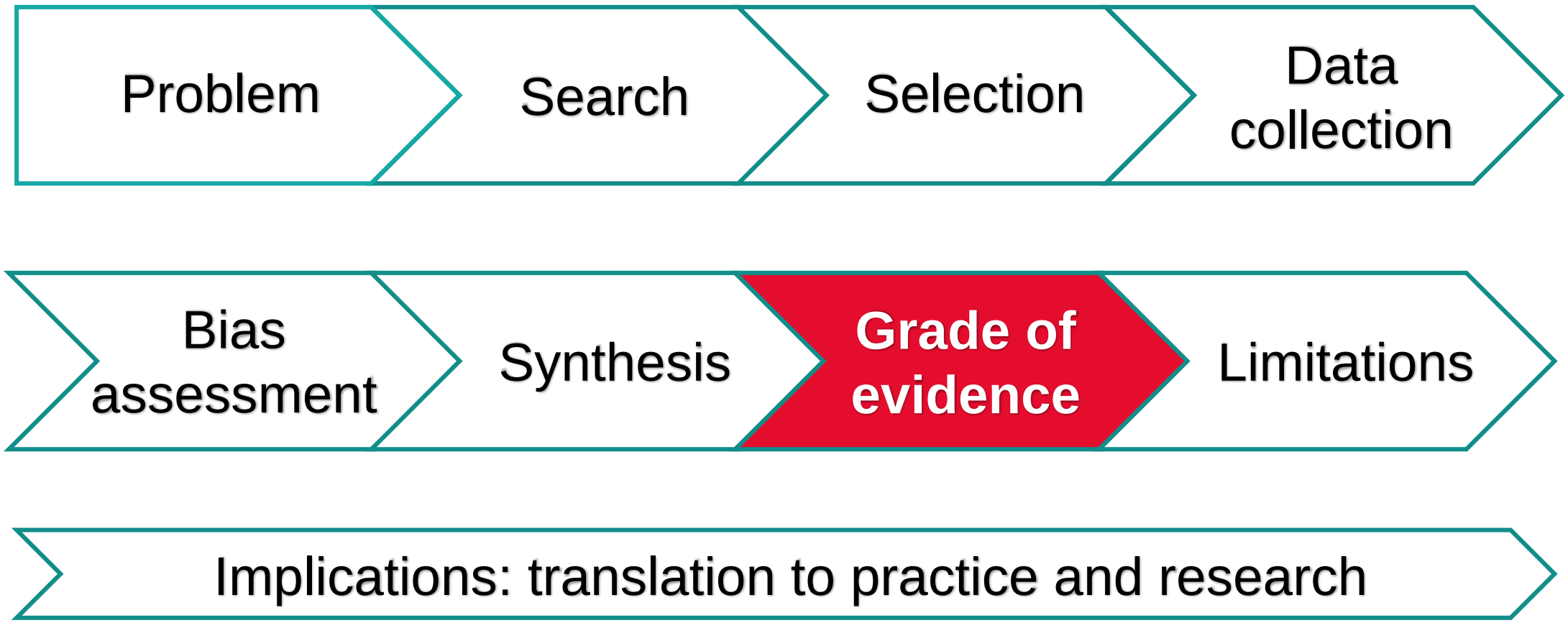
12.	Szakács Zsolt	Limitations and implications
13.	Szakács Zsolt	Future perspectives, **voting**

Flowchart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Grade of evidence
Limitations
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Do you believe that your results are **true**?

Statins reduce 10-y CVD mortality in patients with high CHOL

(**high** grade of evidence)

Grade of evidence

Aim: to assess how confident you are that your results are true

Benefit: evidence graded

The GRADE appraoch

Quality of evidence	Suggested implications
High	Further research is unlikely to change the confidence in an estimated effect; we are confident that we can expect very similar effect in a population for which the recommendation is intended
Moderate	Further research is likely to have an important impact on the confidence in an estimated effect and may change that estimate
Low	Further research is very likely to have an important impact on the confidence in an estimated effect and is likely to change that estimate
Very low	Any estimate of an effect is very uncertain

How to grade?

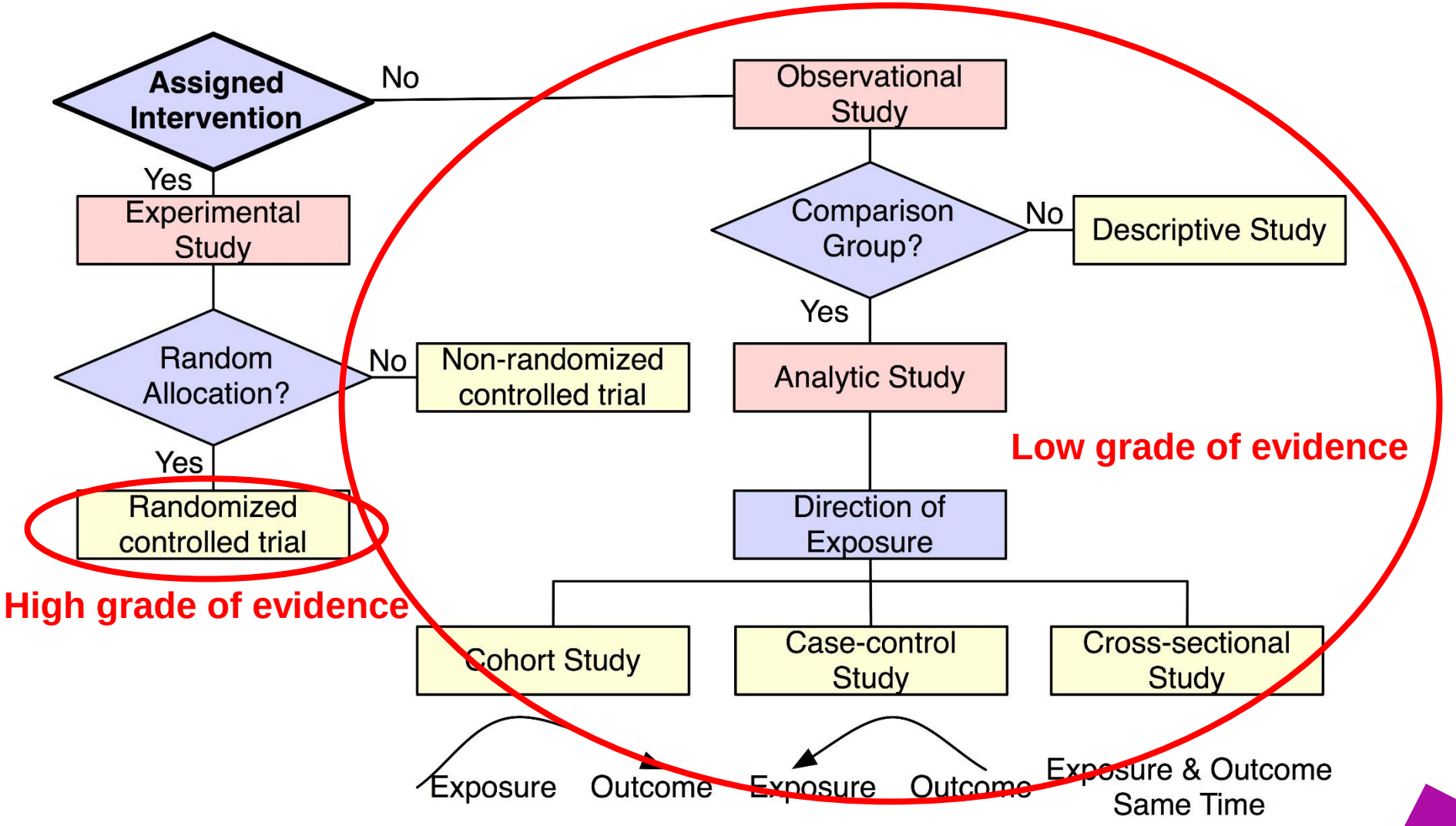
1. Step: assess the design of your studies!

RCTs: high level of evidence

Non-RCTs: low level of evidence

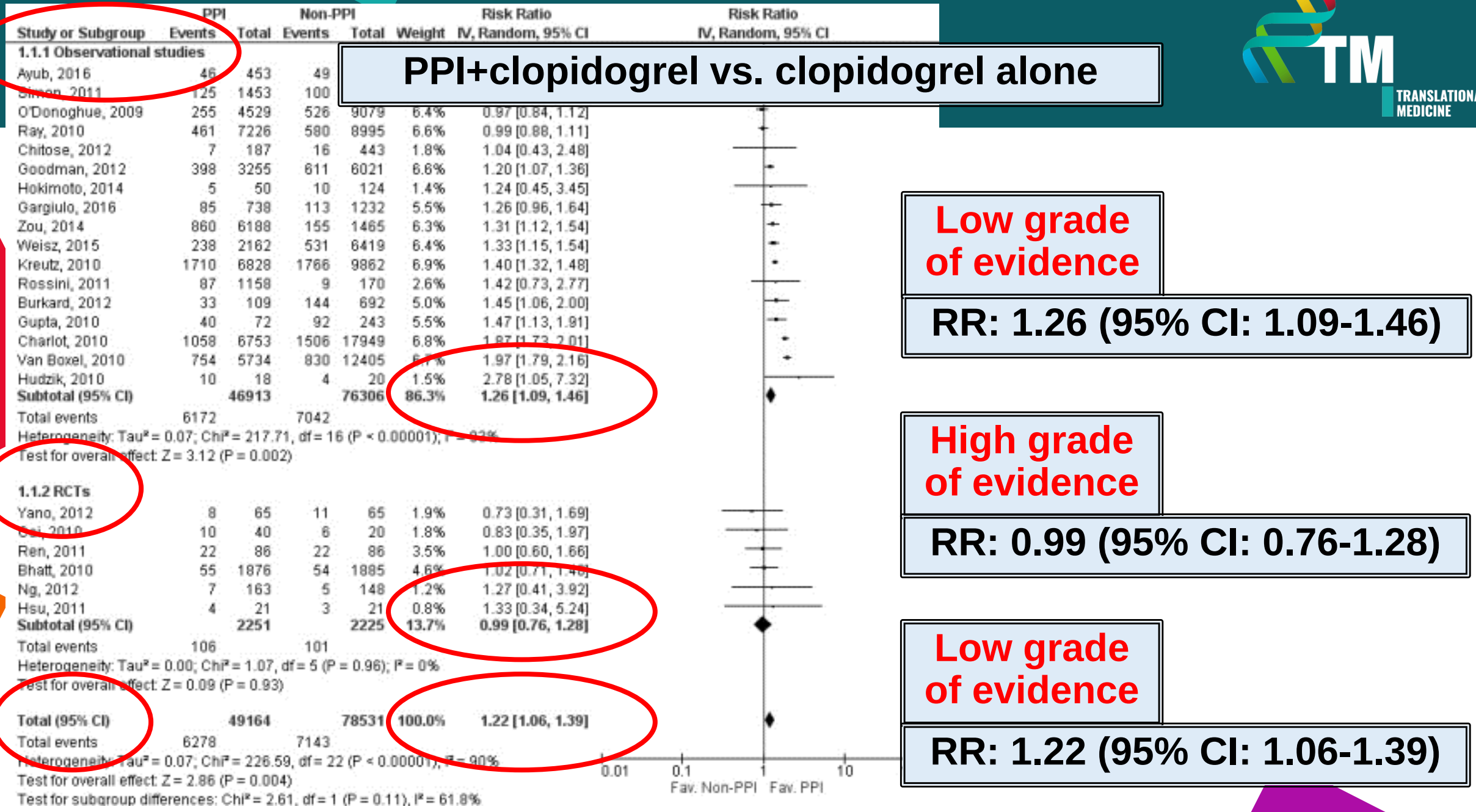
1. Assessment should be done for each outcome separately
2. If you want to draw a concluson from a subgroup, assess only those studies included in that subgroup.
3. If 1 non-RCT is included in an analysis the level of evidene is low

Study designs



https://irb.research.chop.edu/study-design

PPI+clopidogrel vs. clopidogrel alone



Low grade of evidence

RR: 1.26 (95% CI: 1.09-1.46)

High grade of evidence

RR: 0.99 (95% CI: 0.76-1.28)

Low grade of evidence

RR: 1.22 (95% CI: 1.06-1.39)

How to apply the GRADE system?

2. Step: Downgrading items:

1. Risk of bias
2. Inconsistency ➡ heterogeneity
3. Indirectness ➡ PICO (generalizability)
4. Imprecision ➡ Sample and event numbers
5. Publication bias

3. Step: Upgrading items:

1. Large effect
2. Dose response
3. Opposite bias

Rarely used

Overall or subgroups?

Statins reduce 10-y CV mortality in patients with high CHOL

(high grade of evidence)

Statins reduce 10-y CV mortality in patients with high CHOL if started >80 years

(??? grade of evidence)

The output: Summary of Findings (SOF) Table

Heparin prophylaxis compared with no prophylaxis in ambulatory patients with cancer without VTE receiving systemic therapy
P: Ambulatory patients with cancer without VTE receiving systemic therapy
S: Outpatient
I: Heparin prophylaxis
C: No prophylaxis

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with No prophylaxis	Risk difference with Heparin prophylaxis
Mortality follow-up: 12 months	9575 (18 RCTs)	⊕⊕⊕◯ MODERATE [1]	RR 0.98 (0.93 to 1.03)	Study population 504 per 1000	10 fewer per 1000 (35 fewer to 15 more)
Mortality follow-up: 24 months	5229 (14 RCTs)	⊕⊕⊕◯ MODERATE [1]	RR 0.99 (0.96 to 1.01)	Study population 778 per 1000	8 fewer per 1000 (31 fewer to 8 more)

Grade of evidence

COMMON MISTAKE

1. **The GRADE approach is not applied.**
2. **The GRADE approach is misunderstood.**

Grade of evidence

TAKE HOME MESSAGE

1. Learn how to grade the level of your evidence!

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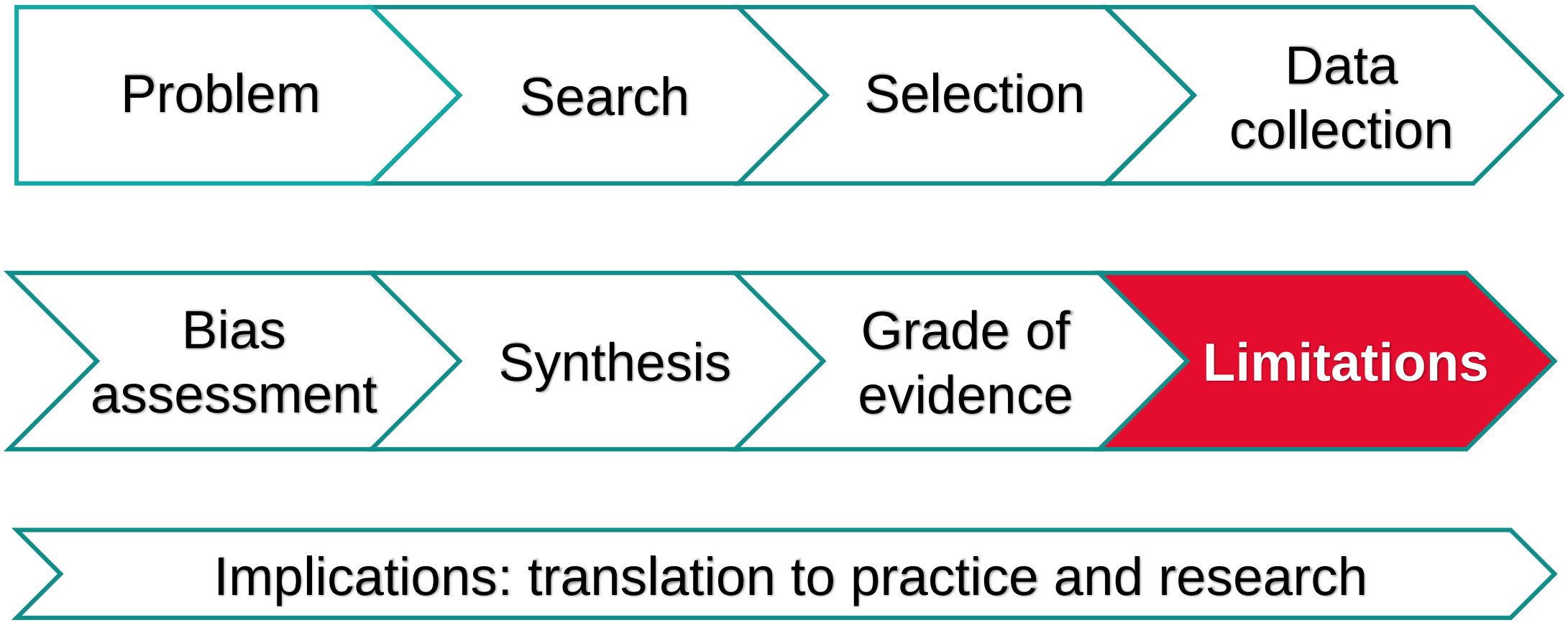
Flowchart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Discussion and conclusions

What to do with the results?

1. Summary of findings - GRADE
2. (Explanation and interpretation)
3. Strengths and limitations
4. Implications for practice
5. Implications for research

Strengths

1. Relevance and novelty
2. Methodology (transparent, reproducible)
3. Comprehensiveness of search
4. Higher statistical power
5. New associations (subgroups, regression)
6. Critical attitude towards the evidence

Limitations

1. Publication bias
2. Indirectness
3. Generalizability and applicability
4. Imprecision
5. Risk of bias
6. Heterogeneity
7. Methodological errors

What is publication bias?

TM TRANSLATIONAL MEDICINE

Comes from prejudice against smaller „negative" studies

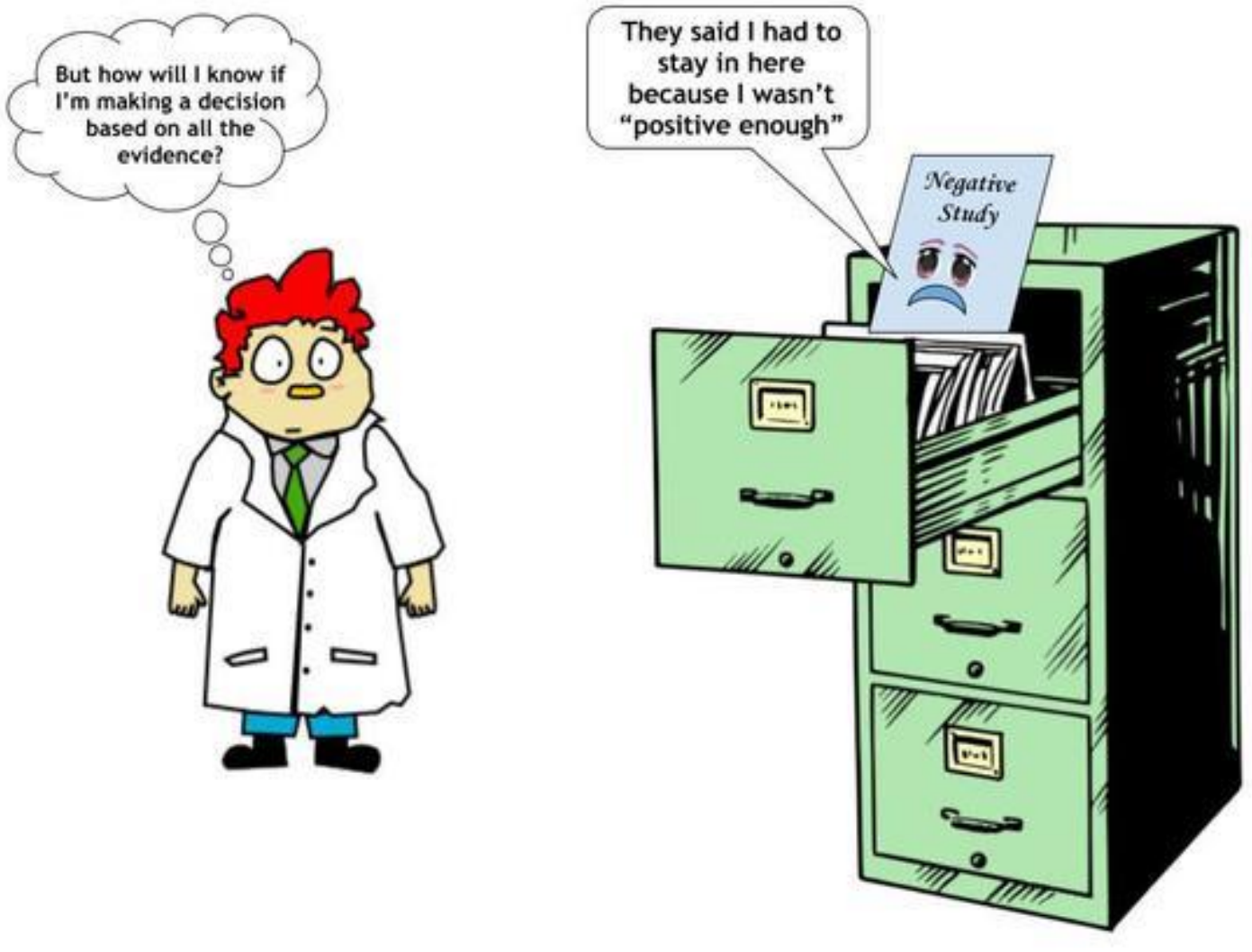
⌄

Less frequent or delayed publication in smaller journals

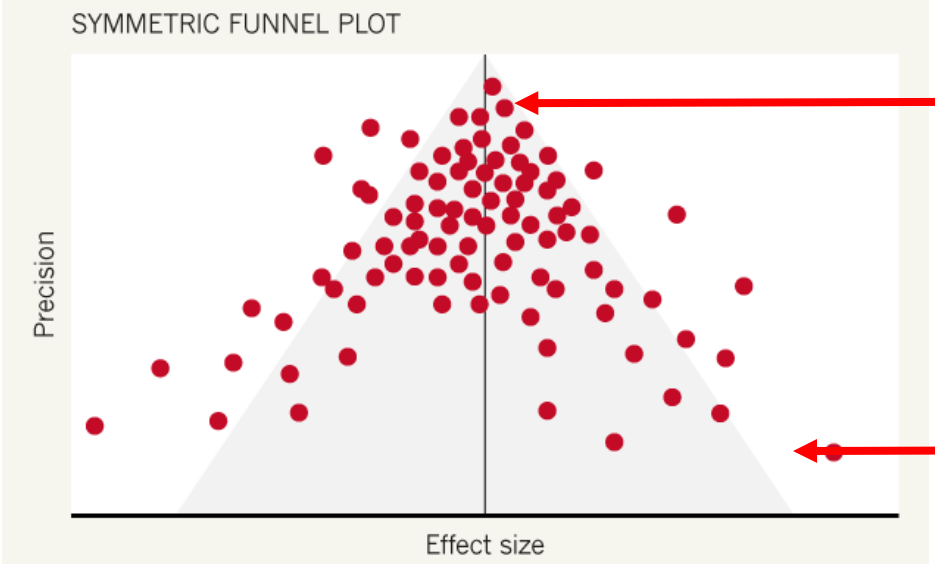
⌄

Bias at the level of meta-analysis (meta-bias)

What is publication bias?



How to estimate publication bias?



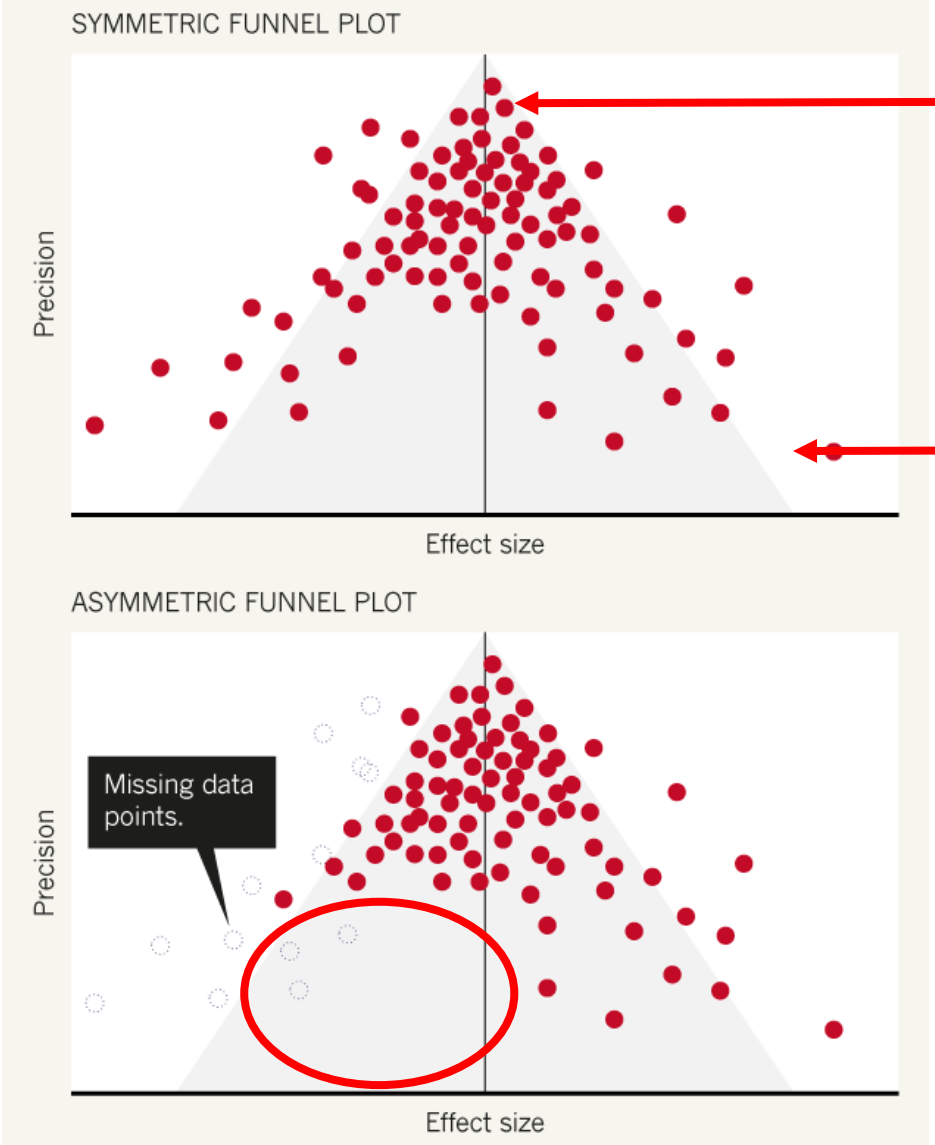
Large studies

Small studies

- „Small-study effect" are a common threat in systematic reviews and may indicate publication bias
- Egger et al. (1997) proposed a test for asymmetry of the funnel plot

Minimum 10 studies!

How to estimate publication bias?



Large studies

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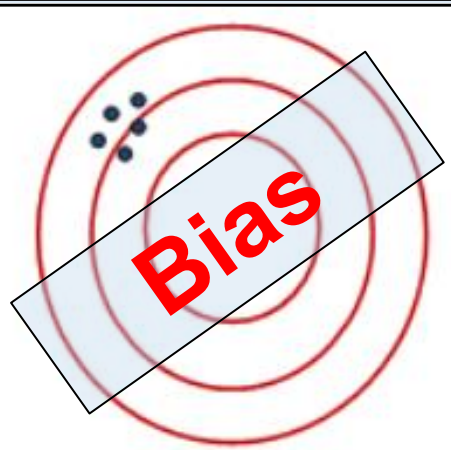
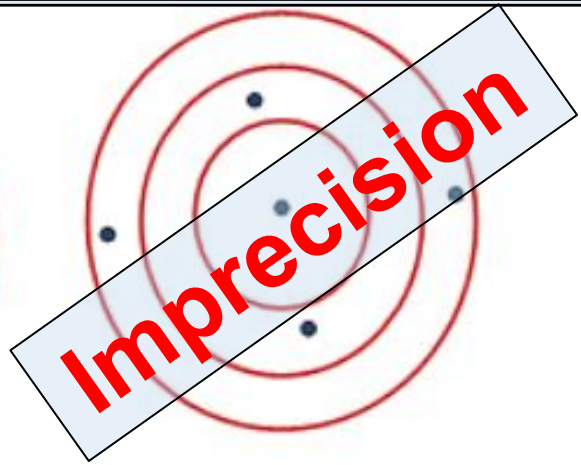
Minimum 10 studies!

Directness vs. indirectness

Meta-analysis	Study 1	Study 2
P: pancreatitis	P: severe pancreatitis	P: pancreatitis
I: antibiotics	I: antibiotics	I: antibiotics
C: placebo	C: placebo	C: placebo
O: in-hosp mortality	O: in-hosp mortality	O: 1-week mortality

PICO of individual studies should match the PICO of meta-analysis!

Errors in epidemiological studies

Risk of bias assessment		Trial sequence analysis
		
Bias		Imprecision
Valid?	✗	✓ ✓
Precise?	✓ ✓	✗

Heterogeneity

Non-statistical

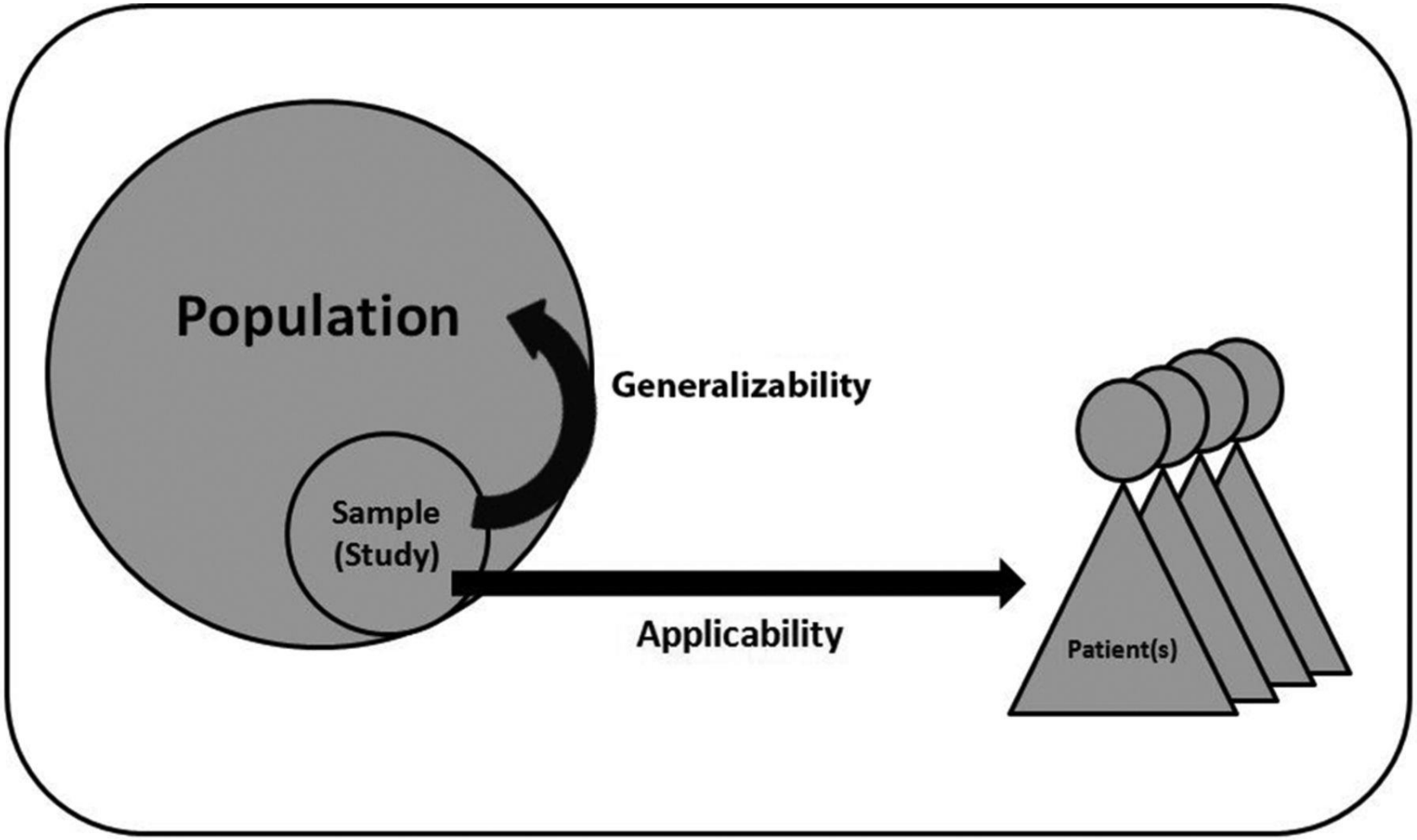
1. Risk of bias
2. Indirectness
3. Study design
4. Chance (imprecision)

Statistical

1. Overlap of confidence intervals
2. Tests (I^2, chi^2)

Must be explored!

Generalizability and applicability



Generalizability and applicability

Common methodological errors

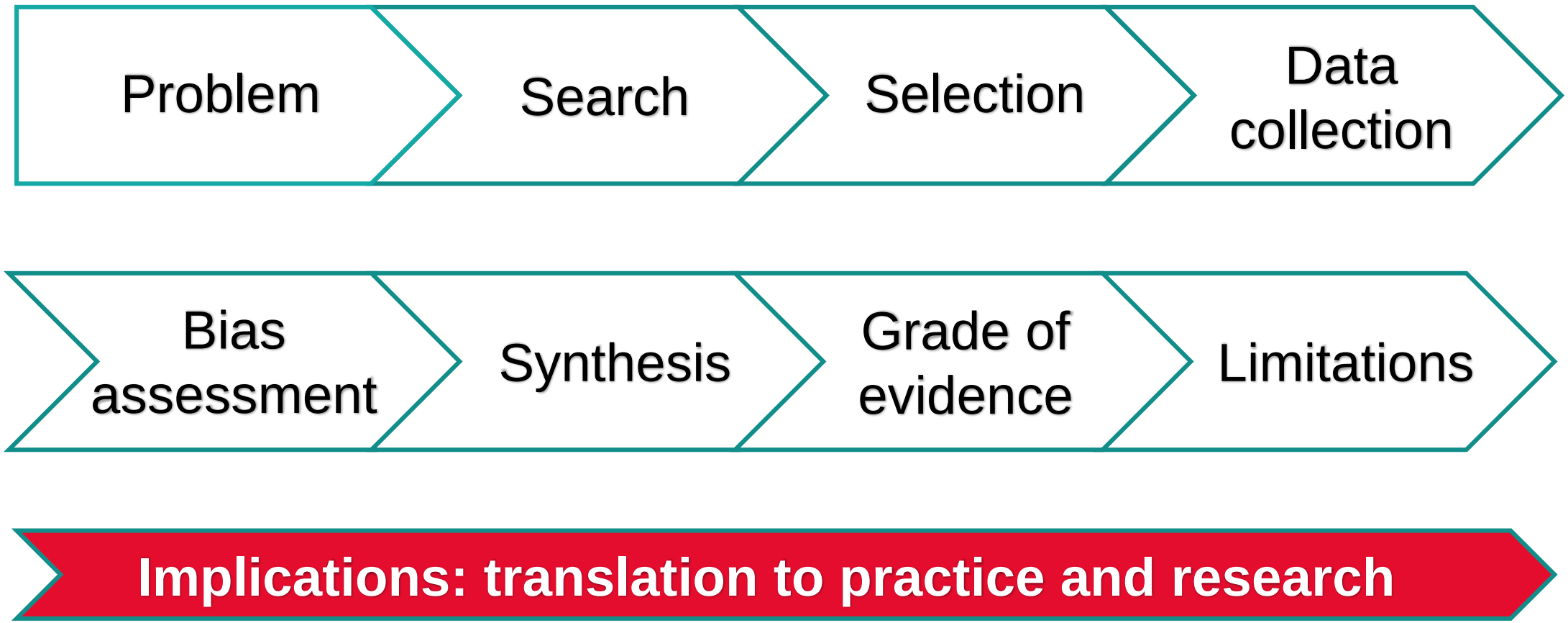
1. protocol is lacking or major deviation without rationale
2. unclear PICO, no hypothesis (so what?), no preliminary search
3. incomprehensive search: use of filters, wrong order of operations, lack of testing (trial and error)
4. selection not done in duplicate, poor documentation
5. data are not collected in duplicate, inaccurate data collection
6. analyses not done by statisticians
7. evidence not graded, results misinterpreted (OR, RR)
8. casuative conclusions from observational studies

Limitations

1. Publication bias
2. Indirectness
3. Generalizability and applicability
4. Imprecision
5. Risk of bias
6. Heterogeneity
7. Methodological errors

- All are assessable
- Some are measureable
- Some are avoidable

Flowchart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Good scientific questions

What is a good scientific question?

„Those questions that are **clearly related to a clinical decision** about whether to use a therapeutic, preventive, or diagnostic intervention are the ones that warrant the most time.” JAMA, 1993

Implication for practice

Implication for research

Good answer

Implication for practice

Implication for research

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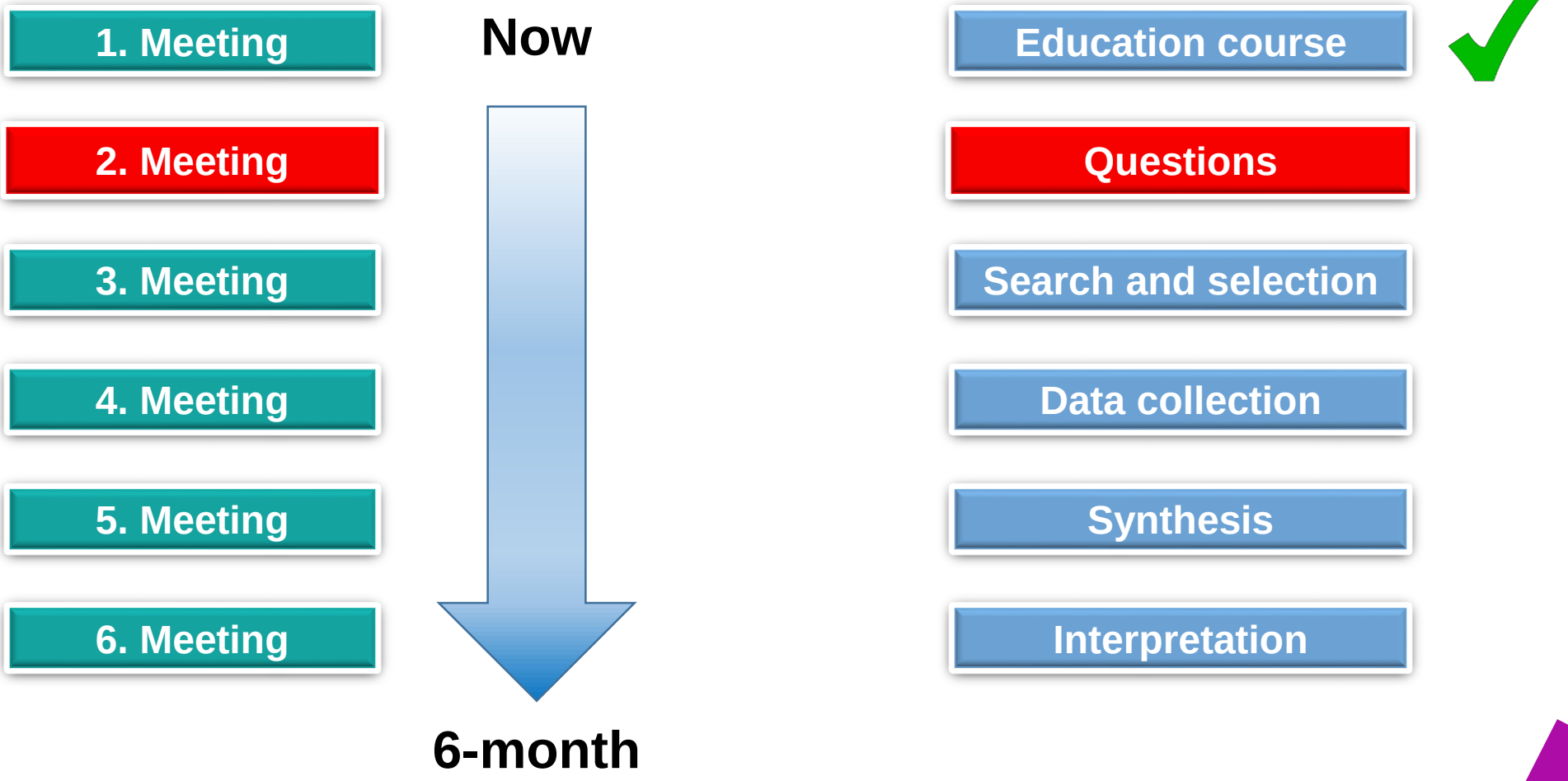
Future perspectives

Future perspectives



Future perspectives

1. Meeting
2. Meeting
3. Meeting
4. Meeting
5. Meeting
6. Meeting

Now

19th March

6-month

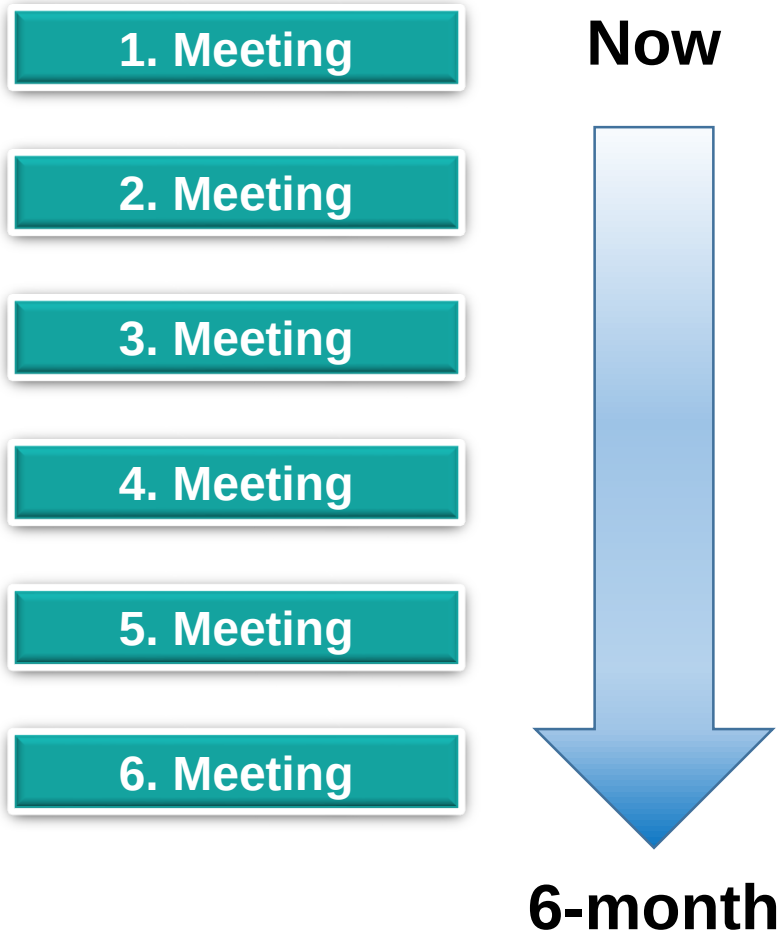
Education course ✓

Questions

- **Pécs (Hungarian team)**
- **Skype (foreign partners)**

Bring your own PICO!

Future perspectives



What we can offer: „a guided tour”

- facilitators and consultations
- statistical analysis
- transparent co-authorship policy

What you should bring:

- a good question
- young and senior fellows: 1(2) + 1 per project
- your time
- future cooperation

Future perspectives

Tomorrow…

- **2:30 pm, Dean's Conference Room (same floor, same building)**
- **Teamwork (6-8 persons/group) with facilitators**
- **Bring you laptop with!**

Aims: critical reading and critical thinking

Thank you for your attention!