체계적 문헌고찰 및 논문작성 개요

코크란연합한국지부 김현정

강의주제

- 체계적고찰의 전반적 개요
- 코크란 핸드북 최신개정과 평가도구 개정 등을 포함한 최근 중요한 연구방향
  - Cochrane Handbook for Systematic Reviews of Interventions Version 6: https://training.cochrane.org/handbook/version-6

AMSTAR 2 : 체계적 고찰의 평가도구

- 2007년 무작위대조군연구의 체계적고찰에 대한 평가도구로서 개발
  - Shea BJ,. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007 Feb 15; 7:10. PMID: 17302989.
- 2017년 무작위대조군연구와 비무작위연구 중 중재에 대한 연구를 포함한 체계적고찰에 대한 평가도구로 업데이트 됨
  - Shea BJ,. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008

PRISMA : 체계적고찰 보고지침

- PRISMA (Preferred Reporting Items of Systematic reviews and Meta-Analyses) 2009, Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
- PRISMA (Preferred Reporting Items of Systematic reviews and Meta-Analyses) 2020, Page MJ, McKenzie JE, Bossuyt PM, et al. Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. Journal of Clinical Epidemiology 2021;134:103-112.

체계적고찰의 다양한 형태에 따른 양식

- PRISMA for Abstracts
- PRISMA for Acupuncture
- PRISMA for Diagnostic Test Accuracy
- PRISMA for EcoEvo
- PRISMA Equity
- PRISMA Harms (for reviews including Harm outcomes)
- PRISMA Individual Patient Data
- PRISMA for Network Meta-Analyses
- PRISMA for Protocols
- PRISMA for Scoping Reviews
- PRISMA for Searching
- Extensions in development

체계적고찰연구방법의 개요

Systematic Review or meta-analysis

- A Systematic Review 는 명백하게 구조화된 질문을 가진 종설로, 체계적이고 엄격한 방법에 따라 관련된 연구를 모두 찾고 선택하여 연구에 포함된 자료를 수집 분석한 것으로 정의됨.
- 통계적인 방법(*meta-analysis*) 은 포함된 연구의 결과를 요약하기위해 사용되거나 사용하지 않을 수 있음
  - A traditional meta-analysis(pair : 개별 연구의 추정된 통계량(aggregate data (AD))을 이용하여 연구결과 합산
  - Meta-analysis of individual patient data (IPD) : 개별 연구의 원자료를(raw data) 이용하여 연구결과 합산
    - 환자 수준에서의 공변량 직접 보정 가능, 대상이 되는 모든 연구에서의 환자수준의 원데이터를 확보할 수 없는 제한점이 있음
  - Network Meta-Analysis(NMA) : 동일한 환자상태에서 서로 다른 비교를 하는 연구를 분석함으로써 여러 개입을 동시에 비교하는 분석 방법(Indirect and mixed-treatment comparison, network, multiple treatments meta-analysis)
    - 동일한 환자상태에서 서로 다른 중재의 효과를 비교, 순위를 정할 수 있음
    - 동일한 환자상태에 대한 가정이 충족되어야 하며, 선택비뚤림 발생가능

체계적 문헌고찰의 핵심 요소

- 명확한 연구목적 제시
- 선정 기준의 사전 명시
- 명백하며 재현가능한 연구방법론
- 체계적 문헌 검색
- 명백한 연구선택기준 제시
- 선정된 연구의 타당도 평가
- 분석결과의 체계적 종합 및 결과 제시

좋은 검색을 위한 엄격한 접근

- 체계적 문헌고찰에서 문헌검색조건
  - 포괄적인(comprehensive)
  - 재생산가능한(reproducible)
- 제한된 검색은 바이어스를 가져올 수 있음
  - 대표적이지 않은 연구들 포함
  - 부정확한 결과
  - 일반화의 감소

VS

AMSTAR 1.0 > AMSTAR 2.0

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

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

Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).

---

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

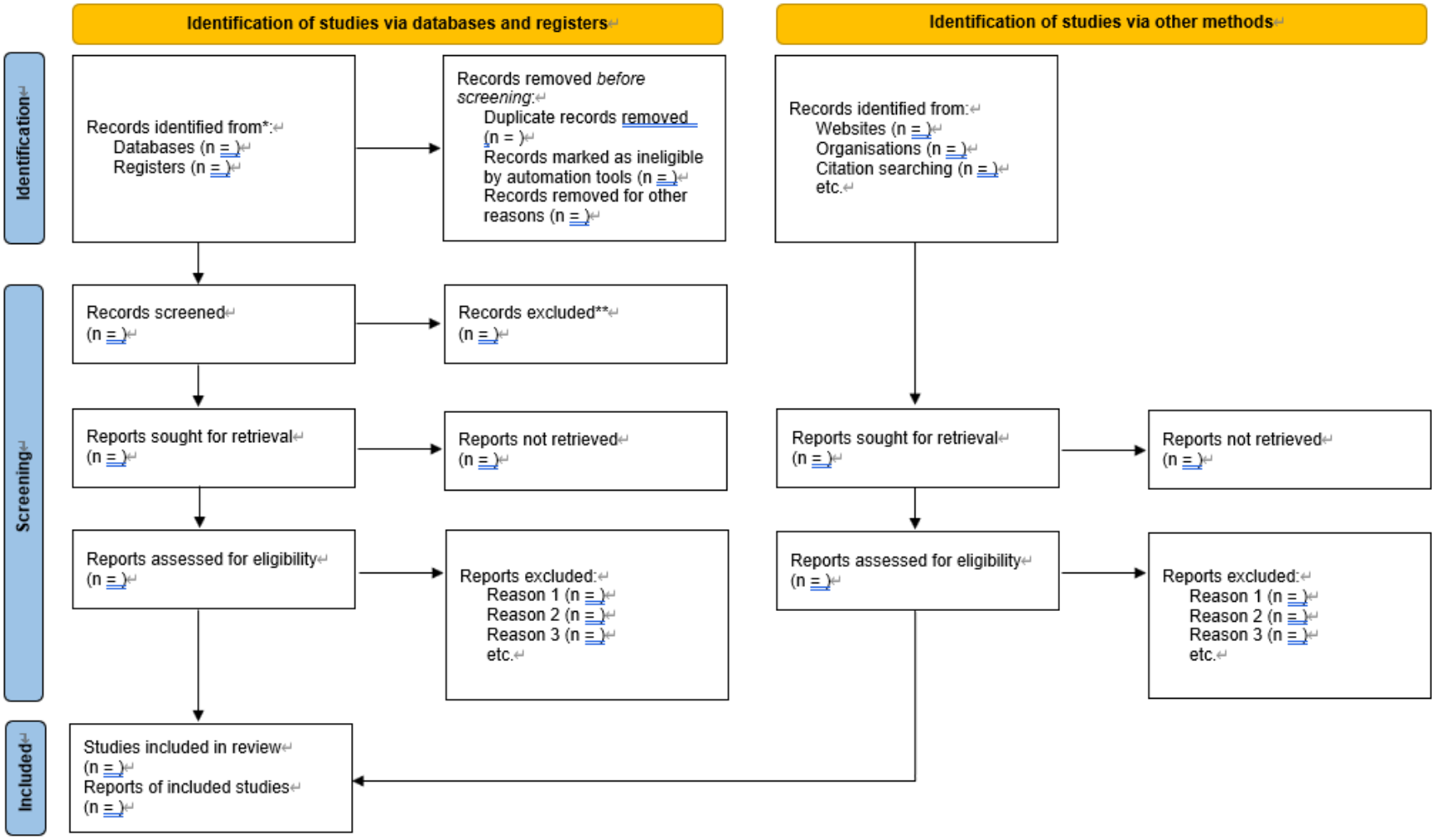
- □ Yes
- □ No
- □ Can't answer
- □ Not applicable

Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.

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

For Partial Yes (all the following):	For Yes, should also have (all the following):	
☐ searched at least 2 databases (relevant to research question)	☐ searched the reference lists/bibliographies of included studies	☐ Yes
☐ provided key word and/or search strategy	☐ searched trial/study registries	☐ Partial Yes
☐ justified publication restrictions (eg, language)	☐ included/consulted content experts in the field	☐ No
	☐ where relevant, searched for grey literature	
	☐ conducted search within 24 months of completion of the review	

연구선택의 흐름도(PRISMA)



•BMJ (OPEN ACCESS) Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 2021;372:n160. doi: 10.1136/bmj.n160
•http://www.prisma-statement.org/PRISMAStatement/PRISMAEandE

Cochrane Gut (**Literature Searching**)

Sources to search

During the development of the review, the CIS executes the search on the following databases,

- The Cochrane Library, which includes The Cochrane Central Register of Controlled Trials (**CENTRAL**) and the **Cochrane Database of Systematic reviews**
- **MEDLINE**
- **Embase**
- Cochrane Specialised Registers

When appropriate, the additional resources are searched, such as:

- **National, regional and subject-specific bibliographic databases** (e.g. CINAHL for nursing-related topics, PsycINFO for psychological interventions, AMED for alternative therapies; LILACS, etc)
- **Ongoing studies and unpublished**
- **Trials registers and trials results registers**
- **Regulatory agency sources and clinical study reports**
- **Other sources**

출간되지 않거나 진행 중 연구

- 비뚤림을 최소화하기 위해 중요함
- 연구자, 기타 정보를 가진 사람과의 연결
- 임상연구 등록원 :ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP), pharmaceutical industry(GSK Study Register -https://www.gsk-clinicalstudyregister.com)
- 규제기관과 임상연구보고서(CSRs) : EU Clinical Trials Register, Drugs@FDA , OpenTrialsFDA
- 회색문헌(Gray (Grey) literatures): 전통적으로 상업 또는 학술적인 출판 및 유통경로 외의 단체에서 생산한 자료 및 연구
- 학회발표(포스터,초록 등)
- 유사한 주제에 대한 기존 종설에서의 연구 참조
- 포함된 연구에 참고문헌 참조

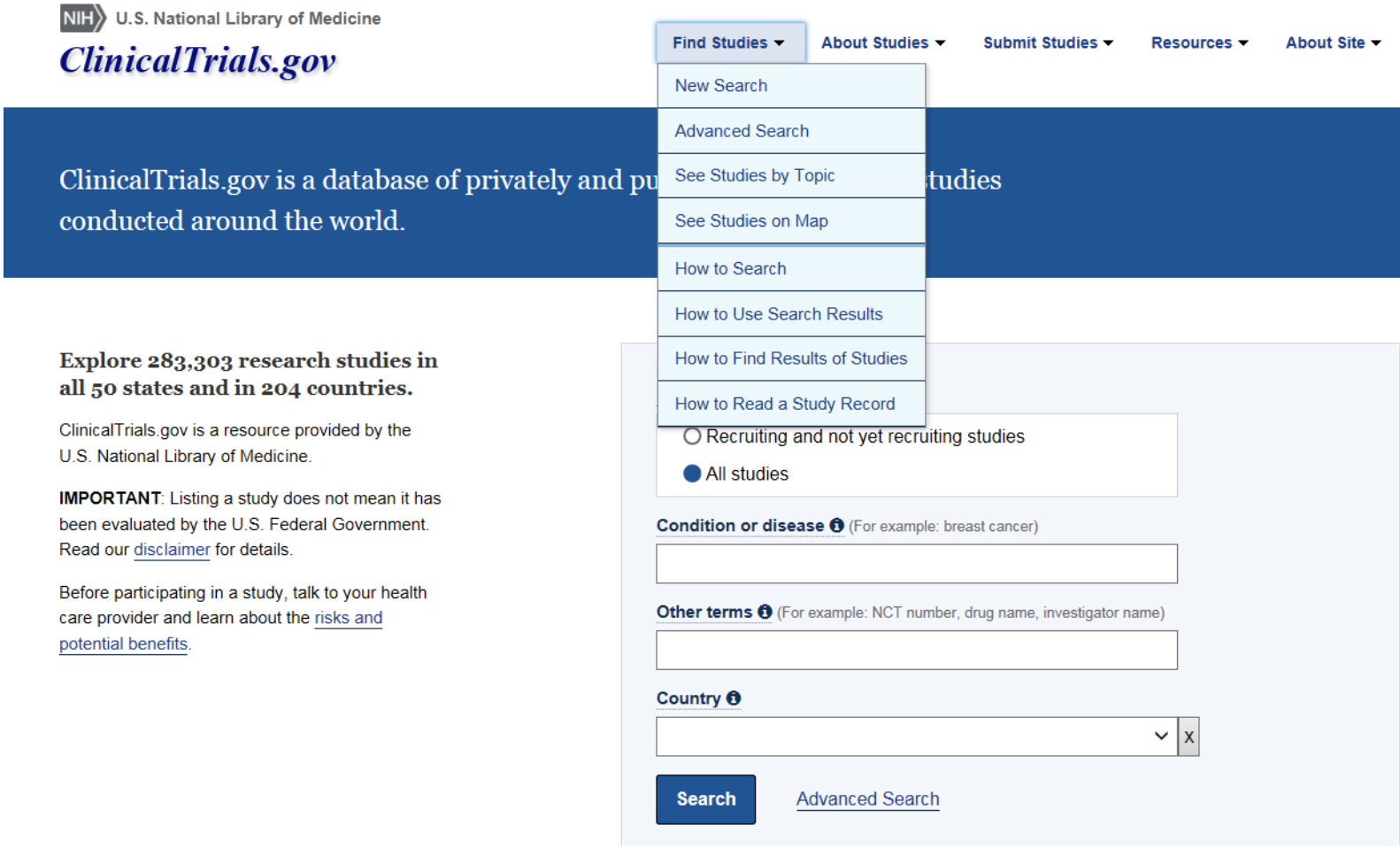
출판편향의 최소화를 위한 다양한 노력(규제기관보고)

4.3.4 Regulatory agency sources and clinical study reports #section-4-3-4

Potentially relevant regulatory agency sources include the EU Clinical Trials Register, Drugs@FDA and OpenTrialsFDA. Details of these are provided in the online Technical Supplement. Clinical study reports (CSRs) are the reports of clinical trials providing detailed information on the methods and results of clinical trials submitted in support of marketing authorization applications. In late 2010, the European Medicines Agency (EMA) began releasing CSRs (on request) under their Policy 0043. In October 2016, they began to release CSRs under their Policy 0070. The policy applies only to documents received since 1 January 2015. The terms of use for access are based on the purposes to which the clinical data will be put.

A recent study by Jefferson and colleagues (Jefferson et al 2018) that looked at use of regulatory documents in Cochrane Reviews, found that understanding within the Cochrane community was limited and guidance and support would be required if review authors were to engage with regulatory documents as a source of evidence. Specifically, guidance on how to use data from regulatory sources is needed. For more information about using CSRs, see the online Technical Supplement. Further guidance on collecting data from CSRs is provided in Chapter 5, Section 5.5.6.

연구계획서 등록사이트


NIH U.S. National Library of Medicine
ClinicalTrials.gov
Find Studies
About Studies
Submit Studies
Resources
About Site
New Search
Advanced Search
See Studies by Topic
See Studies on Map
How to Search
How to Use Search Results
How to Find Results of Studies
How to Read a Study Record
ClinicalTrials.gov is a database of privately and pu tudies
conducted around the world.
Explore 283,303 research studies in all 50 states and in 204 countries.
ClinicalTrials.gov is a resource provided by the U.S. National Library of Medicine.
IMPORTANT: Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.
Before participating in a study, talk to your health care provider and learn about the risks and potential benefits.
Recruiting and not yet recruiting studies
All studies
Condition or disease (For example: breast cancer)
Other terms (For example: NCT number, drug name, investigator name)
Country
Search
Advanced Search

International Clinical Trials Registry Platform (ICTRP)

International Clinical Trials Registry Platform (ICTRP)

Welcome to the WHO ICTRP

The mission of the WHO International Clinical Trials Registry Platform is to ensure that a complete view of research is accessible to all those involved in health care decision making. This will improve research transparency and will ultimately strengthen the validity and value of the scientific evidence base.

WHO/P. Virot

The registration of all interventional trials is a scientific, ethical and moral responsibility.

What is a clinical trial?

For the purposes of registration, a clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Clinical trials may also be referred to as interventional trials. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc. This definition includes Phase I to Phase IV trials.

What is trial registration?

WHO regards trial registration as the publication of an internationally-agreed set of information about the design, conduct and administration of clinical trials. These details are published on a publicly-accessible website managed by a registry conforming to WHO standards.

Trial Registration

Why is trial registration important?

How to register a trial

Organizations with policies on clinical trial registration

검색 T R P

Search for Trials

List By Health Topics

List By Countries

List By Regions/Countries

Useful Resources

International Standards for Clinical Trial Registries

FAQ

Glossary

Communication material

Acknowledgements

Queries & Comments

출판편향의 최소화(Grey literature network)

GreyNet International 2018

Grey Literature Network Service

- Home
- GreyNet Membership
- Newsletter
- GreyForum Series
- GreySource Index
- International Directory
- The Grey Journal
- Training Lab
- DANS Data Archive
- GreyGuide Repository
- OpenGrey Repository
- Grey Literature Textbook

Call for Posters

GreyNet International

Dedicated to Research, Publication, Open Access, Education, and Public Awareness to Grey Literature

DASHBOARD

Publications:

- Grey Journal
- Monograph
- Newsletter
- Proceedings
- Business Report

Organization:

- Membership
- Social Media
- Organizational Directory
- Who's Who in Grey Literature

Events:

- **International Conference 2018**
- GreyForum Workshop Series
- Research, Education and Training
- Annual Award Dinner

Open Sources:

- OpenGrey Repository
- Dans Data Archive
- GreyGuide Repository
- GreySource Web Index


Business Report Mid-Year 2018

The Grey Literature Network Service was founded in 1992. The goal of GreyNet is to facilitate dialog, research, and communication between persons and organisations in the field of grey literature. GreyNet further seeks to identify and distribute information on and about grey literature in networked environments. Its main activities include the International Conference Series on Grey Literature, the creation and maintenance of web-based resources, a moderated Listserv and combined Distribution List, The Grey Journal (TGJ), and curriculum development.

Grey Literature is a field in library and Information science that deals with the production, distribution, and access to multiple document types produced on all levels of government, academics, business, and organization in electronic and print formats not controlled by commercial publishing i.e. where publishing is not the primary activity of the producing body.

Grey Literature Network Service and Providers

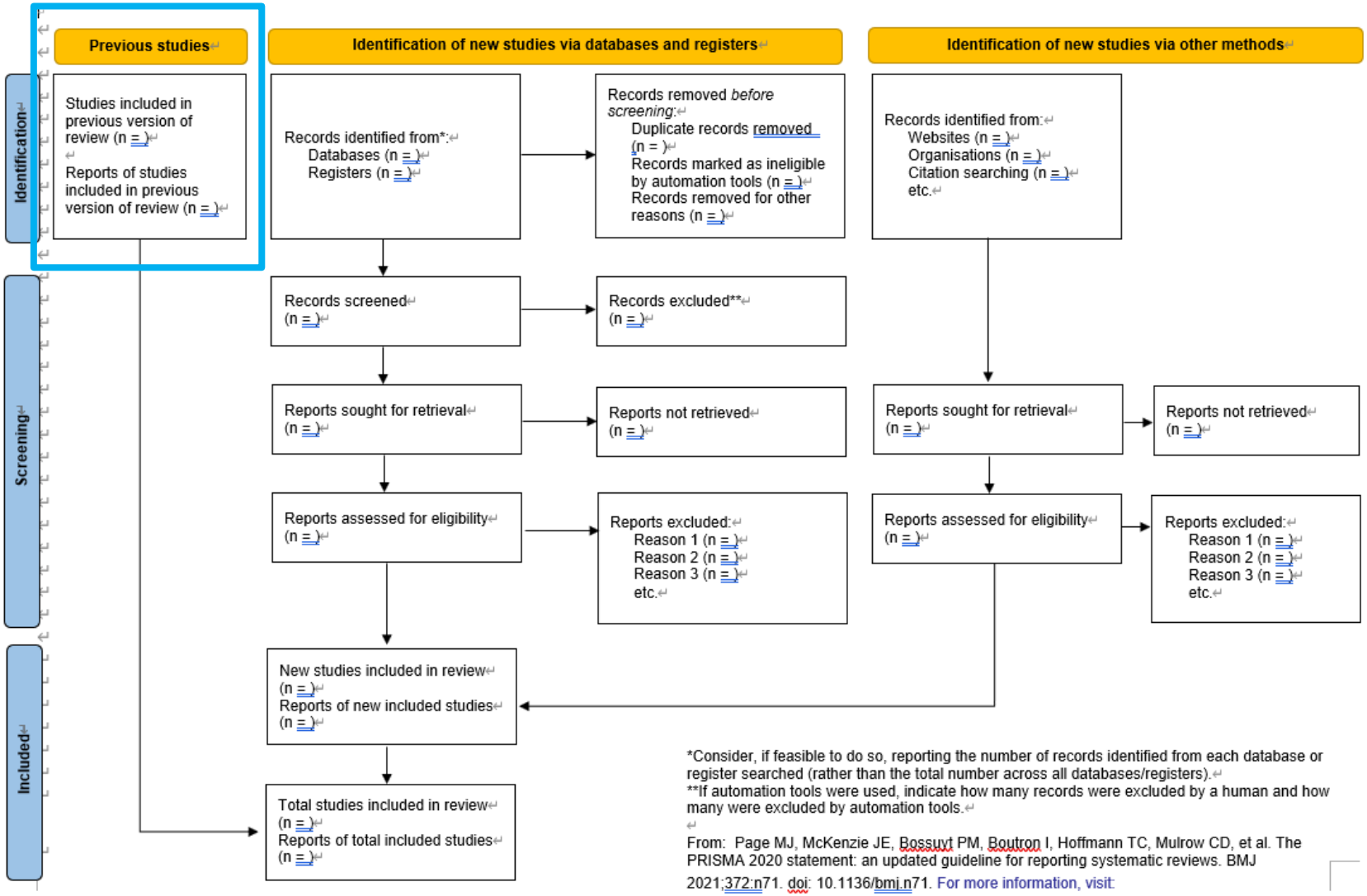
GreyNet is fully open access compliant. Authors and Researchers in grey literature communities worldwide know that their metadata, full-texts, slide presentations, research data, and other outputs are preserved and made openly accessible to the broader public.

- GreyGuide Portal and Repository
- OpenGrey Repository
- Dans Data Archive

OpenGray


Open Grey
System for Information on Grey Literature in Europe
Home
Search
Subjects
Partners
Export
Search
OpenGrey
System for Information on Grey Literature in Europe, is your open access to 700.000 bibliographical references of grey literature (paper) produced in Europe and allows you to export records and locate the documents.
Examples of grey (gray) literature include technical or research reports, doctoral dissertations, some conference papers, some official publications, and other types of grey literature.
OpenGrey covers Science, Technology, Biomedical Science, Economics, Social Science and Humanities.
The site includes preprints from the GL conferences (GreyNet International) in full text.
News
2018 07/27 Due to technical maintenance OpenGrey will not be available on Wednesday August 1st 2018 (French time)
2018 04/04 GL20, Research Data Fuels and Sustains Grey Literature - Call for Papers
2018 04/04 GL18, International Conference on Grey Literature, New York, 28-29 Nov. 2016 - Conference Papers available
2018 04/04 11th annual Conference on Grey Literature and Repositories at the National Library of Technology in Prague (CZ), October 24th, 2018 - Call for Papers
More news
Focus
Citations:1014872
Documents :375
(total number of PDF: 1105)
Number of citations by Sciences: 833,500
Social Science and Humanities: 325,000
Biomedical Science: 116,000
Science: 170,000
Technology: 222,500
Partners:14

PRISMA 2020 flow diagram for updated systematic reviews

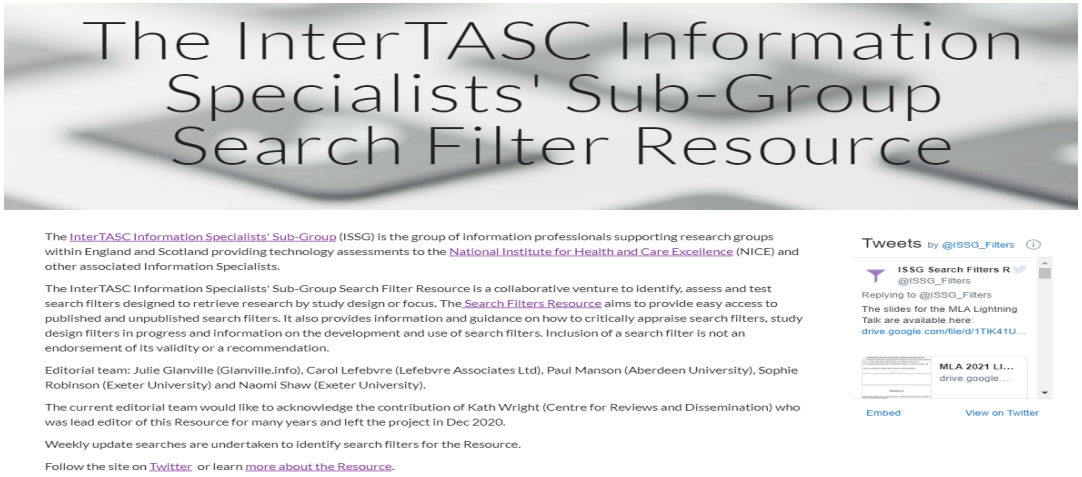


*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit:

검색필터

- 특정 종류의 연구를 찾아내기 위해 사전에 설계된 검색전략
  - 사람을 대상으로 한 무작위 임상연구(MEDLINE, Embase) : *Cochrane Highly Sensitive Search Strategies*
  - 다양한 종류의 검색필터 수집하여 제시 : https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home



제공하는 검색필터

Search filters for specific study design/focus

- Adverse effects
- Aetiology
- Diagnostic studies
- Economic evaluations
- Epidemiological studies
- Guidelines
- Health services research
- Health state utility values
- Mixed methods studies
- Non-randomized studies
- Observational studies / real world data
- Outcome studies
- Prognosis and Prediction Studies
- Public or Patient Views, Values, Issues, Experiences
- Qualitative research
- Quality of life
- Quasi-Experimental Studies
- RCTs and other trials
- Systematic reviews
- Therapy studies

Other filters

- Adherence filters
- Age filters
- Animal studies
- Clinical examination
- Evidence-based health care
- Gender-specific filters
- Geographic filters
- Health applications (apps)
- Health equity
- Health service settings: Primary care, Secondary care, Others
- Knowledge translation
- Patient safety filters
- Population group filters (including prehospital/emergency care, pregnancy, sexual minorities, immigrants, indigenous peoples, people with disabilities, ethnic groups)
- Quality improvement
- Off-label drug use

Filters added recently

- 2021
- 2020
- 2019 and earlier

검색전략의 효율성에 대한 고민 : 다른 연구설계 및 주제

- 무작위 연구 외에 연구설계에 대한 검색전략의 부정확성

Use of methodological search filters to identify diagnostic accuracy studies can lead to the omission of relevant studies

M.M.G. Leeflang[a,b,*], R.J.P.M. Scholten[a,b], A.W.S. Rutjes[a], J.B. Reitsma[a], P.M.M. Bossuyt[a]

[a]*Academic Medical Center, Amsterdam, The Netherlands*
[b]*Dutch Cochrane Centre, Department of Clinical Epidemiology and Biostatistics, Academic Medical Center, J1B-210, P.O. Box 22700, 1100 DE Amsterdam, The Netherlands*

Accepted 4 July 2005

Abstract

Objective: To determine the usefulness of methodological filters in search strategies for diagnostic studies in systematic reviews.

Study Design and Setting: We made an inventory of existing methodological search filters for diagnostic accuracy studies and applied them in PubMed to a reference set derived from 27 published systematic reviews in a broad range of clinical fields. Outcome measures were the fraction of not identified relevant studies and the reduction in the number of studies to read.

Results: We tested 12 search filters. Of the studies included in the systematic reviews, 2%–28% did not pass the sensitive search filters, 4%–24% did not pass the accurate filters, and 39%–42% did not pass the specific filters. Decrease in number-needed-to-read when a search filter was used in a search strategy for a diagnostic systematic review varied from 0% to 77%.

Conclusion: The use of methodological filters to identify diagnostic accuracy studies can lead to omission of a considerable number of relevant studies that would otherwise be included. When preparing a systematic review, it may be preferable to avoid using methodological filters.

Keywords: Diagnosis; Evidence-based medicine; Human; Information storage and retrieval; Medline; PubMed

예후연구에 대한 검색

- Geersing et al, PLOS One 2012 : Search Filters for Finding Prognostic and Diagnostic Prediction Studies in Medline to Enhance Systematic Reviews
  - ''Stratification'' OR ''ROC Curve''[Mesh] OR ''Discrimination'' OR ''Discriminate'' OR ''c-statistic'' OR ''c statistic'' OR ''Area under the curve'' OR ''AUC'' OR ''Calibration'' OR ''Indices'' OR ''Algorithm'' OR ''Multivariable''
- Haynes et al, BMJ 2005
  - (Predict*[tiab] OR Predictive value of tests[mh] OR Scor*[tiab] OR Observ*[tiab] OR Observer variation[mh])
- Ingui et al, J Am Med Inform Assoc 2001
  - (Validat$ OR Predict$.ti. OR Rule$) OR (Predict$ AND (Outcome$ OR Risk$ OR Model$)) OR ((History OR Variable$ OR Criteria OR Scor$ OR Characteristic$ OR Finding$ OR Factor$) AND (Predict$ OR Model$ OR Decision$ OR Identif$ OR Prognos$)) OR (Decision$ AND (Model$ OR Clinical$ OR Logistic Models/)) OR (Prognostic AND (History OR Variable$ OR Criteria OR Scor$ OR Characteristic$ OR Finding$ OR Factor$ OR Model$))

검색필터의 민감도

Table 5. Updated search strings for predictor finding studies.

	Meta-analysis search	
Ingui filters	**Sensitivity (95% CI)**	**NNR**
"Ingui filter" OR "update"	0.47 (0.36–0.59)	569
Haynes filter		
"Haynes broad filter" OR "update"	0.84 (0.74–0.91)	1010

CI = confidence interval; NNR = number needed to read.
Updated search string = "Stratification" OR "ROC Curve"[Mesh] OR "Discrimination" OR "Discriminate" OR "c-statistic" OR "c statistic" OR "Area under the curve" OR "AUC" OR "Calibration" OR "Indices" OR "Algorithm" OR "Multivariable".
Meta-analysis for predictor finding studies = Systematic review of prognostic models in patients with acute stroke – C Counsell et.al. Cerebrovasc Dis 2001; 12:159–70.
doi:10.1371/journal.pone.0032844.t005

Table 6. Updated search strings for finding clinical prediction models studies.

	Meta-analysis 1		Meta-analysis 2	
Ingui filters	**Sensitivity (95% CI)**	**NNR**	**Sensitivity (95% CI)**	**NNR**
"Ingui filter" OR "update"	0.97 (0.83–0.99)	68	0.94 (0.74–0.99)	125
Haynes filter				
"Haynes broad filter" OR "update"	0.90 (0.74–0.96)	208	0.89 (0.67–0.97)	395

CI = confidence interval; NNR = number needed to read.
Updated search string = "Stratification" OR "ROC Curve"[Mesh] OR "Discrimination" OR "Discriminate" OR "c-statistic" OR "c statistic" OR "Area under the curve" OR "AUC" OR "Calibration" OR "Indices" OR "Algorithm" OR "Multivariable".
Meta-analysis 1 for clinical prediction models studies = Clinical prediction rules for pulmonary embolism: a systematic review and meta-analysis – E Ceriani et.al. JTH 2010;8:957–70.
Meta-analysis 2 for clinical prediction models studies = Accuracy and quality of clinical decision rules for syncope in the emergency department: a systematic review and meta-analysis – LA Serrano et.al. Ann of Emerg Med 2010;56:362–73.
doi:10.1371/journal.pone.0032844.t006

연구의 질적 수준 : 비평과 선택(연구의 비평적 평가)

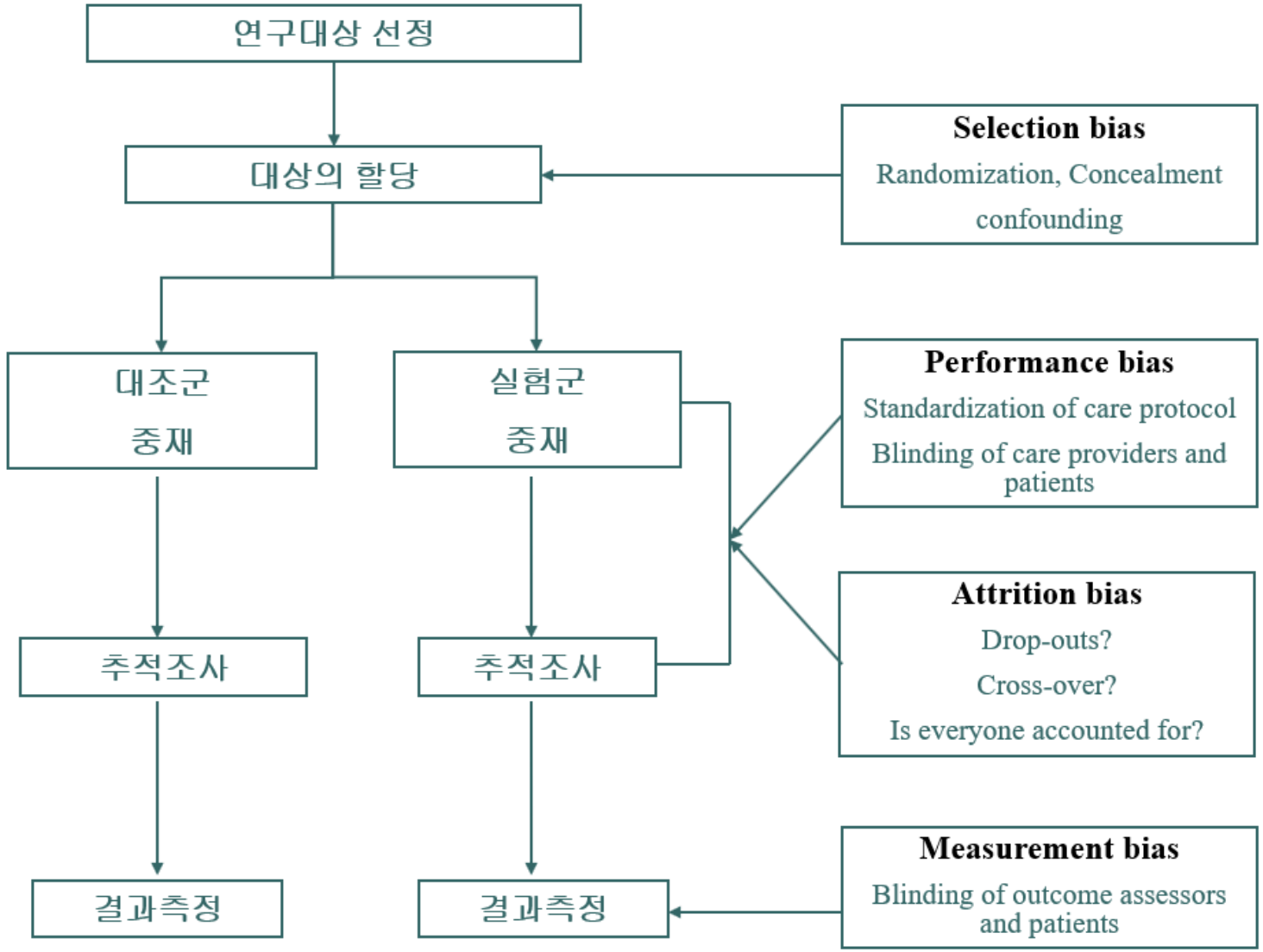
The question we ask ourselves is “Is the study informative?” rather than “Is the study perfect?”

근거의 수준이란 무엇인가?

- 특정 주재가 효과가 있을 것이라는 것에대한 우리의 신뢰에 대한 판단을 어떻게 할 것인가?
- 특정 근거에 대한 확실성(The certainty in the evidence)은 관련성이 있거나 혹은 원인결과관계라는 것에 대한 신뢰성에 대한 판단
- 기존에 연구결과 추정치에 대한 신뢰성 또는 근거의 질(quality)과 같음

근거수준의 결정요소 : 첫번째 : 연구설계

근거수준의 결정요소 : 연구설계 + 연구설계에 따른 과정 중 발생가능한 다양한 비뚤림위험과 해석의 문제



연구의 비뚤림 위험을 평가하는 방법

- 연구설계+ 과정에 대한 비뚤림 위험요소의 평가

- 연구설계에 따라 문헌평가방법을 적용
  - 무작위대조군 연구 :
    - Cochrane Risk of Bias 2.0(무작위 방법, 배정은폐, 맹검적용, 불완전한 보고 …)
  - 비무작위 대조군 연구 :
    - The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool(7개 도메인)
    - The Newcastle-Ottawa Scale(선택,비교,결과)
  - 진단방법 : QUADAS 2.0
  - 단면연구 :
    - Appraisal tool for Cross-Sectional Studies (AXIS)
- 적절한 도구를 선택

예후연구에 대한 분류

- Average/overall prognosis : 특정 건강상태에 있는 개인의 특정 기간동안 가장 가능성이 높은 원인과 결과는 무엇인가?
- Prognostic factor studies : 특정건강상태에 있는 개인에게 있어 특정 요인과 결과와의 관련성은 무엇인가?
- Prognostic model studies : 특정 건강상태내에서 예후요인의 어떤 조합이 특정 결과를 예측하거나 잘 검증하는가?
- Treatment selection factors : 어떤 요인과 혹은 요인의 조합이(모델) 특정건강상태내에서의 개인의 특정 중재의 효과의 예측하는가?

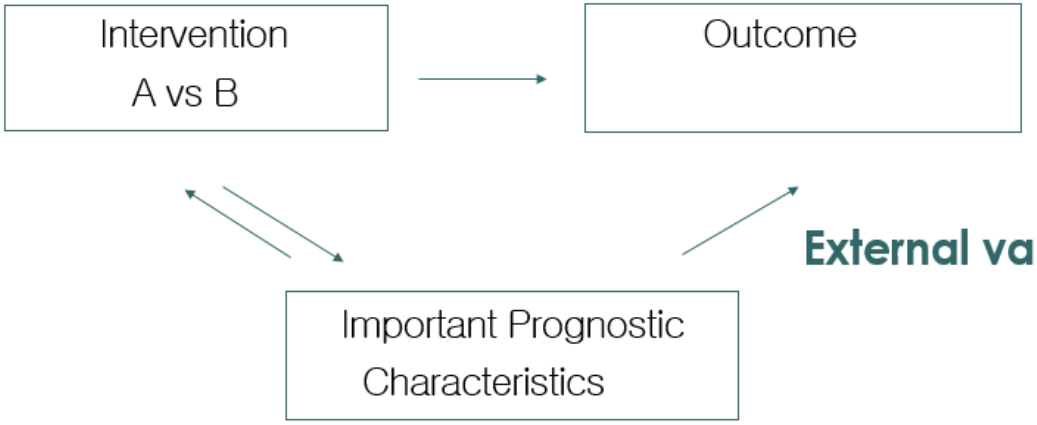
- Introducing systematic reviews of prognosis studies to Cochrane: what and how?, Cochrane Prognosis Methods Group (PMG)

예후에 대한 질평가도구

- Prognostic factor/predictor finding studies
  - RoB tool : QUIPS(**Evaluation of the quality of prognosis studies in systematic reviews)** J Hayden, Ann Int Med 2006
- Prediction modelling
  - Critical Appraisal: CHARMS(**Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist)** K Moons, Plos Med 2014
  - Risk of Bias: PROBAST(**PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies)** ,Ann Intern Med. 2019 : 4개의 항목, 20개 하위질문으로 구성되어 있음

개별연구설계별 타당성 검증의 문제

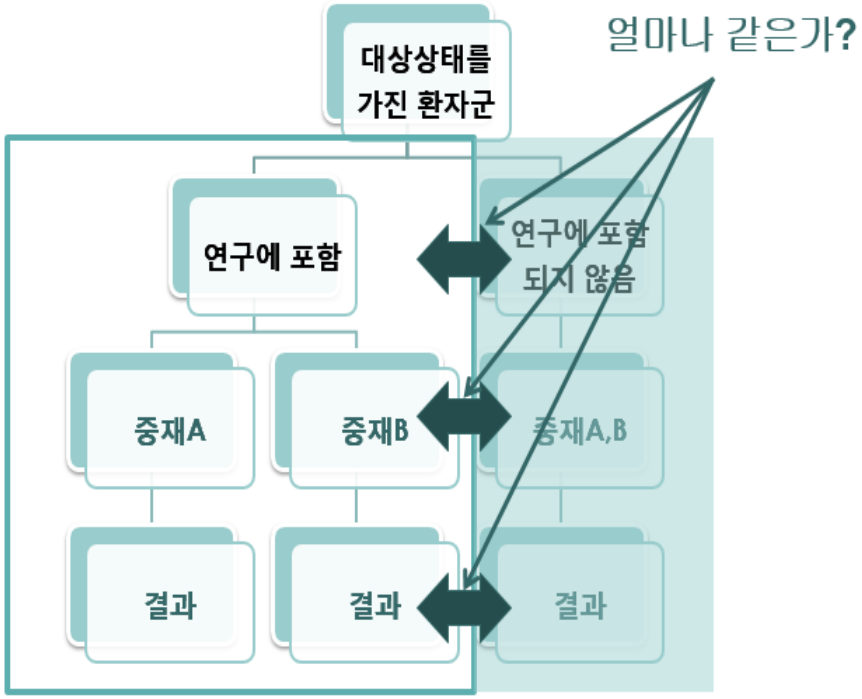
Internal validity



External validity

연구의 합산에서의 비뚤림 위험
(cumulative evidence)

biases that are **internal** to the study, and not to issues of **indirectness** (generalizability, applicability or transferability to people who were excluded from the study)



PRISMA에서의 비뚤림 위험(결과) 보고내용

Risk of bias in studies	18	Present assessments of risk of bias for each included study.	개별연구 단위
Results of syntheses	20 a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20 b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20 c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20 d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	고찰단위
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	

연구의 질의 합산 : 체계적고찰은 다양한 비뚤림을 가진 개별연구의 합산

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

For Yes:

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

☐ Yes
☐ No
☐ No meta-analysis conducted

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

For Yes:

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

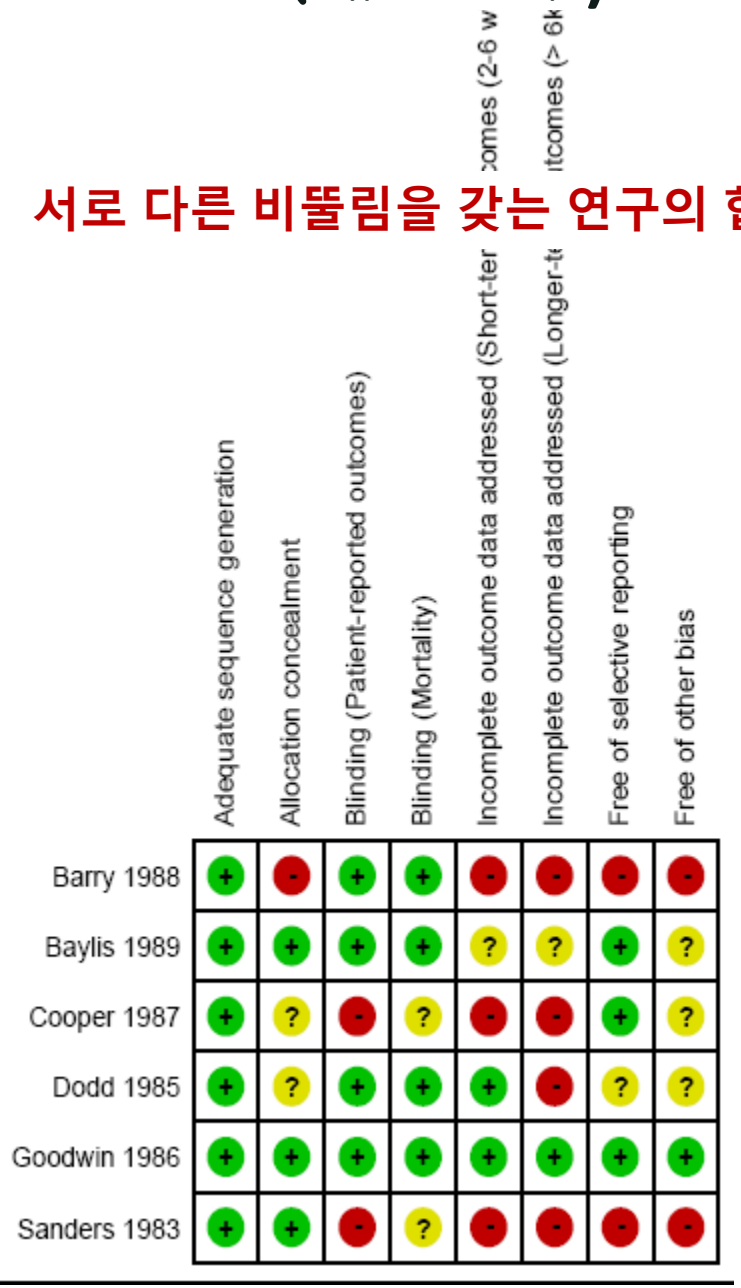
☐ Yes
☐ No

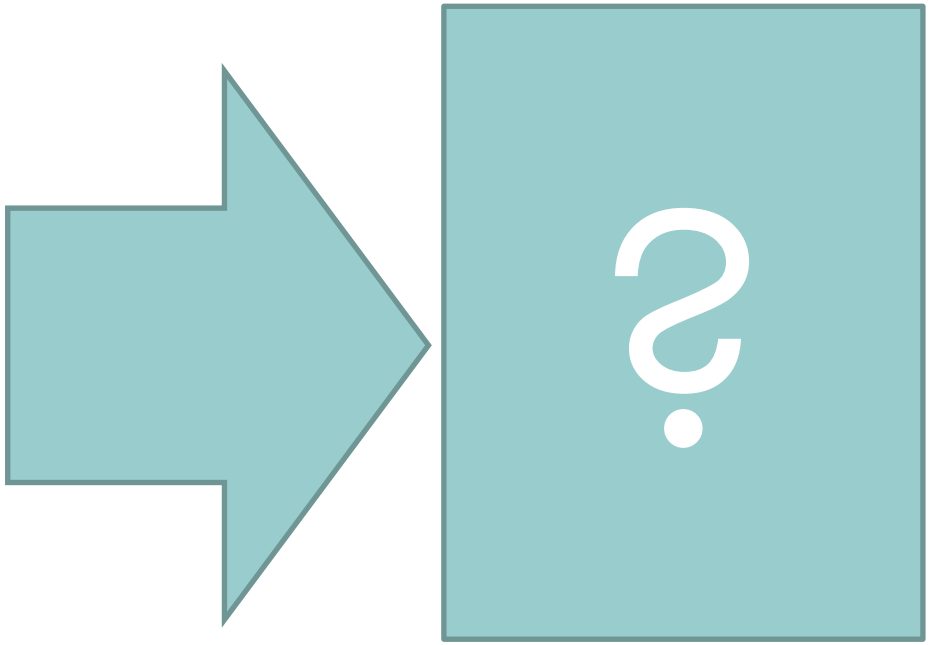
AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or nonrandomised studies of healthcare interventions, or both, BMJ. 2017 Sep 21;358:j4008

Risk of bias (개별연구)

Level of evidence(메타분석)

서로 다른 비뚤림을 갖는 연구의 합에서의 근거의 수준은 무엇인가?





Risk of bias within studies & Risk of bias across studies

- Risk of bias within studies : 개별 연구들의 연구주제, 연구방법에 따른 비뚤림 위험
  - 개별연구에 맞게 적정한 도구 선택하여 개별연구의 내적타당도를 평가함
  - 무보고에 대한 평가를 수행하지 않음: 무보고로 인해 보고된 결과가 비뚤림의 위험이 증가하지 않기 때문
- Risk of bias across studies : 연구들을 모으기 때문에 생기는 비뚤림 위험
  - 연구들 간의 이질성, 정확성, 모인 연구들의 비뚤림 위험, 간접성, 출판편향 등에 대한 평가
  - 개별연구의 무보고로 인해 연구결과의 누락이 있다면 연구를 모았을 때 출판편향의 문제를 발생시킬 수 있음
  - 연구주제에 맞는 타당한 연구설계가 존재함

연구 주제별 타당한 연구설계에 대한 접근

연구주제	중재	진단연구	예후연구3)
타당한 연구설계	무작위 대조군 연구	1. 진단적 불확실성을 가지고 있는 환자를 대상으로 한 환자대조군 연구 혹은 코호트 연구 2. 동일한 연구내에서의 직접비교를 수행한 연구 3. 적절한 표준검사가 있는 경우	코호트연구, 레지스트리 예후에 대한 2차분석을 수행하는 무작위대조군 연구는 포함과 배제기준의 적용으로 인해 예후요인에 대한 비뚤림 위험을 발생시킬 수 있음

1) GRADE guidelines: 21 part 1. Study design, risk of bias,and indirectness in rating the certainty across a body of evidence for test accuracy, H.J. Sch€unemann et al. / Journal of Clinical Epidemiology 122 (2020) 129e141

2) GRADE Guidelines 28: Use of GRADE for the assessment of evidence about prognostic factors: rating certainty in identification of groups of patients with different absolute risks, F. Foroutan et al. Journal of Clinical Epidemiology 121 (2020) 62-70

11. 만약 메타분석이 시행되었다면 개별연구결과를 합산하는 적절한 통계방법을 사용하였는가?

-무작위대조군 실험연구-
Yes : ☐ 메타분석에 포함된 데이터를 합산하는 타당성을 제시하고 있음 ☐ 그리고 적절한 가중치 적용방식을 통해 연구결과를 합산하였고 만약 이질성이 존재 한다면 이질성을 보정하였음 ☐ 그리고 이질성의 원인을 위한 분석을 추가하였음
-비무작위대조군연구-
Yes : ☐ 메타분석에 포함된 데이터를 합산하는 타당성을 제시하고 있음 ☐ 그리고 적절한 가중치 적용방식을 통해 연구결과를 합산하였고 만약 이질성이 존재 한다면 이질성을 보정하였음 ☐ 그리고 비무작위 대조군 연구는 원래의 원자료 보다 교란변수를 통제한 방법에 의한 결과를 이용하였거나, 보정된 추정치를 사용하는 것이 가능하지 않아 원자료를 이용한 자료분석을 했다면 합산의 타당성을 제시 ☐ 그리고 무작위대조군연구와 비무작위 대조군 연구를 모두 포함하는 경우 이를 분리하여 요약된 추정치를 제시함

적절한 방법(appropriate methods)

- 적절한 가중치 (Appropriate weighted technique) : fixed(true effect) or random effects(average effect) models
- 이질성에 대한 분석 (Heterogeneity) : subgroup, meta regression
- 비무작위대조군 연구 :
  - 통계적 검정력이 높을 가능성이 있으나 비뚤릴 가능성precise(sample size) but biased
  - 교란변수(Confounders): 효과에 대한 영향력을 반드시 보정이 필요
- 연구설계 별 분리된 연구결과 합산(separately for the different study types)

PRISMA 2020 _ synthesis methods

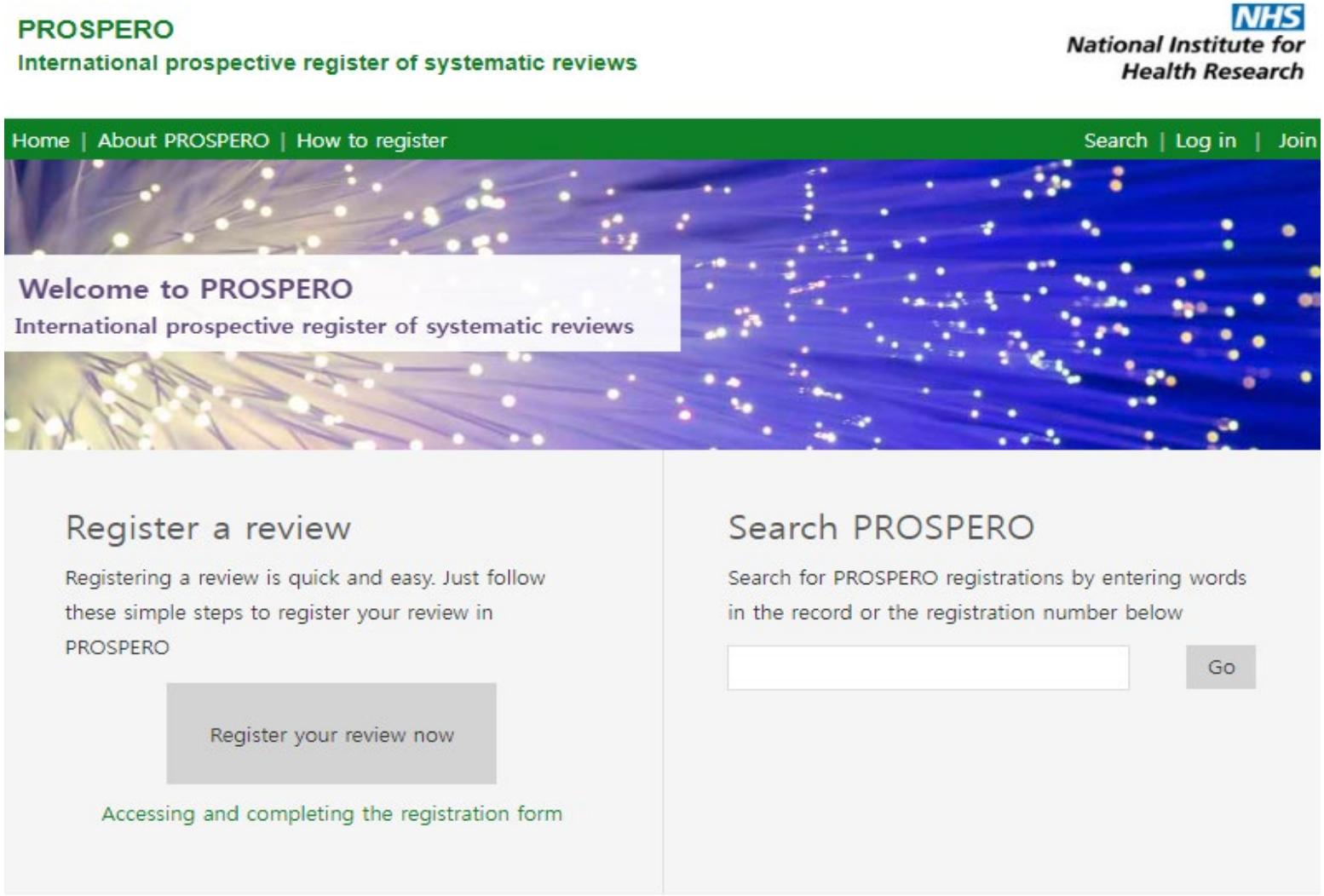
13a	각 **연구결과 합성에 적합한 연구를 결정하는데 사용된 프로세스를** 설명(예: 연구의 중재 특성 표 작성 및 각 연구결과 합성에 대한 계획된 그룹과 비교)
13b	**결측(누락)된 요약통계 처리 또는 데이터 변환과** 같이 연구결과 제시 및 합성을 위해 데이터 준비하는데 필요한 방법 설명
13c	개별연구 및 합성결과를 표로 작성하거나 시각적으로 표시하는데 사용되는 방법 설명
13d	결과 합성에 사용되는 방법을 설명하고 선택에 대한 근거 제공. 메타분석을 수행한 경우 모델선택, 통계적 이질성의 존재와 정도를 식별하는 방법 및 사용된 통계프로그램을 기술
13e	연구결과에 따른 이질성의 가능한 원인을 탐구하기 위해 사용되는 방법을 설명(예: 하위그룹 분석, 메타회귀분석)
13f	합성결과의 견고성을 평가하기 위해 사용된 민감도 분석방법을 설명

체계적고찰 연구의 관찰 연구로서의 특성

- 무작위대조군 실험연구들을 체계적고찰 한다 하더라도 고찰 그 자체는 관찰연구에 해당
  - 즉, 잠재적인 관찰연구의 비뚤림의 가능성을 가짐
    - 다른 특성을 가진 무작위 연구의 결과를 비교하는 것은 비교군 간에 무작위가 되지 않았으므로, 결과를 교란시킬 수 있음
    - 메타분석에서의 하위그룹분석은 결과에서 우연한 관련성을 증가시킬 수 있음

- 자료선택과 분석계획에 관한 계획서(protocol) 필요
- 연구보고에 사전에 계획한 비교결과인지 결과에서 도출된 것 에 따른(data-driven) 결과인지에 대한 명확한 구분 필요

프로토콜에 대한 사전 등록 : 사전에 계획된 대로의 분석



최근 체계적고찰의 연구방법의 변화

코크란 핸드북의 주요 목차

주요 변경사항

MECIR	NON-STATISTICAL METHODS OF SYSTHESIS
INTERVENTION COMPLEXITY	CONFLICT OF INTEREST
LOGIC MODEL	CLINICAL STUDY REPORTS AND REGULATORY SOURCES
NETWORK META-ANALYSIS	SEMI-AUTOMATION OF TASKS
RISK OF BIAS DUE TO MISSING RESULTS	ROBINS-I

- 새로운 메타분석 : 네트워크 메타, 자동화 이슈
- 평가도구의 점검(좀더 엄격한 방법론의 적용)
  - 무작위대조군연구의 평가도구 업데이트
  - 비무작위연구에 대한 평가도구 개발
  - 보고비뚤림(비보고(무보고)결과로 기인된 비뚤림)에 대한 재평가
- 다양한 연구설계에 대한 고려 및 비무작위연구에 대한 확장
  - 복합중재, 정량적이지 않은 데이터에 대한 연구결과 합, 비무작위 연구에 대한 고려
- 이해관계의 충돌

Conflict of interests(이해관계의 충돌)

- "일차적 이익에 관한 전문적인 판단이나 행동이 부차적인 이익에 부당하게 영향을 받을 위험을 야기하는 일련의 상황"
- Financial vs non-financial(individual, intellectual, institutional)
- 다양한 영향 가능

- 이해관계의 충돌에 대한 평가도구 : TACIT(Tool for Addressing Conflicts of Interest in Trials, http://tacit.one/)

PRISMA 2020의 주요변경내용

Information sources	**6**	**Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.**
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.

PRISMA 2020의 주요변경내용(결과)

Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.

PRISMA 2020의 주요변경내용(기타내용)

Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing interests	26	Declare any competing interests of review authors.
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found ; template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

체계적고찰과정의 요약

- 적절한 질문
- 연구의수
  - 2~4개 사이의 논문은 메타분석이 오히려 비뚤림을 유발할 수 있음
  - 포괄적이고 민감도 높은 검색
  - 검색전략 구현 시 도서관 사서와의 의사소통을 통한 협업이 필요
  - 최소 3개 이상의 검색원 및 다양한 수기검색이용
  - 회색문헌에 대한 검색포함
- 연구의 질적수준에 대한 평가
  - 연구설계별 적절한 평가도구 선정
  - 연구내용에 적합한 평가항목의 개발 및 적용
  - 개별연구수준 외 전체 연구에 대한 근거수준에 대한 평가와 고찰필요(GRADE 포함)

체계적고찰과정의 요약

- 연구들 간의 유사성/이질성 탐색
  - 이질성의 원인에 대한 탐구(사전에 엄격한 기준설정 필요)
  - 통계적 이질성이 분석되지 않은 경우에도 임상적 이질성이 있는 경우 반드시 이에 대한 분석이 필요
  - 다중분석에 대한 유의(사전에 분석계획 수립 및 보고)
- 모든 연구에서의 결과보고
  - 10개 이하의 연구에 대한 출판편향에 대한 검정은 검정력이 낮음으로 권고되지 않음
  - 연구의 수와 관계없이 출판편향에 대한 문제, 출판편향으로 기인한 연구결과의 방향에 대한 해석 및 고찰
  - 무보고(부작용 등), 결측 자료로 기인된 비뚤림의 위험에 대한 보고 및 처리방안제시

체계적고찰과정의 요약

- 적절한 통계방법의 적용
  - 가중치 적용방법의 선택(모집단에 대한 가정 : 고정효과모델 vs 변량효과모델
  - 연구설계별 분리된 분석
- 사전에 연구계획서 작성 및 등록(PROSPERO)
- 체계적고찰의 보고지침에 따라 작성(PRISMA)

경청해 주셔서 감사합니다

고려대학교 의과대학 코크란연합한국지부

E-mail : moole02@naver.com

김현정