

INTRODUCTION TO SYSTEMATIC REVIEWS

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OBJECTIVES

- What is a Systematic Review?
- Different Types of Reviews
- Conducting a Review
 - Develop a research question and protocol
 - Searching process
 - Choosing Databases
 - Publication Bias
 - Term Harvesting
 - Grey Literature
 - Specialty Techniques
 - Evidence Rankings
 - Presenting the Data: systematic reviews and meta-analysis
 - Writing the Methods Section

WHAT IS A SYSTEMATIC REVIEW?

“A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria to answer a specific research question. It uses explicit, systematic methods that are selected to minimize bias, thus providing reliable findings from which conclusions can be drawn and decisions made.”

Liberati, et al., 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009; 62: e1-e34.

WHY DO A SYSTEMATIC REVIEW?

- Save clinicians and researchers valuable time
 - Take a large mass of literature and make concise sense of it
 - Objectively evaluate the quality of evidence on a topic
 - Resolve or highlight contradictions in the literature
 - Guide clinical decisions
 - Form the basis for practice guidelines and health care policy
 - Identify the need for additional research
 - Prevent unnecessary studies from being carried out
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KEY CHARACTERISTICS

A systematic review:

- IS A RESEARCH STUDY
- Is based on a well-defined research question
- Is comprehensive
- Is objective
- Evaluates the quality of included evidence



WARNING

Not all “reviews” are true “systematic reviews”

Just because it calls itself a “systematic review,” doesn’t mean that it actually *is* a systematic review or that it is a *good-quality* systematic review



TYPES OF REVIEWS

- **Narrative reviews** – Broad perspective on topic (like a textbook chapter), no specified search strategy, significant bias issues, may not evaluate quality of evidence
 - **Structured reviews** – Includes a structured, but limited search, less bias, but not comprehensive, usually evaluates quality of evidence
 - A partial systematic review
 - **Systematic reviews** – Comprehensive and minimized bias, qualitative, evaluates quality of evidence
 - Based on randomized controlled clinical trials (RCTs) – Best evidence
 - Based on other types of clinical studies or literature – Best *available* evidence
 - **Meta-analysis** – A quantitative systematic review that applies statistical analysis
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SYSTEMATIC REVIEWS & META-ANALYSIS

Systematic Reviews are *qualitative* research studies in which primary studies summarized but not statistically combined

Meta-analyses are *quantitative* systematic reviews and involve combining the results of multiple primary studies using statistical methods

Meta-analysis is just a special (quantitative) type of systematic review.



STEPS TO CONDUCT A SYSTEMATIC REVIEW

1. Develop a research question
 2. Define inclusion and exclusion criteria
 3. Locate studies
 4. Select studies
 5. Assess study quality
 6. Extract data
 7. Analyze and present results
 8. Interpret results
 9. Update the review as needed
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RESEARCH QUESTION: INTRODUCING PICO

Method of structuring the research question:

PICO

- **Patient population**
 - Children aged 3-8 yrs diagnosed with croup
- **Intervention**
 - Use of dexamethasone to treat croup
- **Comparison**
 - Use of betamethasone to treat croup
 - *(optional, depending on the study question)*
- **Outcomes**
 - Comparative relief of symptoms A, B, C; results of observations D, E, F; or test results G, H, I...

<http://healthlinks.washington.edu/ebp/pico.html>

DEFINE INCLUSION/EXCLUSION CRITERIA

- Often called “Limits” during search process
- Determined by research question
- Defines which ‘subjects’ (studies) will be included in or excluded from the review
- Define prior to starting the search
- Broader inclusion criteria allows more generalization of the review
- May include choice of languages, publication dates, publication types, etc.

Be aware limits may introduce bias as they may cause loss of valuable data.



PRE-ESTABLISH SEARCH PROTOCOL

- Identify databases and other resources
 - Identify search terms, develop search strategies, conduct searches
 - Need to have *at least 2* independent reviewers to select studies based on pre-established inclusion/exclusion criteria and *another* available to resolve 'ties'
 - Study selection process is usually reiterative...
 - Review title/abstract
 - Review full-text
 - Keep a log of excluded studies with reasons for exclusion
 - Keep track of numbers of results from searches, number of duplicates found, number of studies excluded at each step
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CHOOSING DATABASES

To reduce bias multiple databases must be searched

- Each database should be searched with a database-specific search strategies
- Common minimum is usually Medline(PubMed), Embase, Cochrane Central Registry of Controlled Trials
- Choice of others depends on nature of question: Bioscience Literature Databases, Nursing Literature Databases, Pharmacology Literature Databases, Education Literature Databases, etc.

Issues

- Balancing sensitivity and specificity
 - When to stop?
 - Effect of limits (inclusion/exclusion criteria)
- Access to resources
- Bias

PUBLICATION BIAS

**“Publication bias is the term for what occurs whenever the research that appears in the published literature is systematically unrepresentative of the population of completed studies.”
(Rothstein, 2005)**

Systematic reviews aim to include ALL high quality studies about the research question. This is difficult to accomplish, but a missed study or studies may affect results and conclusions.

Rothstein H, Sutton AJ, & Borenstein M. (2005). Publication bias in meta-analysis prevention, assessment and adjustments. Chichester, England; Hoboken, NJ: Wiley.

FROM THE COCHRANE COLLABORATION

“Publication bias and other related biases can be summarised as statistically significant, 'positive' results being:

- *more likely to be published (publication bias)*
- *more likely to be published rapidly (time lag bias)*
- *more likely to be published in English (language bias)*
- *more likely to be published more than once (multiple publication bias)*
- *more likely to be cited by others (citation bias)*

All of these reporting biases make positive studies easier to find than those with non-significant results, something that we can try to minimise by extensive searching.”

MINIMIZE BIAS

Negative studies, equivocal results studies, non-English studies are less likely to get published, less likely to get into the top journals, and less likely to get cited.

Not everything gets published in peer-reviewed journals

Be aware you are introducing bias if you not looking beyond the obvious sources.

Don't forget meeting/conference abstracts, clinical trial registry sources, websites, dissertations, patents, etc. (Grey Literature)

Be cautious of using language limits.



TERM HARVESTING

Methods for gathering and utilizing search vocabulary (search terms) for the literature review.

Issues

- Clearly defined search question, inclusion/exclusion criteria, and outcomes required
- A few 'good' articles pre-identified can be useful resources
- Knowledge of databases including scope, use of controlled vocabularies, search interfaces is valuable
- Knowledge of search strategy logic and construction is valuable
- Keep EXCELLENT records (use a 'term harvesting form')

Use available expertise



consider collaborating with your medical librarian!

SAMPLE TERM HARVESTING FORM - PUBMED

Question: Are steroids effective in treating croup in young children?

Concept:	steroids	croup	young children
MeSH Terms			
Pharmacological Action Terms			
Textwords			

MORE ON TERM HARVESTING

To find more terms:

- Read about topic (textbooks, older reviews, other articles, other sources)
- Talk to experts (other members of team, clinicians, colleagues, etc.)
- Look at indexing of pre-identified 'good' articles
- Brainstorm, brainstorm, brainstorm

Know how to use controlled vocabularies effectively and when to combine with textwords

Know the idiosyncrasies of each database. Searching only one database is NEVER enough.

- Not all have controlled vocabularies
 - Each controlled vocabulary tends to be unique
 - How do they handle phrase searching?
 - How do they handle limits?
 - How do they handle field searching?
 - What are the options for saving searches and exporting search results?
- 

DEVELOPING SEARCH STRATEGIES

- **Develop search strategies for each database**
 - Dependent on specific search interface for each database
 - Usually will have multiple search strategies for each database
 - Usually will need to combine controlled vocabulary searching with textword searching
 - Author searching can be helpful
 - Be familiar with how ‘related articles’ features work and track how you use them
 - If you use automated limits, track how that affects the yield of your results. What are you losing?
- **Record and keep ALL search strategies**
 - Record the yield of articles from each strategy
 - Record the number of abstracts selected from each strategy

GREY LITERATURE & OTHER SOURCES

Definition

1997- The Luxembourg Convention on Grey Literature

“that which is produced on all levels of government, academics, business and industry in print and electronic formats, but which is not controlled by commercial publishers” (Farace 1998)

Synonyms: Fugitive literature, gray literature

Forms of Grey Lit include: Reports, Conference Abstracts, Dissertations & Theses, Registered Clinical Trials, Interviews, Patents, Newsletters, White Papers, Book Chapters

Farace DJ. GL '97 Proceedings. In: D. F, J. F, editors. Third International Conference on Grey Literature: Perspectives on the design and transfer of scientific and technical information. Luxembourg, 13-14 November 1997. Amsterdam: GreyNet/TransAtlantic; 1998. p. iii.

USING THE GREY LITERATURE

Advantages

- Minimizes bias
- Finds valuable data that would otherwise be missed
- Increases currency and accuracy,
- Broadens applicability of review

Disadvantages

- Takes time and effort
- Difficult to find and access; may have associated costs
- Indexing and search interfaces may be poor quality
- Often isn't peer-reviewed



GREY LITERATURE SOURCES

Clinical Trial Registers

- ISRCTN Register - <http://www.isrctn.org/>
- Clinicaltrials.gov - <http://clinicaltrials.gov/>
- WHO ICTRP - <http://apps.who.int/trialsearch/>

Clinical Study Results Databases

- PhRMA Clinical Study Results Database – <http://www.clinicalstudyresults.org/home/>
- IFPMA Clinical Trial Results Portal - <http://clinicaltrials.ifpma.org/en/myportal/index.htm>

COLLECTING ARTICLES

- **Two independent reviewers should run the searches and select abstracts**
- **Track the number of abstracts selected**
 - Count the number of duplicates eliminated
- **Selection of abstracts is compared and disagreements resolved***
 - An additional round (or two) of abstract weeding may be needed
 - Agree on selected abstracts for which full-text will be examined*
 - Use of a citation management program is recommended to save time/effort
- **Two independent reviewers should read and rate full-text articles***
 - Agree on selected articles for inclusion in the review
 - Use selected articles as source for snowballing and handsearching

***Have a third independent reviewer to help resolve differences**

HANDSEARCHING

Handsearching is the process of

- Selecting journals of topical interest to the review question
- Looking through the issues (at least TOCs) of these selected journals 'by hand' to identify possibly-missed studies
- Preferably with print, but can be done electronically (see <http://www.cochrane.org/training/handsearchers-tscs> for additional information)

Why do it?

- Some journals are not indexed in major literature databases
 - Journal supplements, news, editorials, letters, etc. may not be well indexed
 - Many journals contain conference proceedings that may not be well indexed
- 

SNOWBALLING

Snowballing is the process of

- citation tracking from one article to another
- using the reference lists of selected articles to locate other articles of importance (backtracking)
- seeing who cited a selected article to locate other articles of importance (forward tracking)

Why do it?

- Locate old articles of importance that might predate online literature databases or not be indexed in them
 - Locate newer literature
 - Gain a sense of the history and relationships of the literature on the topic
 - Identify the authors who publish the most on the topic (the experts)
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EVALUATING STUDIES– BASIC STUDY DESIGNS

EXPERIMENTAL

Investigator manipulates a variable and examines effect on an outcome

- Randomized Controlled Trials
- Controlled Trials

OBSERVATIONAL

Investigator observes the outcome of naturally occurring differences in a variable

- Cohort Studies
- Case Control Studies
- Case Series

EVALUATING STUDY QUALITY

There are a number of scales used to evaluate the level of evidence quality in clinical studies. Some journals and professional associations have their own rankings.

Choose an evidence ranking scale that is appropriate for the specialty area and targeted journal for publication of the review. Be consistent in your use of the one you create or select.



EBM QUALITY RATING SCALES

For RCTs, one of the most important quality reporting checklists is CONSORT (Consolidated Standards of Reporting Trials)

More general scales (beyond just RCTs) are provided from various sources including:

- The Centre for Evidence-Based Medicine:
<http://www.cebm.net/index.aspx?o=1025>
- American Association of Family Physicians: Levels of Evidence in AFP
- GRADE: <http://www.gradeworkinggroup.org/intro.htm>
- MOOSE:(Meta-analysis of Observational Studies in Epidemiology)
<http://jama.jamanetwork.com/article.aspx?volume=283&issue=15&page=2008>

RESULTS – STATS OR NOT

The design and quality of selected studies will indicate whether the data is amenable to meta-analysis (statistical analysis) or not.

Meta-analysis is most powerful when used to combine the results of highly-similar randomized controlled trials.

Best if...

- Similar populations
- Same intervention/control
- Same measurements
- Same outcomes recorded
- Full data available

Note: If you plan to do meta-analysis, get a statistician onboard early! Like your medical librarian, use available expertise to make things easier!



PRESENTING THE DATA – SYSTEMATIC REVIEW

Schnuriger, Beat; Inaba, Kenji; Konstantinidis, Agathoklis; Lustenberger, Thomas; Chan, Linda; Demetriades, Demetrios.
Outcomes of Proximal Versus Distal Splenic Artery Embolization After Trauma: A Systematic Review and Meta-Analysis. Journal of Trauma-Injury Infection & Critical Care. 70(1):252-260, January 2011.
 DOI: 10.1097/TA.0b013e3181f2a92e

TABLE 1. Studies Included Into the Analysis

Author	Embolized Trauma Patients	Proximal	Distal	Combination	Material	Failure, % (n)	Radiological Follow-up	Major Complications Reported	Minor Complications Reported
Bessoud et al. ¹⁶	37	37	0	0	Coils	2.7 (1)	CT	Yes	Yes
Cooney et al. ¹⁷	9	6	3	0	Coils/gelatin particles	33.3 (3)	—	Yes	No
Davis et al. ¹⁸	20	0	20	0	Coils/polyvinyl alcohol particles	0.0 (0)	—	Yes	No
Dent et al. ¹⁹	13	0	13	0	Coils/polyvinyl alcohol particles	7.7 (1)	—	Yes	No
Ekeh et al. ²⁰	15	10	1	4	Coils/gelatin particles	6.7 (1)	CT	Yes	Yes
Gaarder et al. ⁸	27	21	2	4	Coils/gelatin particles	3.7 (1)	CT	Yes	Yes
Haan et al. ²¹	140	83	48	9	—	12.9 (18)	CT	No	Yes
Hagiwara et al. ²²	15	9	1	5	Coils/gelatin particles	0.0 (0)	CT/scintigraphy	Yes	Yes
Kaseje et al. ¹⁵	11	8	3	0	—	18.2 (2)	—	Yes	No
Liu et al. ²³	6	0	6	0	Coil/gelatin particles	16.7 (1)	CT/scintigraphy	Yes	Yes
Sclafani et al. ²⁴	60	58	0	2	Coils/gelatin particles	6.7 (4)	CT	Yes	Yes
Smith et al. ²⁵	41	27	9	5	Coils/gelatin particles	22.0 (9)	CT	Yes	Yes
Wei et al. ²⁶	51	14	37	0	—	2.0 (1)	CT	Yes	Yes
Widlus et al. ²⁷	13	13	0	0	Amplatzer vascular plug	15.4 (2)	CT	Yes	Yes
Wu et al. ²⁸	21	3	16	2	Coils/gelatin particles	23.8 (5)	CT/sonography	Yes	Yes
Total	479	289 (60.3%)	159 (33.2%)	31 (6.5%)		10.2 (49)			

CT, computed tomography.

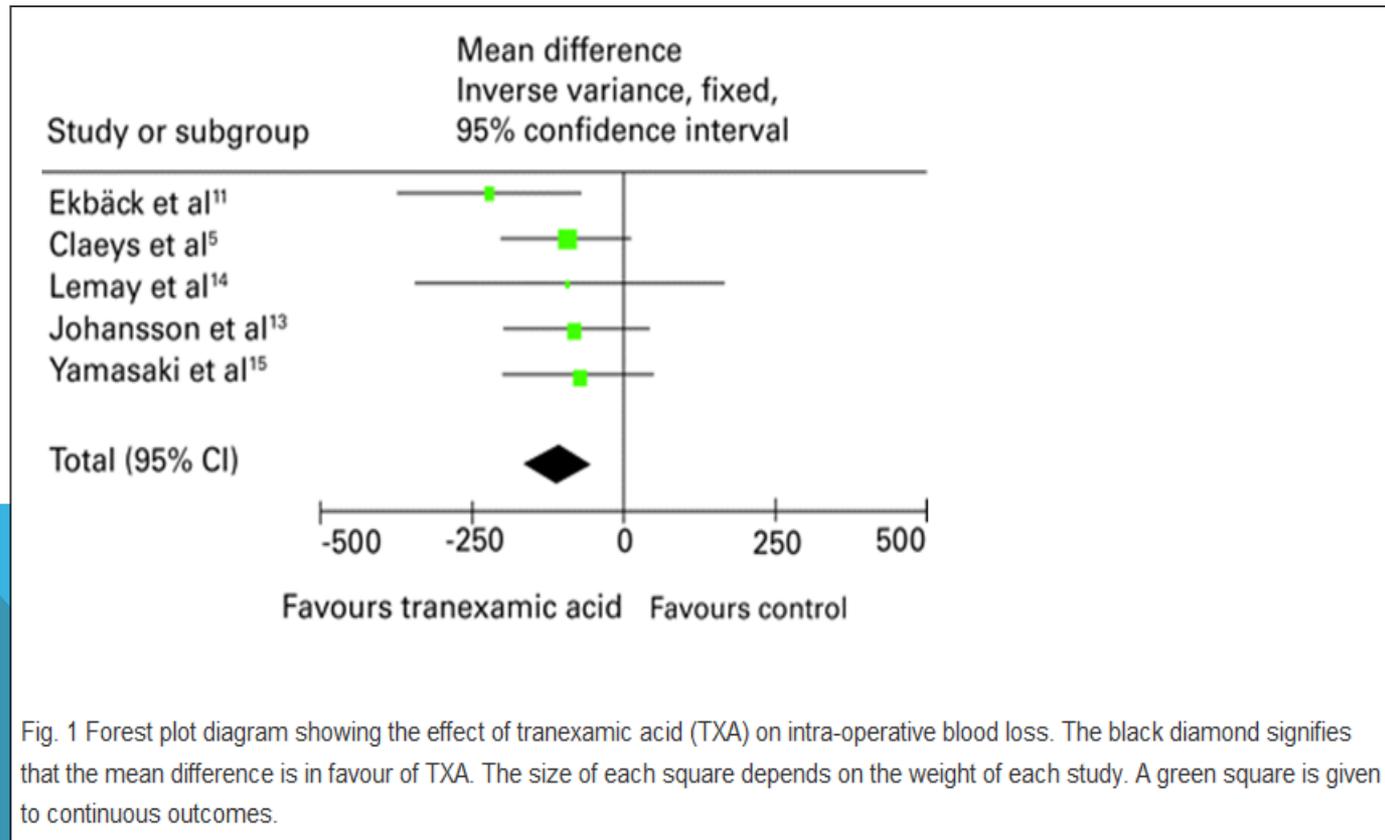
PRESENTING DATA – META-ANALYSIS

One of the most common ways to present meta-analysis data is with a forest plot (AKA blobbogram)

The forest plot illustrates the relative strength of treatment effects (via Odds Ratios) from a set of quantitative clinical studies that address the same question.

EXAMPLE FROM:

Sukeik M, Alshryda S, Haddad FS, Mason JM. Systematic review and meta-analysis of the use of tranexamic acid in total hip replacement. *J Bone Joint Surg Br.* 2011 Jan;93(1):39-46. Review. PubMed PMID: 21196541.



WRITING UP THE METHODS SECTION

Check author guidelines for targeted journal; look at other systematic reviews in that journal

Follow one of the high-quality guides such as PRISMA, Cochrane, or MOOSE

More detail is better than less

TRACK YOUR NUMBERS!



PRISMA

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement is the result of an international collaboration and agreement.

This replaces the older QUORUM,

These standards were developed to promote quality and transparency in reporting systematic review research.

PRISMA is the 'gold standard' for reporting systematic reviews and meta-analyses.

It was published simultaneously in the BMJ, Annals of Internal Medicine, Journal of Clinical Epidemiology, and PLoS Medicine

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

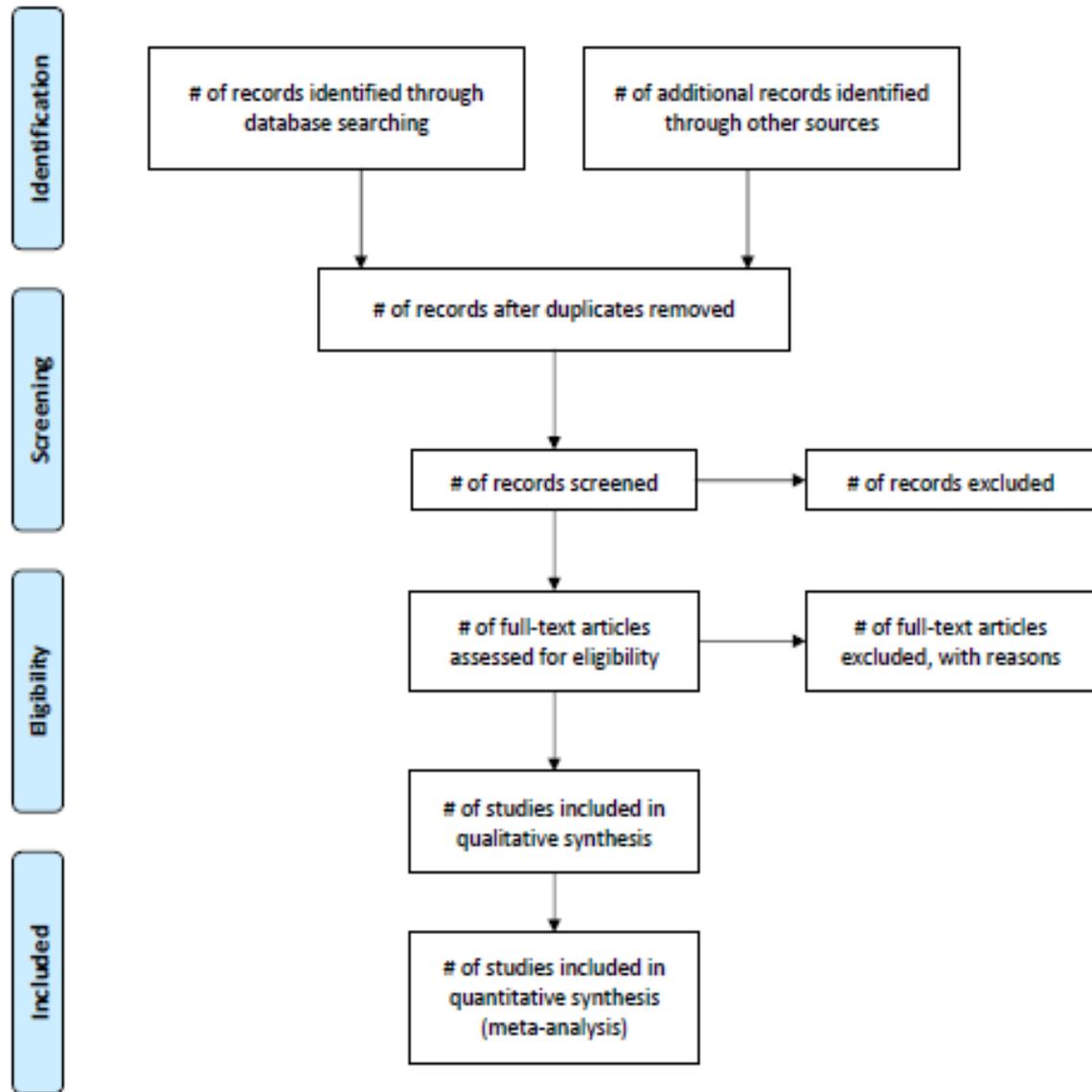
Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. [PLoS Med 6\(6\): e1000097](https://doi.org/10.1371/journal.pmed1000097). doi:10.1371/journal.pmed1000097

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, et al. (2009) The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. [PLoS Med 6\(7\): e1000100](https://doi.org/10.1371/journal.pmed.1000100). doi:10.1371/journal.pmed.1000100



PRISMA 2009 Flow Diagram

Display your search process and track the number of citations through that process in a flow diagram.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items

EXAMPLE: SEARCH FLOW-CHART

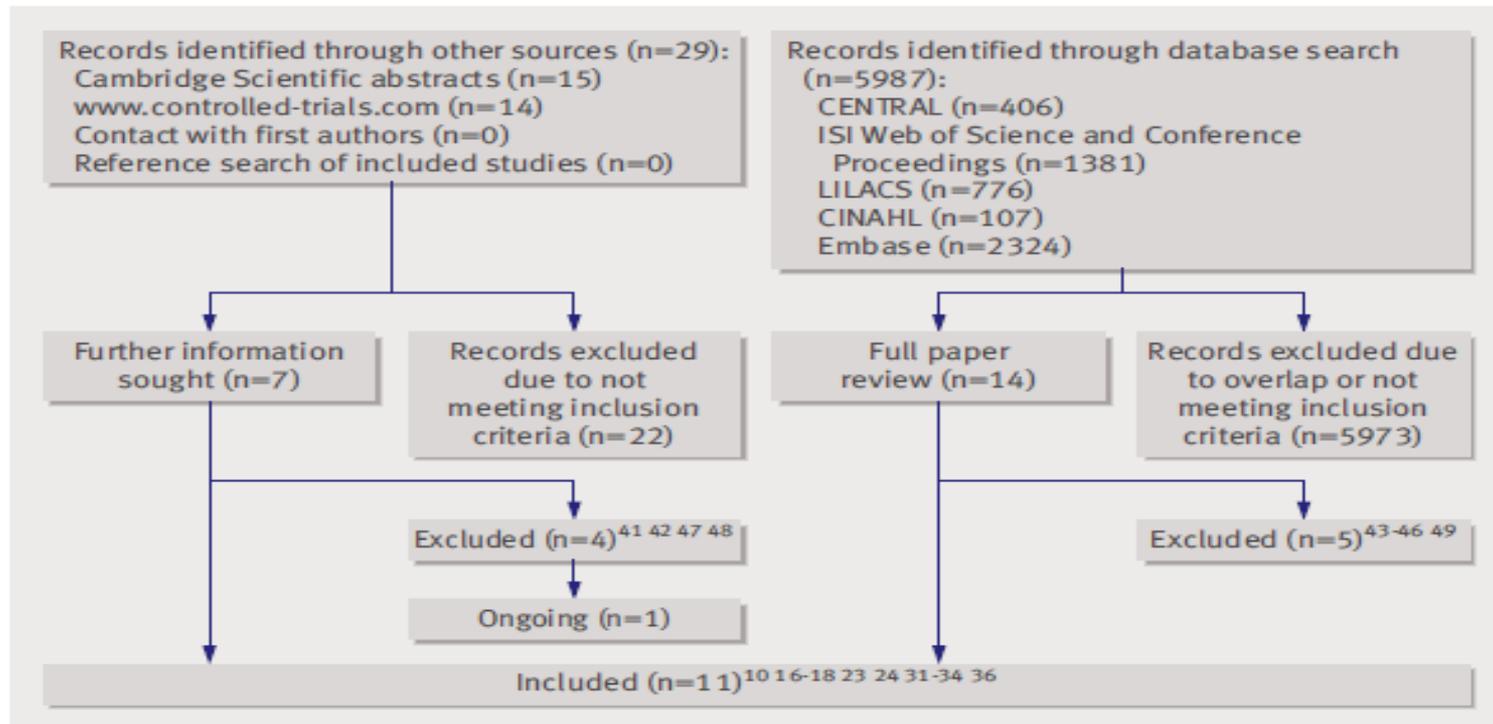
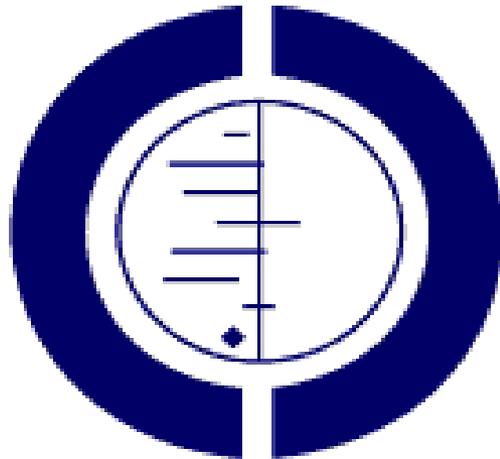


Fig 1 | Identification of studies on weaning from mechanical ventilation

Blackwood B, Alderdice F, Burns K, Cardwell C, Lavery G, O'Halloran P. Use of weaning protocols for reducing duration of mechanical ventilation in critically ill adult patients: Cochrane systematic review and meta-analysis. *BMJ*. 2011 Jan 13;342:c7237. PMID: 21233157; PMCID: PMC3020589. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3020589/pdf/bmj.c7237.pdf>

THE COCHRANE COLLABORATION

An organization that is internationally recognized for being an important leader in creating high-quality systematic reviews and advancing Evidence-Based Medicine is the Cochrane Collaboration



**THE COCHRANE
COLLABORATION®**

Circle formed by the 'C' of Cochrane and the mirror image 'C' of Collaboration reflects the international collaboration that makes our work relevant globally

The inner part of the logo illustrates a systematic review of data from seven randomized controlled trials (RCTs), comparing one health care treatment with a placebo

Each horizontal line represents the results of one trial (the shorter the line, the more certain the result); and the diamond represents their combined results

<http://www.cochrane.org/>

A USEFUL GUIDE

The Dartmouth Guide to Searching for Systematic Reviews:

<http://researchguides.dartmouth.edu/sys-reviews>

Provides useful information on term harvesting, search strategy development, and project management including downloadable forms that can be adapted to your needs.



THINGS TO REMEMBER

PLAN in advance!

Remember that this takes time: a systematic review is a RESEARCH project.

Use available expertise: involve a medical librarian and a biostatistician early.

Keep careful and complete records.

Follow the PRISMA Guidelines.



Questions? Need Help? Contact your librarian!

Gainesville: <http://www.library.health.ufl.edu/services/liaisons.html>

Borland: <http://www.library.health.ufl.edu/borland/index.html>

Or Contact Me!

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