Systematic review and Meta analysis

Dr Parvin Abedi

Associate Professor in Midwifery Department

Definition

* In statistics, a **meta-analysis** combines the results of several studies that address a set of related research hypotheses.

Definition, continue…

* **Meta-analysis is a statistical technique for combining the** findings from independent studies.

* **Systematic Review is most often used to assess the clinical effectiveness of healthcare interventions; it does this by** combining data from two or more randomized control trials.

*

Definition, continued…

* **Systematic Review of trials provides a precise estimate of treatment effect, giving due weight to the size of the** different studies included.

* **The validity of the meta-analysis depends on the quality of the systematic review on which it is based.**
* **Good Systematic Review aim for complete coverage of all relevant studies, look for the presence of heterogeneity,** and explore the robustness of the main findings using **sensitivity analysis.**

Literature reviews vs Systematic Review

* Literature review is different from **Systematic Review** , in this way in the Literature review we just review and not manipulate of the published information, also they are subjective and scientifically unsound.

* But in the **Systematic Review** we perform statistical analysis and they are more accurate.

A **Systematic Review** answers three general questions

1- Central tendency – The central purpose of a meta analysis is to test the relationship between two variables such that X affects Y.

Central tendency refers to identifying whether X affects Y via statistically summarizing significance levels, effect sizes, and/or confidence intervals and how strong is that effect size.

Continued…

2- Variability – There is always going to be some degree of variation between the outcomes of the individual studies that compose the meta-analysis.

The question is whether the degree of variability is signficantly different than what we would expect by chance alone. If so, then its called heterogeneity.

Continued…

3- **Prediction** – If there is heterogeneity (variability), then we look for moderating variables that explain the variability.

In other words, does the effect of X on Y differ with moderator variables?

Why Systematic Review

* **Daily**
* 46 RCTs
* 1000 Medline new articles
* 6000 biomedical articles
* **Annually**
* 3 million articles
* 30,000 journals

Explosion of data, cont…

* Doubling time of biomedical science was about 19 years in 1991.
* Doubling time of biomedical science is about 20 months in 2001.
* To keep up to date in internal medicine, need to read 17 articles a day, 365 days a year.

* Not all of this information is valid or useful.
* Most research published in medical journals are;
* Too poorly done or
* Insufficiently relevant or
* Conflicting findings

* This can be difficult given the large amounts of information generated by individual studies which may be biased, methodologically flawed, and can be misinterpreted and misrepresented.
* In such situations, it is not always clear which results are the most reliable, or which should be used.

Difference between systematic review and meta analysis

* One slight complication is that these two terms are often used interchangeably, particularly in North America.

* The term ‘systematic review’ will refer to the entire process of collecting, reviewing and presenting all available evidence, while the term ‘meta-analysis’ will refer to the statistical technique involved in extracting and combining data to produce a summary result.

* Use "meta-analysis" to refer to statistical methods of combining evidence, leaving other aspects of 'research synthesis' or 'evidence synthesis', such as combining information from qualitative studies, for the more general context of systematic reviews.

Types of review articles

In practice, not all meta-analyses are conducted as part of systematic reviews

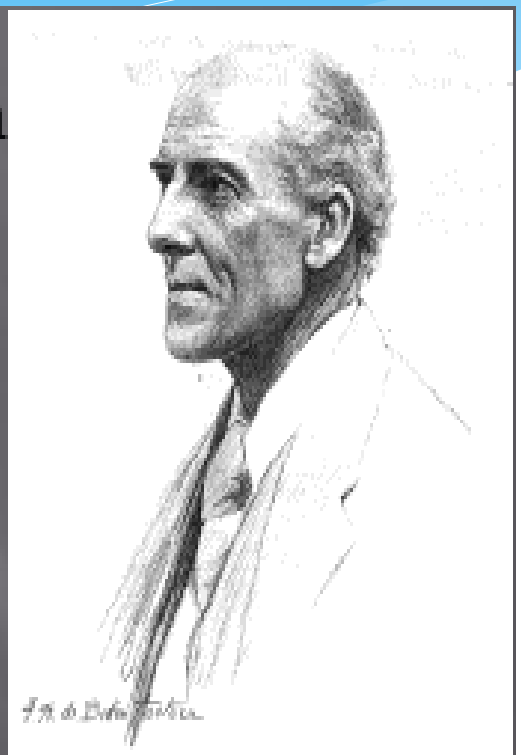
History

Karl Pearson is probably the first medical researcher to use **formal techniques** to combine data from different studies (1904):

He synthesized data from several studies on efficacy of typhoid vaccination

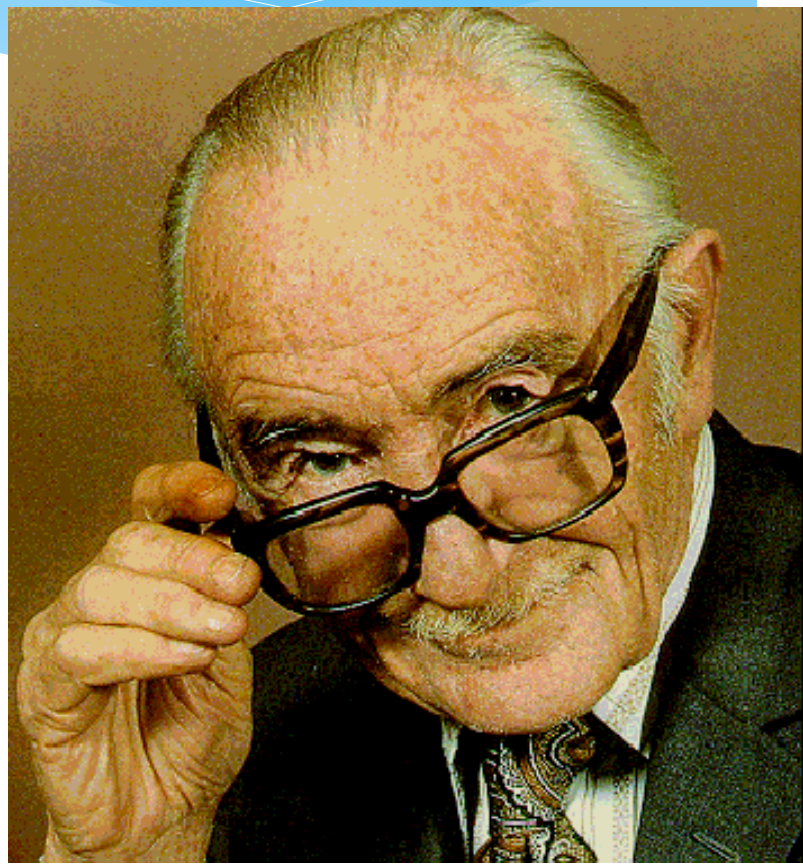
His rationale for pooling data:

- "Many of the groups… are far too small to allow of any definite opinion being formed at all…."



Prof Archibald Cochrane (1909-1988)

* The Cochrane Collaboration is named in honor of Archie Cochrane, a British researcher.
* In 1979 he wrote, *"It is surely a great criticism of our profession that we have not organized a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomized controlled trials"*



Cochrane collaboration

* The **Cochrane Collaboration is a group of volunteers who review the effects of health care interventions tested in biomedical randomized controlled trials.**
* A few more recent reviews have also studied the results of non-randomized, observational studies. The results of these systematic reviews are published as "Cochrane Reviews" in the Cochrane Library.

* The Cochrane Collaboration is an international, independent, not-for-profit organization of over **27,000 contributors from more than 100 countries, dedicated to making up-to-date, accurate information about the effects of health care readily available worldwide.**

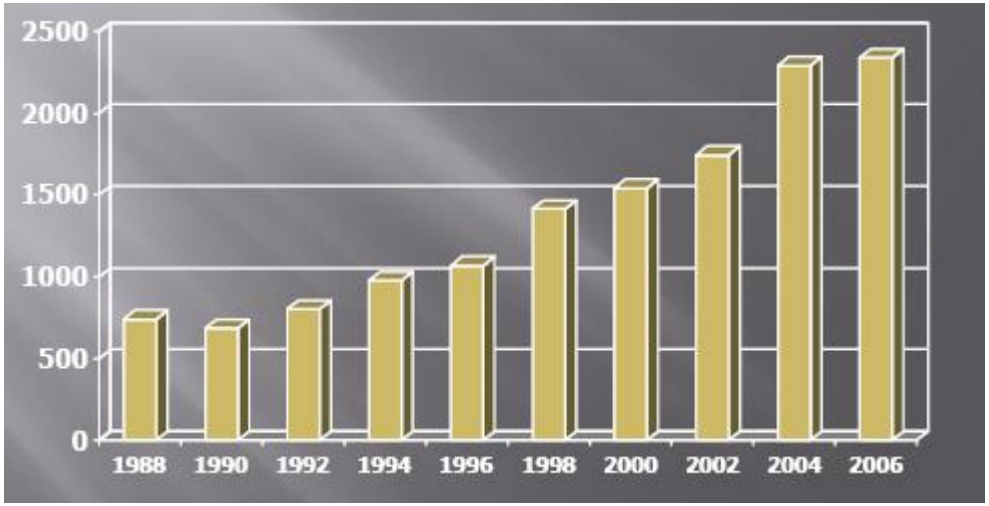
* The Cochrane Collaboration is an international organization that aims to help people make well-informed decisions about healthcare by

  preparing, maintaining and promoting the accessibility of systematic reviews of the effects of healthcare interventions.

An international organization

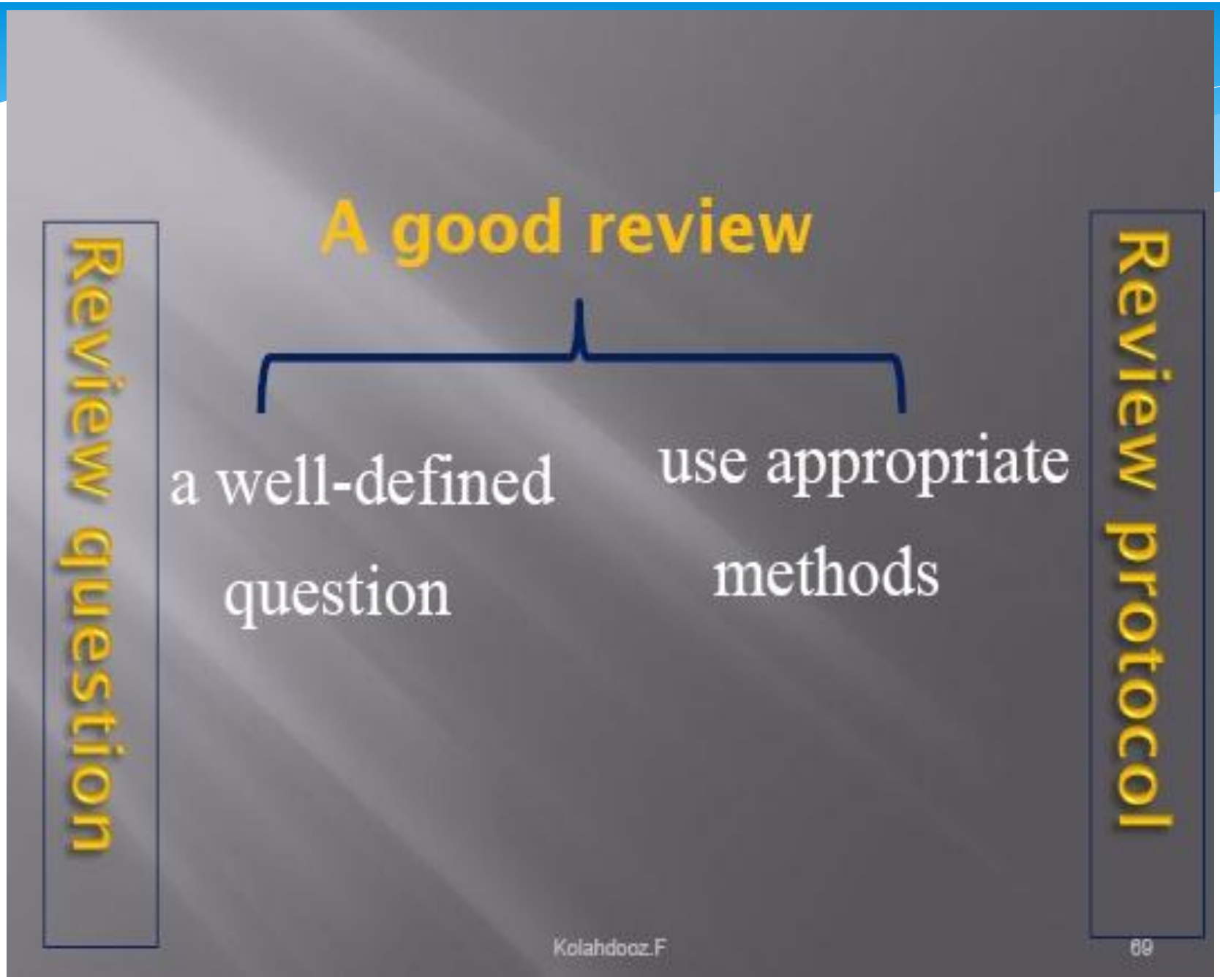

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.
Cochrane.org
Search title, abstract, keyword
Browse
Advanced Search
Cochrane Reviews
Trials
More Resources
About
Help
Patient reminders and recalls
Can they improve immunization rates?
Read the review
Yoga for health and well-being
Read the Special Collection
Health systems overviews
Read the editorial
Highlighted Reviews
Editorials
Special Collections
Family and carer smoking control programmes for reducing children's exposure to environmental tobacco smoke
Cochrane Interactive Learning

Systematic reviews/meta-analyses indexed in PubMed



Steps of a Cochrane systematic review

1. define the question → Register title
2. plan eligibility criteria
3. plan methods → Publish Protocol
4. search for studies
5. apply eligibility criteria
6. collect data
7. assess studies for risk of bias
8. analyse and present results
9. interpret results and draw conclusions → Publish Review
10. improve and update review → **publish update**

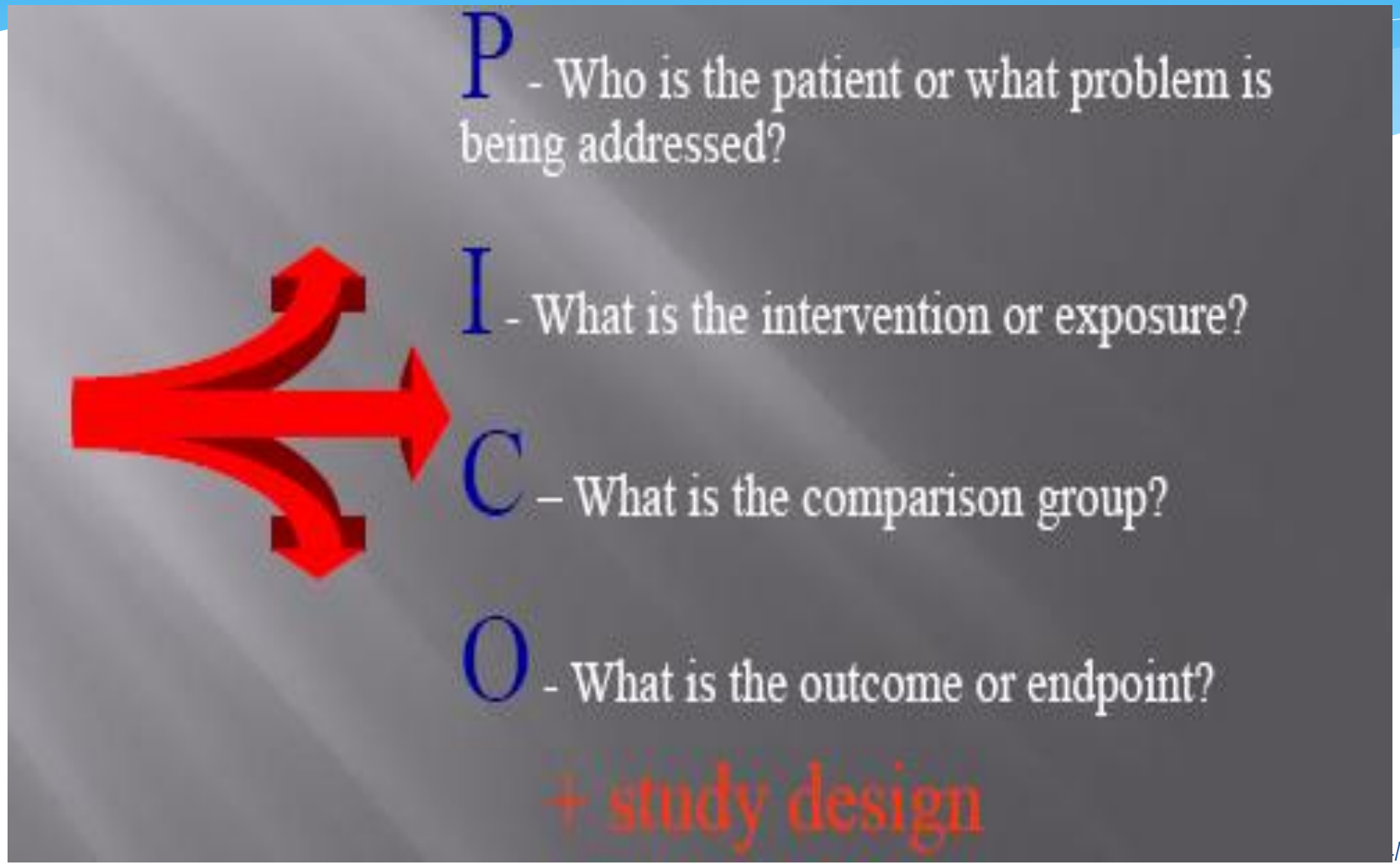

A good review
Review question
a well-defined question
use appropriate methods
Review protocol
Kolahdooz.F
69

Review team for **Systematic Review**

* **Team will manage and conduct the review and should have a range of skills**
* **Somebody to do the work**
* **Somebody to get the money**
* **Somebody who is willing to write the review**

  an information specialist (a librarian, or someone with in-depth knowledge of how to locate and retrieve studies)
* **A methodologist**
* **Content experts , the relevant clinical/topic area– people who know about the condition from both the clinical and the consumer perspective**

What is PICO


P - Who is the patient or what problem is being addressed?
I - What is the intervention or exposure?
C – What is the comparison group?
O - What is the outcome or endpoint?
+ study design

Formulation of a therapy question

Intervention

Outcome

Is Zinc effective in treating cold?

Patient/problem

Intervention

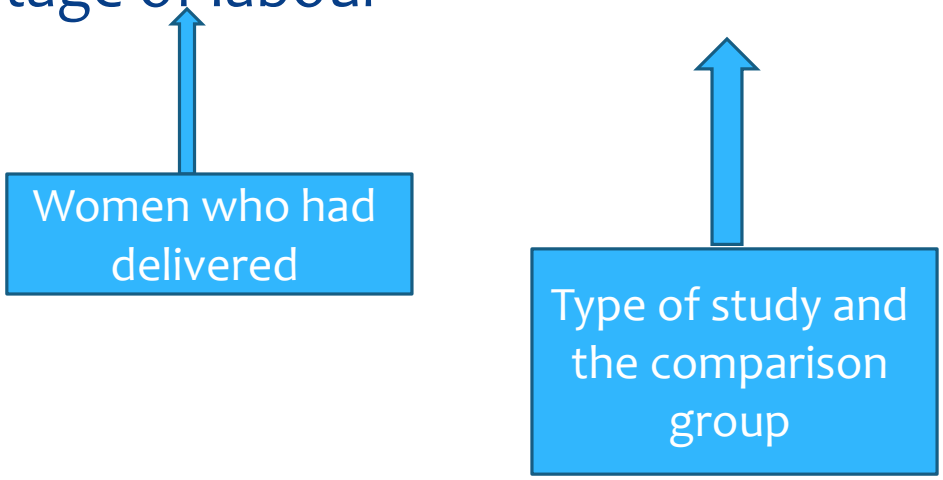
In children with common cold, is oral Zinc effective in reducing the duration of symptoms, as compared to placebo?

Outcome

+ RCTs

Comparison

* Breast stimulation for reducing blood loss in the third stage of labour



First step in registering title in Cochrane

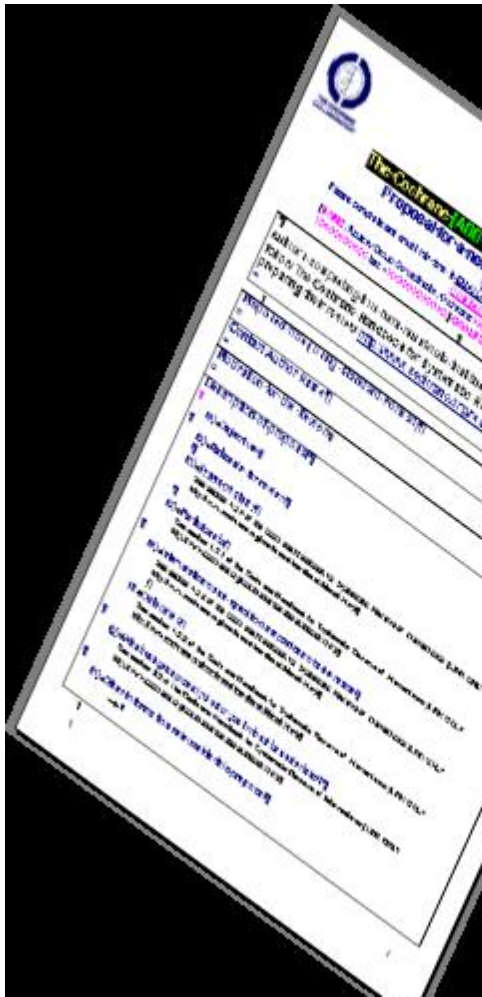
1- Define your hypothesis – First you must have a well-defined statement of the relationship between the variables under investigation so that you can carefully define the inclusion and exclusion criteria when locating potential studies.

Search Cochrane Library

* Chose your Cochrane CRG e.g. “Gynecology and Fertility”
* Search Cochrane Library to sure about your title has been not published before
* Search to find at least 5 article related to your topic.
* Go to your CRG homepage and find “Title registration form”
* Fill-up the form and submit to the CRG.
* You must have Cochrane workshop certificate.

Title registration form

- members of your team
- names, expertise, conflict of interest
- roles and responsibilities
- proposed review question
- population or condition, intervention to be tested, outcomes to be measured and study designs included
- identify available resources
- estimate timeframe
- agreement to publish in *The Cochrane Library*
- commitment to keep the review up to date



DATABASE TOOLS
Save to My Profile
Recommend to Your Librarian

DATABASE MENU
Database Home

FIND ARTICLES
A-Z
By Topic
New Reviews
Updated Reviews
By Review Group

OTHER RESOURCES
Other Reviews
Trials
Methods Studies
Technology Assessments
Economic Evaluations

Intervention Protocol

Behavioural interventions as adjuncts to pharmacotherapy for smoking cessation

Lindsay F Stead*, Tim Lancaster

Database Title
The Cochrane Library

Editorial Group: Cochrane Tobacco Addiction Group

Published Online: 15 FEB 2012

DOI: 10.1002/14651858.CD009670

Additional Information **(Hide All)**

How to Cite | Author Information | Publication History

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Author Information

University of Oxford, Department of Primary Care Health Sciences, Oxford, UK

*Lindsay F Stead, Department of Primary Care Health Sciences, University of Oxford, 23-38 Hythe Bridge Street, Oxford, OX1 2ET, UK. lindsay.stead@phc.ox.ac.uk.

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Published Online: 15 FEB 2012

SEARCH
Title, Abstract, Keywords
Search >
Medical Terms (MeSH) >
Search Manager >

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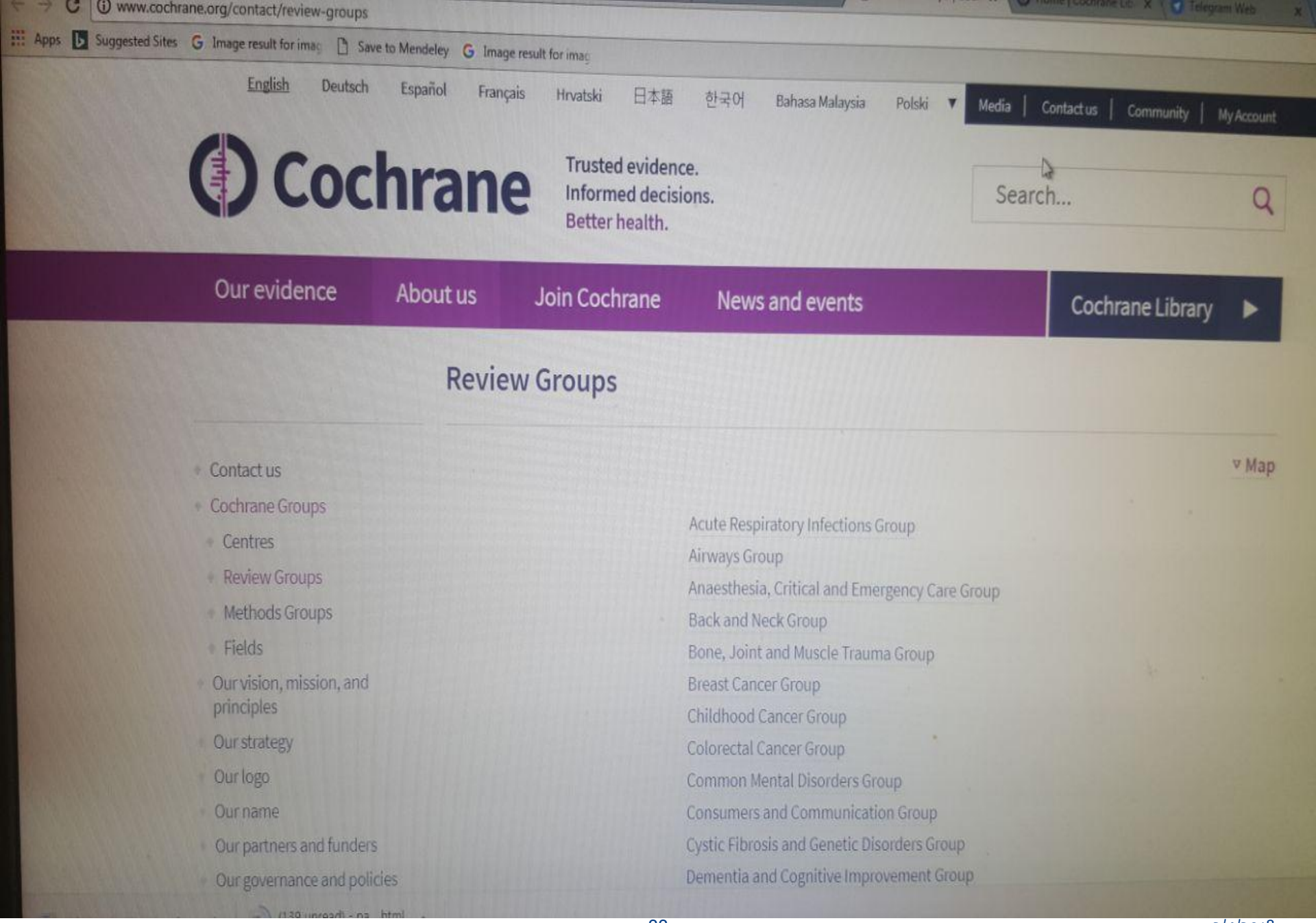
Abstract

Jump to...

This is the protocol for a review and there is no abstract. The objectives are as follows:


www.cochrane.org/contact/review-groups
Apps
Suggested Sites
Image result for imag
Save to Mendeley
Image result for imag
English
Deutsch
Español
Français
Hrvatski
日本語
한국어
Bahasa Malaysia
Polski
Media
Contact us
Community
My Account
Cochrane
Trusted evidence.
Informed decisions.
Better health.
Search...
Our evidence
About us
Join Cochrane
News and events
Cochrane Library
Review Groups
Map
Contact us
Cochrane Groups
Centres
Review Groups
Methods Groups
Fields
Our vision, mission, and principles
Our strategy
Our logo
Our name
Our partners and funders
Our governance and policies
Acute Respiratory Infections Group
Airways Group
Anaesthesia, Critical and Emergency Care Group
Back and Neck Group
Bone, Joint and Muscle Trauma Group
Breast Cancer Group
Childhood Cancer Group
Colorectal Cancer Group
Common Mental Disorders Group
Consumers and Communication Group
Cystic Fibrosis and Genetic Disorders Group
Dementia and Cognitive Improvement Group

After acceptance of your title you will have access to Review Manager (RevMan)

- mandatory software
- access your review from the **Archie database**
- template for protocol or review structure
- write the text of your review
- statistical analysis
- editorial and publication
- need a user name and password
- ask your CRG
- available from www.ims.cochrane.org/revman

Cochrane Handbook for Systematic Reviews of Interventions

Rationale for protocols

- •Systematic reviews involve judgments
- •e.g. question definition, eligibility, outcome measures
- •Retrospective research - decisions should not be based on known results
- •Decide and document methods in advance
- •Reduce impact of bias
- •Allow peer review
- •Reduce duplication
- •Plan tasks and allocate resources
- •Published in *The Cochrane Library*
- •Published review will contain a link to your protocol

Objectives

- A precise statement of the primary objective usually one sentence

May also include specific objectives relating to different

- Participant groups
- Comparisons of interventions
- Outcome measures

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

Methods

- plan what you will do before you start
- minimize bias
- divide work among review authors and establish timeline
- enough detail so that the decisions and methods could be replicated
- select methods likely to deliver the best evidence on which to base decisions
- consult your CRG – they may have a standard template
- anticipate that a useful number of studies will be found
- may be the case in future updates, if not now

When your protocol is complete

- check the details
- spell check, validation check, CRG checklist
- submit to your CRG for editorial approval
- expect internal and peer review
- ME, Editor(s), Statistical Editor, peer referees, consumer
- like any journal, may take several months
- when it has been approved
- complete License for Publication & Declaration of Interest forms
- commence review
- will be published immediately

Search for studies

* Included studies
* Excluded studies (reasons for exclusion)
* Studies awaiting classification (translation)

How to chose the study for **Systematic Review**

* **1-Search of literature**

* 2. **Selection of studies** ('incorporation criteria') Based on quality criteria, e.g. the requirement of randomization and blinding in a clinical trial .
* Selection of specific studies on a well-specified subject, e.g. the treatment of breast cancer.

* **Decide whether unpublished** studies are included to avoid publication bias (file drawer problem)

* 3. **Decide which dependent variables** or summary measures are allowed. For instance: Differences (discrete data) , Means (continuous data)

Sampling in **Systematic Review**

* Sampling is a critical design issue.
* Sample consists of the primary studies that have addressed the research question.

* Researchers must state the exclusion and inclusion criteria for the study, which include substantive, methodological and practical elements.

Quality of the primary studies

* Screening out studies of lower quality can occur indirectly if the met analyst excludes studies that did not use a randomized design, or studies that were not published in a peer-reviewed journals.

* The analyst need to decide how to asses quality and what to do with the assessment information.

Evaluation of study quality

* Strong studies should be given more weight than weaker one in coming to conclusions about a body of evidence.

* Different rating scales are available for rating studies.

* No gold-standard exist for determining the scientific rigor and validity of primary studies.

How should we conduct a search?

* The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE (if access is available to either the review author or TSC Trials Search Co-ordinator) should be searched for all Cochrane reviews, either directly or via the CRG's Specialized Register.
* Both free-text and subject headings should be used (for example Medical Subject Headings (MeSH) and (EMTREE) for EMBASE).

Search, cont…

* The Cochrane Central Register of Controlled Trials (CENTRAL) serves as the most comprehensive source of reports of controlled trials.
* CENTRAL is published as part of The Cochrane Library and is updated quarterly. As of January 2008 (Issue 1, 2008), CENTRAL contains nearly 530,000 citations to reports of trials and other studies potentially eligible for inclusion in Cochrane reviews, of which 310,000 trial reports are from MEDLINE, 50,000 additional trial reports are from EMBASE and the remaining 170,000 are from other sources such as other databases and handsearching.

* MEDLINE currently contains over 16 million references to journal articles from the 1950s onwards. Currently 5,200 journals in 37 languages are indexed for MEDLINE:
* o www.nlm.nih.gov/pubs/factsheets/medline.html

* PubMed provides access to a free version of MEDLINE that also includes up-to-date citations not yet indexed for MEDLINE:
* o www.nlm.nih.gov/pubs/factsheets/pubmed.html

* EMBASE currently contains over 11 million records from 1974 onwards. Currently 4,800 journals are indexed for EMBASE in 30 languages.
* o www.info.embase.com/embase_suite/about/brochures/embase_fs.pdf
*
* EMBASE.com is Elsevier's own version of EMBASE that, in addition to the 12 million EMBASE records from 1974 onwards, also includes over 7 million unique records from MEDLINE from 1966 to date, thus allowing both databases to be searched simultaneously.
* www.info.embase.com/embase_com/about/index.shtml

Database overlap

* Of the 4,800 journals indexed in EMBASE, 1,800 are not indexed in MEDLINE. Similarly, of the 5,200 journals indexed in MEDLINE, 1,800 are not indexed in EMBASE.
* o www.info.embase.com/embase_suite/about/brochures/embase_fs.pdf
*

National and regional databases

* In addition to MEDLINE and EMBASE, which are generally considered to be the key international general healthcare databases, many countries and regions produce electronic bibliographic databases that concentrate on the literature produced in those regions, and which often include journals and other literature not indexed elsewhere.
* Access to many of these databases is available free of charge on the internet. ISC is one of the examples that is not included in the MEDLINE.

Grey literature databases

* here are many definitions of grey literature, but it is usually understood to mean literature that is not formally published in sources such as books or journal articles. Conference abstracts and other grey literature have been shown to be sources of approximately 10% of the studies referenced in Cochrane reviews (Mallett 2002).
* Thus, failure to identify trials reported in conference proceedings and other grey literature might affect the results of a systematic review.

Unpublished and ongoing studies

* National and international trials registers
* No language restrictions should be included in the search strategy.
* Date restrictions should be applied only if it is known that relevant studies could only have been reported during a specific time period, for example if the intervention was only available after a certain time point.
* Format restrictions such as excluding letters are not recommended because letters may contain important additional information relating to an earlier trial report or new information about a trial not reported elsewhere.
*

Which studies should be included

* The eligibility criteria for studies to be included in the review will inform how the search is conducted. The eligibility criteria will specify the types of designs, types of participants, types of intervention (experimental and comparator) and, in some cases, the types of outcomes to be addressed.

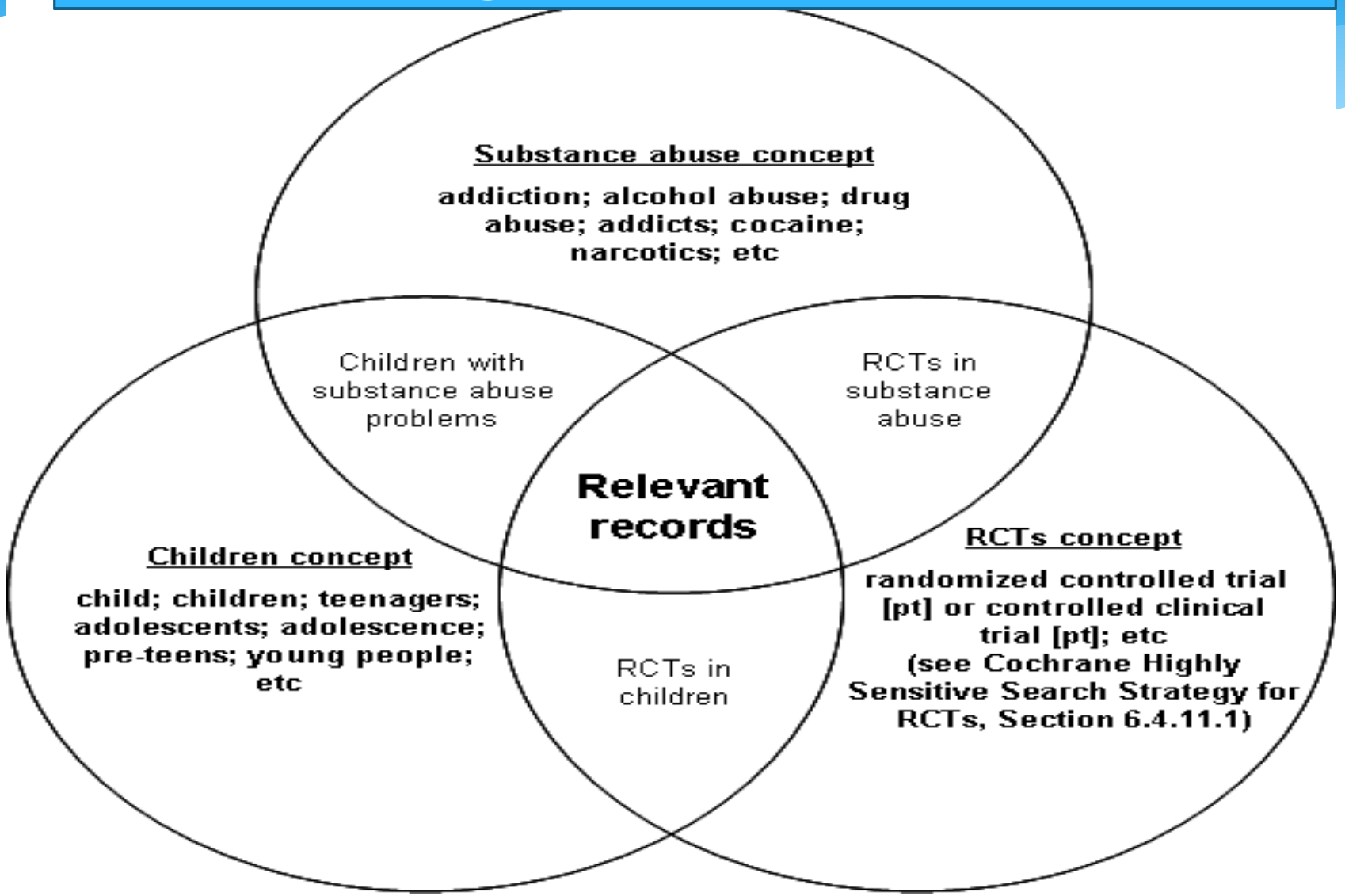
Structure of search strategy

* Aims to contain only reports with study designs possibly relevant for inclusion in Cochrane reviews, so searches of CENTRAL should not use a trials 'filter'.
* Filters to identify randomized trials and controlled trials have been developed specifically for MEDLINE and guidance is also given for searching EMBASE:

Synonyms, related terms, variant spellings, truncation and wildcards

* When designing a search strategy, in order to be as comprehensive as possible, it is necessary to include a wide range of free-text terms for each of the concepts selected. For example:
* synonyms: 'pressure sore' OR 'decubitus ulcer', etc;
* related terms: 'brain' OR 'head', etc; and
* variant spellings: 'tumour' OR 'tumor'.
* truncation: random* (for random or randomised or randomized or randomly, etc); and
* wildcard: wom?n (for woman or women).

Combining concepts as search sets



Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); PubMed format

#1	randomized controlled trial [pt] (publication type)
#2	controlled clinical trial [pt]
#3	randomized [tiab] (Title –Abastract)
#4	placebo [tiab]
#5	drug therapy [sh] (MESH)
#6	randomly [tiab]
#7	trial [tiab]
#8	groups [tiab]
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10	animals [mh] NOT humans [mh]
#11	#9 NOT #10

Search Field Descriptions and Tags

Affiliation [AD]
Article Identifier [AID]
All Fields [ALL]
Author [AU]
Author Identifier [AUID]
Book [book]
Comment Corrections
Corporate Author [CN]
Create Date [CRDT]
Completion Date [DCOM]
Conflict of Interest [COIS]
EC/RN Number [RN]
Editor [ED]
Entrez Date [EDAT]

* Location ID [LID]
* MeSH Date [MHDA]
* MeSH Major Topic [MAJR]
* MeSH Subheadings [SH]
* MeSH Terms [MH]
* Modification Date [LR]
* NLM Unique ID [JID]
* Other Term [OT]
* Owner
* Pagination [PG]

Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format

1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomized.ab.
4	placebo.ab.
5	drug therapy.fs.
6	randomly.ab.
7	trial.ab.
8	groups.ab.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp animals/ not humans.sh.
11	9 not 10

Demonstration search strategy for MEDLINE (Ovid format), for the topic 'Tamoxifen for breast cancer'

1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomized.ab.
4	placebo.ab.
5	drug therapy.fs.
6	randomly.ab.
7	trial.ab.
8	groups.ab.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	animals.sh. not (humans.sh. and animals.sh.)
11.	9 not 10
12.	exp Breast Neoplasms/
13.	(breast adj6 cancer$).mp.
14.	(breast adj6 neoplasm$).mp.
15.	(breast adj6 carcinoma$).mp.
16.	(breast adj6 tumour$).mp.
17.	(breast adj6 tumor$).mp.
18.	12 or 13 or 14 or 15 or 16 or 17
19.	exp Tamoxifen/
20.	tamoxifen.mp.
21.	19 or 20
22.	11 and 18 and 21

Summary points

* Cochrane review authors should contact their Trials Search Co-ordinator before starting a search.
* For most Cochrane reviews, the search structure in most databases will be comprised of a subject search for population or condition and intervention together with a methodological filter for the study design, such as randomized trials.
* For searches of CENTRAL, do not apply a randomized trial filter and do not limit to human.
* Avoid too many different search concepts but use a wide variety of synonyms and related terms (both free text and controlled vocabulary terms) combined with 'OR' within each concept.
* Combine different concepts with 'AND'.

Summary points

* Avoid use of the 'NOT' operator in combining search sets.
* Aim for high sensitivity and be prepared to accept low precision.
* Do not apply language restrictions to the search strategy.
* Searches designed for a specific database and service provider will need to be 'translated' for use in another database or service provider.
* Ensure awareness of any retracted publications (e.g. fraudulent publications), errata and comments.
* For identifying randomized trials in MEDLINE, begin with the sensitivity-maximizing version of the Cochrane Highly Sensitive Search Strategy. If this retrieves an unmanageable number of references, use the sensitivity- and precision-maximizing version instead.
* For update searches, where possible, separate database files should be selected and searched separately for the MEDLINE-indexed records and the non-indexed in-process records.
*

Please search Medline for following topic:

* Comparison the effect of oxytocin with misoprostol in management of the third stage of labour and postpartum hemorrhage

* Comparison the effect of heat therapy and massage on feet pain of

Covidence

* **Use Covidence software for screening studies**.
* Create an account under the **Cochrane**
* Put any study that you think is relevant in your topic
* Two members of study should screen titles and also abstract for their eligibility to include in the review.

Extraction data

* Use extraction data form that may different for each CRG.
* Two review members should extract data individually
* Conflict should be resolved by the third member.

Extraction and Encoding of Data for Analysis

* The next step in a systematic review is to extract and record relevant information about the findings, methods and study characteristics.

Which data should be extracted?

* Publication year
* Country where data collected
* Sample size
* Randomization
* Blinding
* Response to attrition rate
* Period of follow-up
* Characteristics of participants (e.g. percentage of female, mean age of participants)

Review Manager 5.3

Risk of Bias in studies

* Assess all included studies regarding risk of bias using form provided in RevMan

Bias is not the same as

Imprecision

- random error due to sampling variation
- reflected in the confidence interval

Quality

- bias can occur in well-conducted studies
- not all methodological flaws introduce bias

Reporting

- good methods may have been used but not well reported

Quality scales and checklists

- many scales available
- not supported by empirical evidence
- different scales, different conclusions
- may include criteria not related to bias
- numerical weighting not justified
- difficult for readers to interpret the score

Quality scales should not be used in Cochrane reviews

Cochrane 'Risk of bias' assessment

- 7 evidence-based domains
- review authors' judgement
  - ✓ **Low risk** of bias
  - ✘ **High risk** of bias
  - ? **Unclear**
- support for judgement
  - evidence/quotes from the paper or other sources
  - review author's explanation

Domains to address

- random sequence generation
- allocation concealment
- blinding of participants and personnel
- blinding of outcome assessment
- incomplete outcome data
- selective reporting
- other bias

You MUST consult the Handbook before completing your Risk of Bias assessment

What about non-randomised studies?

- risk of bias must still be carefully assessed
  - you may wish to add domains to your assessment
  - you may wish to use an alternative, appropriate tool
  - your Review Group may have a recommended option

See Section 13.5 of the Handbook

Overview

- risk of bias in systematic reviews
- **assessing sources of bias**
- putting it into practice: ‘Risk of bias’ tables
- incorporating findings into your review

Sources of bias

Selection

Performance

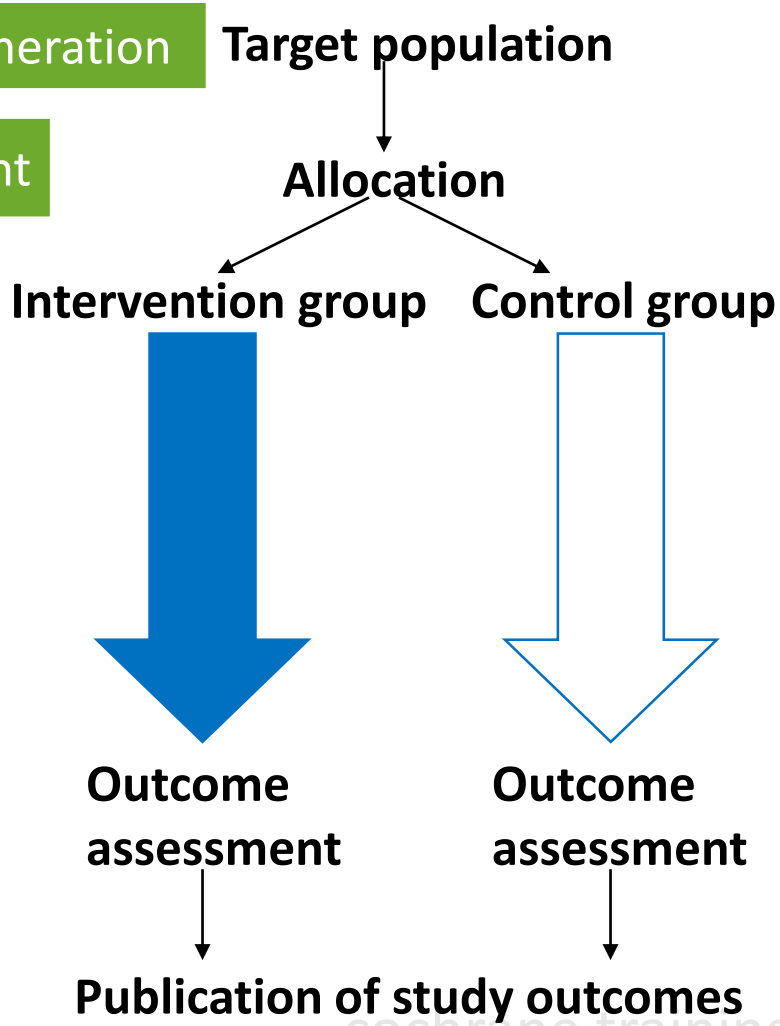
Detection

Attrition

Reporting

Random sequence generation

Allocation concealment



Random sequence generation

- occurs at the start of a trial before allocation of participants
- avoids **selection bias**
- determines a random order of assigning people into intervention and control groups
- avoids systematic differences between groups
- accounts for known and unknown confounders

Random sequence generation

Low risk – unpredictable

- random number table
- computer random number generator
- stratified or block randomisation
- minimisation
- low tech - coin toss, shuffling cards or envelopes, throwing dice, drawing lots

High risk – predictable

- quasi-random – date of birth, day of visit, ID or record number, alternate allocation
- non-random – choice of clinician or participant, test results, availability

See Section 8.9 of the Handbook

Allocation concealment

- occurs at the start of the trial during allocation of participants
- avoids **selection bias**
- when a person is recruited to the study, no-one can predict which group they will be allocated to
- ensures the strict implementation of the random sequence
  - prevents changing the order
  - prevents selecting who to recruit

Allocation concealment

Low risk – unpredictable

- central allocation (phone, web, pharmacy)
- sequentially numbered, sealed, opaque envelopes
- sequentially numbered, identical drug containers

High risk – predictable

- random sequence known to staff in advance
- envelopes or packaging without all safeguards
- non-random, predictable sequence

See Section 8.10 of the Handbook

Sources of bias

Selection

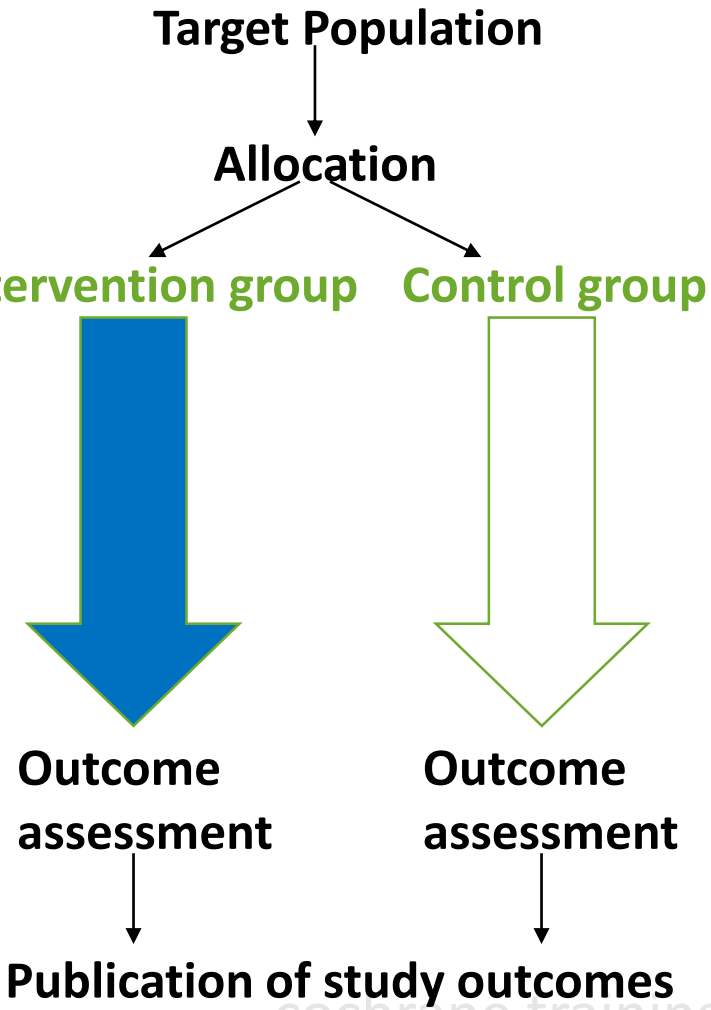
Performance

Blinding of participants, personnel

Detection

Attrition

Reporting



Blinding of participants & personnel

- avoids **performance bias**
  - different treatment of the intervention groups
  - different participant expectations
  - leads to changes in the actual outcomes
- assess carefully
  - avoid terms like “single blinding” and “double blinding”
  - is it likely that blinding was broken?
  - consider impact even if not feasible for this intervention

Blinding of participants & personnel

Low risk

- blinding, and unlikely that the blinding could have been broken
- no blinding or incomplete blinding, but outcome unlikely to be influenced

High risk

- no blinding, incomplete or broken blinding, and outcome likely to be influenced

See Section 8.11 of the Handbook

Sources of bias

Selection

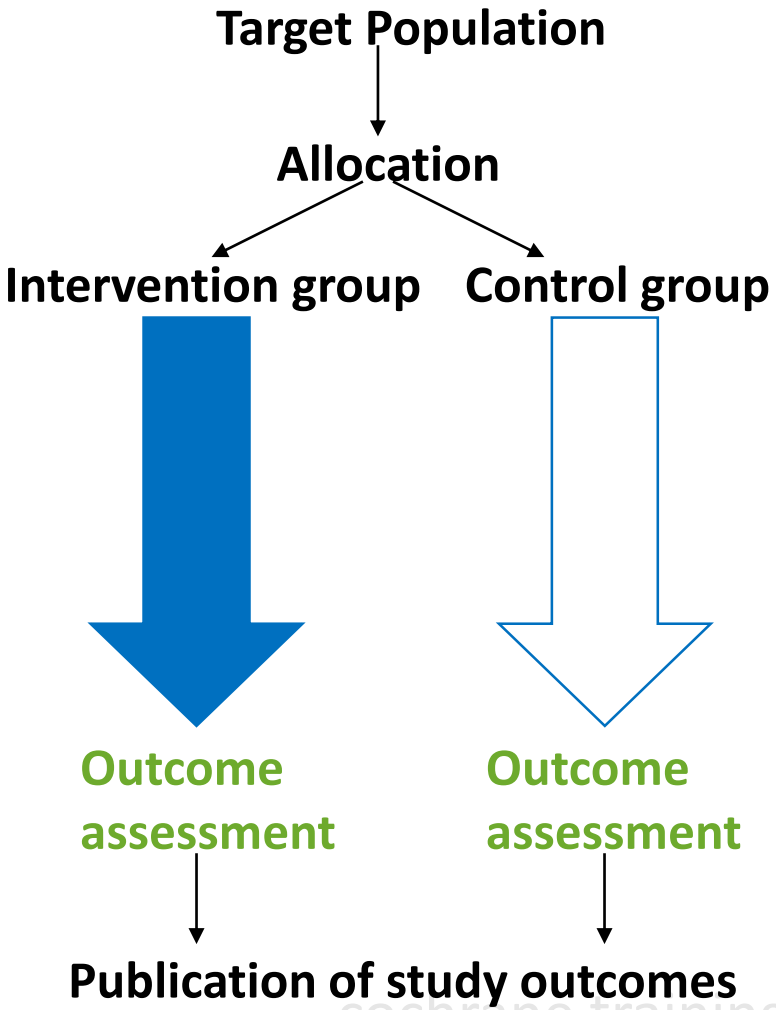
Performance

Detection

Blinding of outcome assessment

Attrition

Reporting



Blinding of outcome assessment

- avoids **detection bias**
  - measurement of outcomes affected by knowledge of the intervention received
- assess carefully
  - avoid terms like “single blinding” and “double blinding”
  - is it likely that blinding was broken?
  - may be feasible even where blinding of participants and care providers is not
  - remember that participants and personnel may also be outcome assessors

Blinding of outcome assessment

Low risk

- blinding, and unlikely that the blinding could have been broken
- no blinding, but measurement unlikely to be influenced

High risk

- no blinding or broken blinding, and measurement likely to be influenced

See Section 8.12 of the Handbook

Assessing blinding by outcome

- may reach different conclusions for different outcomes
  - measurement of only some outcomes may be blinded
  - subjective outcomes may be more vulnerable to bias
    e.g. death vs quality of life
- may apply to both **performance bias** and **detection bias**
- option to design your table with two or more outcome groups for these categories

Sources of bias

Selection

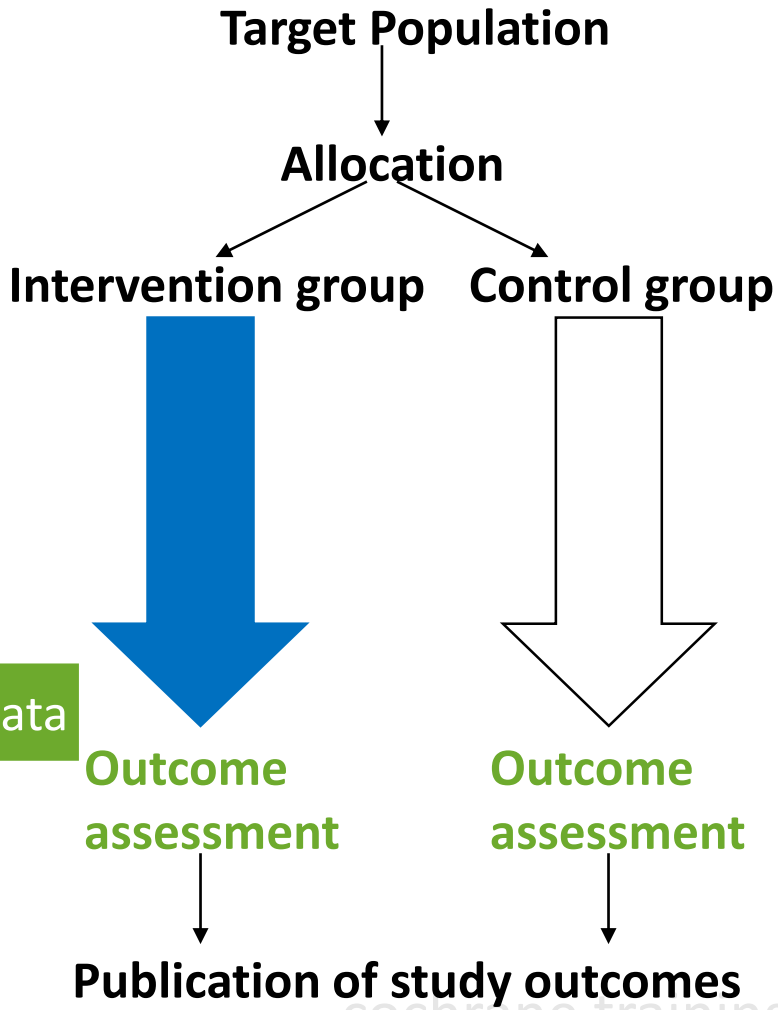
Performance

Detection

Attrition

Reporting

Incomplete outcome data



Incomplete outcome data

- when complete outcome data for all participants is not available for your review
  - attrition - loss to follow up, withdrawals, other missing data
  - exclusions – some available data not included in report
- can lead to **attrition bias**
- considerations
  - how much data is missing from each group? (include numbers in your description)
  - why is it missing?
  - how were the data analysed?

How much is too much missing data?

- **no simple rule**
- enough missing to meaningfully affect the results
  - overall proportion of missing data
  - event risk (dichotomous outcomes)
  - plausible effect size (continuous outcomes)
- reasons related to study outcomes
  - e.g. recovered, adverse event, refusal
  - reasons can have different meaning in each group
- missing data or reasons not balanced between groups

Intention-to-treat analysis

- all participants analysed in the groups randomised
  - regardless of what happened during the study
- issues that may arise
  - **per protocol** analysis
    - non-compliers excluded from analysis
  - **as-treated** analysis
    - non-compliers moved between groups
  - **imputation** of missing values
    - assumptions may be inappropriate - consult a statistician
- it may be possible to re-include some excluded data

Assessing incomplete data by outcome

- may reach different conclusions for different outcomes
  - may be more missing data at different time points
  - some outcomes may have more missing data
    e.g. sensitive questions, invasive tests
- option to design your table with two or more outcome groups for ‘incomplete data’

Incomplete outcome data

Low risk

- no missing data
- reasons for missing data not related to outcome
- missing data balanced across groups, and reasons similar
- proportion missing or plausible effect size not enough to have a clinically relevant effect

High risk

- reasons related to outcome, and imbalance in numbers or reasons
- proportion missing or plausible effect size enough to have a clinically relevant effect
- 'as-treated' analysis with substantial departure from allocation
- inappropriate use of imputation

See Section 8.13 of the Handbook

Sources of bias

Selection

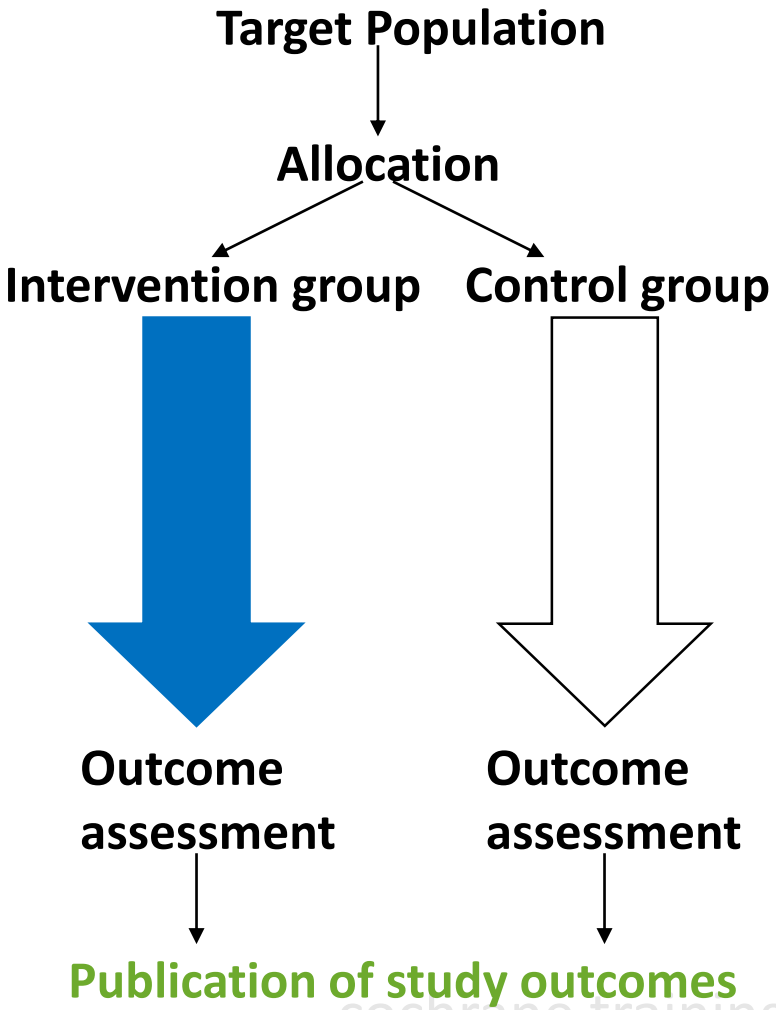
Performance

Detection

Attrition

Reporting

Selective reporting



Selective reporting

- can lead to **reporting bias**
- statistically significant results more likely to be reported
  - as planned
  - in detail
- difficult to determine
  - compare methods to results – look for:
    - outcomes measured (or likely to be measured) but not reported
    - outcomes added, statistics changed, subgroups only
    - reporting that cannot be used in a review
      (e.g. stating non-significance without numerical results)
  - refer to study protocol or trial register
- focus on outcomes of interest to your review

Selective reporting

Low risk

- protocol is available and all pre-specified outcomes of interest to the review reported in the pre-specified way
- protocol not available but it is clear that all pre-specified and expected outcomes of interest are reported

Unclear risk

- **most studies will be judged in this category**

High risk

- outcomes not reported as pre-specified or expected
  - e.g. missing, added, subsets, unexpected measurements or methods
- outcomes reported incompletely so they cannot be entered in a meta-analysis

See Section 8.14 of the Handbook

Other sources of bias

- must be a clear rationale why a factor may cause bias
- do **not** include
  - imprecision (e.g. small sample size)
  - diversity (e.g. inadequate dose, unusual population)
  - other measures of quality (e.g. ethics approval, funding)
- if possible, identify important issues in your protocol
- option to add rows to your table for items to be assessed across all studies

Other sources of bias

Low risk

- study appears to be free of other sources of risk

High risk

- issues specific to the study design
  - carry-over in cross-over trials
  - recruitment bias in cluster-randomised trials
  - non-randomised studies
- baseline imbalance
- blocked randomisation in unblinded trials
- differential diagnostic activity
- other bias

See Section 8.15 of the Handbook

Overview

- risk of bias in systematic reviews
- assessing sources of bias
- **putting it into practice: 'Risk of bias' tables**
- incorporating findings into your review

Completing the assessments

- at least two assessors
  - ensure all understand the methodological issues
  - include content and methods experts
- pilot on 3-6 studies to check consistency of assessment
- define in advance how you will resolve disagreements
- look for missing information
  - study protocol
  - contact authors

‘Risk of bias’ tables

- one for each included study
- your judgement for each domain

  ✓ **Low risk**

  ✘ **High risk** - consider risk of **material** bias, not any bias

  ? **Unclear** = not enough information to make a clear judgement
- support for judgement
  - direct quotes from the paper or study author where possible
  - additional comments
  - rationale for any assumptions (e.g. “probably done”)
  - state explicitly if no information available

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "...participants born on even days were assigned to the experimental group and participants born on odd days were assigned to the control group."
Allocation concealment (selection bias)	High risk	Comment: allocation by date of birth would allow prediction of the allocation sequence.
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "Caffeinated and decaffeinated coffee... was identical in appearance, colour and taste." Comment: it is likely that participants were blinded. Blinding of study personnel was not described.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Unclear risk	Comment: Blinding of outcome assessors was not described.
Blinding of outcome assessment (detection bias) Reaction time	Low risk	Comment: Blinding of outcome assessors was not described, but is unlikely to affect measurement of this outcome.
Incomplete outcome data (attrition bias)	High risk	Comment: outcome data for adverse events were only reported for 53 of 58 participants in the caffeine group. Reasons for loss to follow-up were not described.
Selective reporting (reporting bias)	High risk	Comment: alertness was the primary outcome of the study, but data were not reported. Study protocol was not available to identify any other unreported outcomes. Outcome data were presented for drowsiness although this was not listed as an outcome of interest in the study methods.
Other bias	Low risk	Comment: none were identified.

Overview

- risk of bias in systematic reviews
- assessing sources of bias
- putting it into practice: 'Risk of bias' tables
- **incorporating findings into your review**

Prioritise domains for your review

- all reviews address all domains, but you can select one or more as priorities for your review
  - specify in your protocol
- give a rationale, considering:
  - empirical evidence of impact
  - likely direction of impact
    - bias most likely to exaggerate effect
    - if likely to underestimate and a significant effect observed, may be ok
  - likely magnitude of impact in relation to observed effect

See Handbook Sections 8.5-8.14

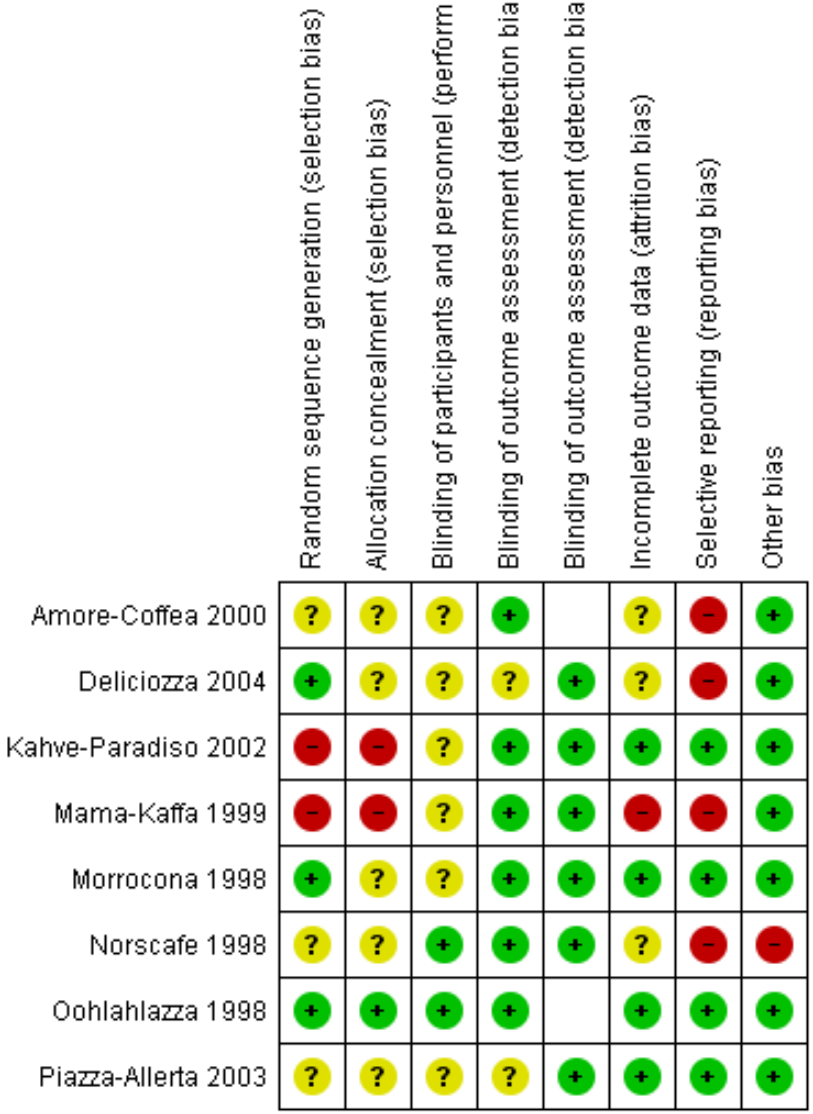
Reaching an overall interpretation

- don't try to summarise all outcomes and all studies at once
- summarise by **outcome**
  - outcome may have different risk assessments (e.g. blinding, incomplete data)
  - not all studies contribute to each outcome
  - start by summarising **within a study**, then **across studies**
- studies at 'unclear' risk should not be grouped with 'low risk' without a rationale

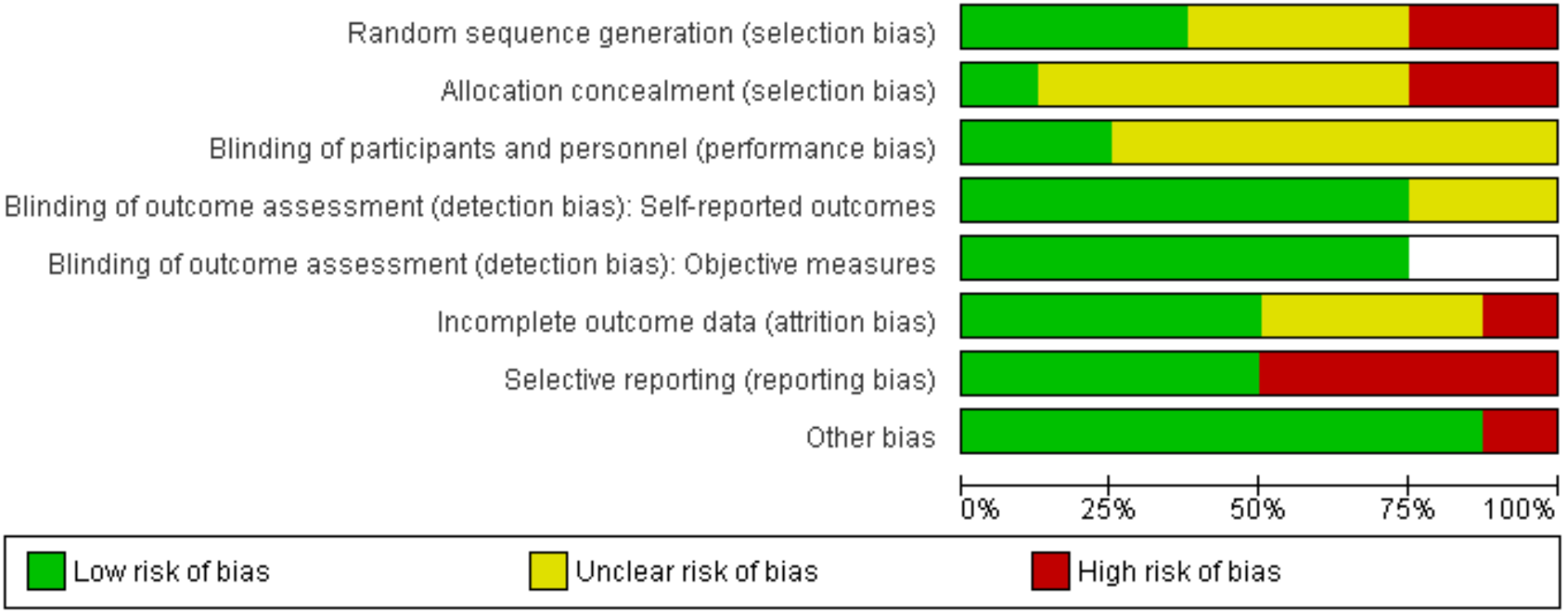
Incorporating findings into your review

- always give a narrative description
  - may be missed by readers
  - does not address impact on results
- may restrict primary analysis to studies at low risk
  - based on reasoned (but arbitrary) key domains
  - always conduct sensitivity analysis
- may present a stratified analysis
- may explore the impact further
  - subgroup analysis
  - meta-regression - get statistical advice

Risk of bias summary

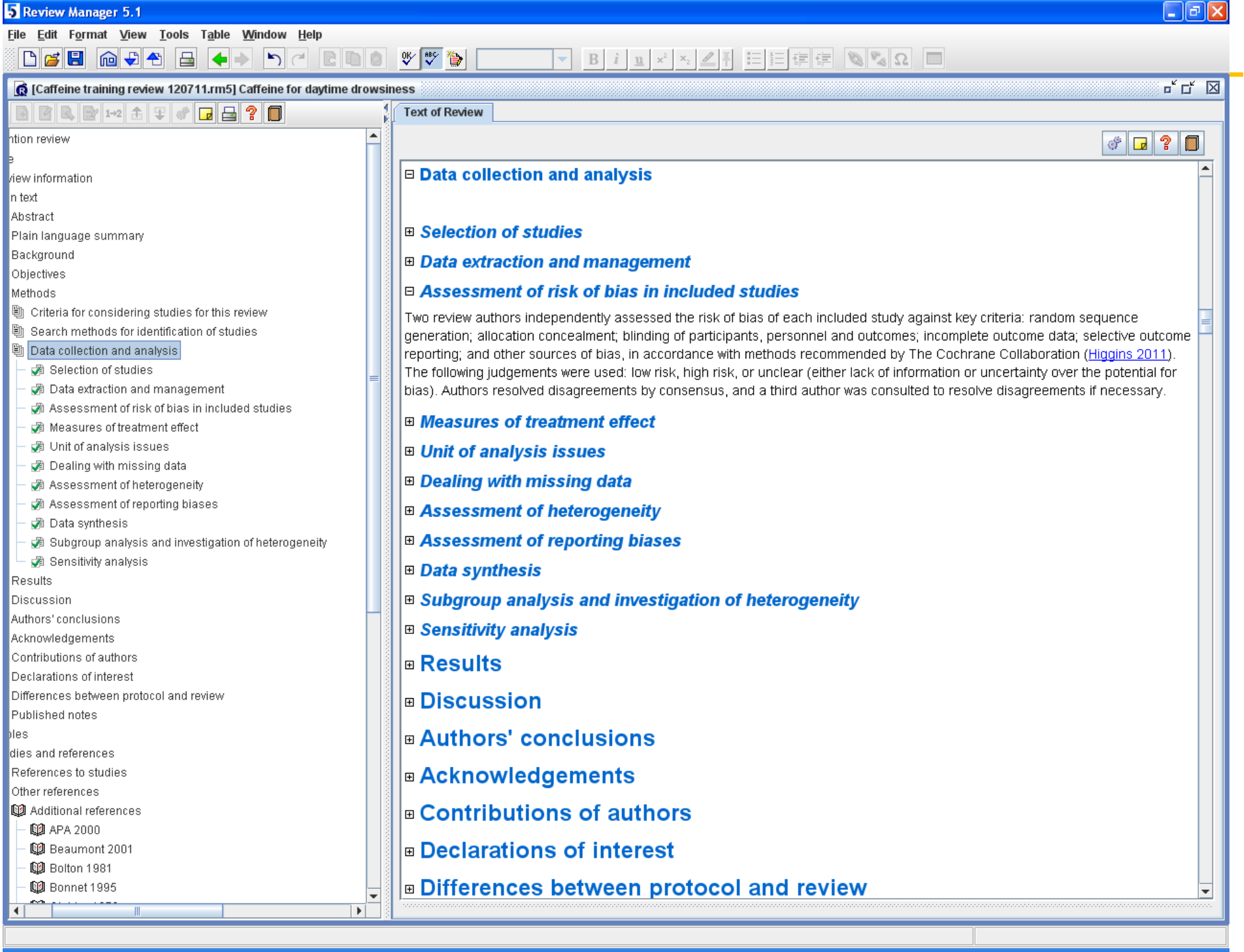


Risk of bias graph



What to include in your protocol

- check with your CRG for standard text
- brief description of risk of bias assessment tool
  - list domains
  - refer to Handbook Chapter 8
- more than one author will assess risk of bias
- how will disagreements will be resolved?
- are there specific domains you consider to be important for the review?
- how will you incorporate findings into your analysis?


Review Manager 5.1
File Edit Format View Tools Table Window Help
[Caffeine training review 120711.rm5] Caffeine for daytime drowsiness
Text of Review
ntion review
iew information
n text
Abstract
Plain language summary
Background
Objectives
Methods
Criteria for considering studies for this review
Search methods for identification of studies
Data collection and analysis
Selection of studies
Data extraction and management
Assessment of risk of bias in included studies
Measures of treatment effect
Unit of analysis issues
Dealing with missing data
Assessment of heterogeneity
Assessment of reporting biases
Data synthesis
Subgroup analysis and investigation of heterogeneity
Sensitivity analysis
Results
Discussion
Authors' conclusions
Acknowledgements
Contributions of authors
Declarations of interest
Differences between protocol and review
Published notes
les
dies and references
References to studies
Other references
Additional references
APA 2000
Beaumont 2001
Bolton 1981
Bonnet 1995
Data collection and analysis
Selection of studies
Data extraction and management
Assessment of risk of bias in included studies
Two review authors independently assessed the risk of bias of each included study against key criteria: random sequence generation; allocation concealment; blinding of participants, personnel and outcomes; incomplete outcome data; selective outcome reporting; and other sources of bias, in accordance with methods recommended by The Cochrane Collaboration (Higgins 2011). The following judgements were used: low risk, high risk, or unclear (either lack of information or uncertainty over the potential for bias). Authors resolved disagreements by consensus, and a third author was consulted to resolve disagreements if necessary.
Measures of treatment effect
Unit of analysis issues
Dealing with missing data
Assessment of heterogeneity
Assessment of reporting biases
Data synthesis
Subgroup analysis and investigation of heterogeneity
Sensitivity analysis
Results
Discussion
Authors' conclusions
Acknowledgements
Contributions of authors
Declarations of interest
Differences between protocol and review

References

* 1-Denise F et al. Essential of Nursing Research. 7th ed. Lippincott Williams & Wilkins. 2010.
* 2-Crombie et al. What is meta-analysis? 2009.
* available on the internet at :www.whatisseries.co.uk
* Higgins JPT, Altman DG, Sterne JAC (editors). **Chapter 8: Assessing risk of bias in included studies**. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org


With Best Wishes