The Cochrane Collaboration and Systematic Reviews

Loma Linda University
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The Cochrane Collaboration
Trusted evidence. Informed decisions. Better health.

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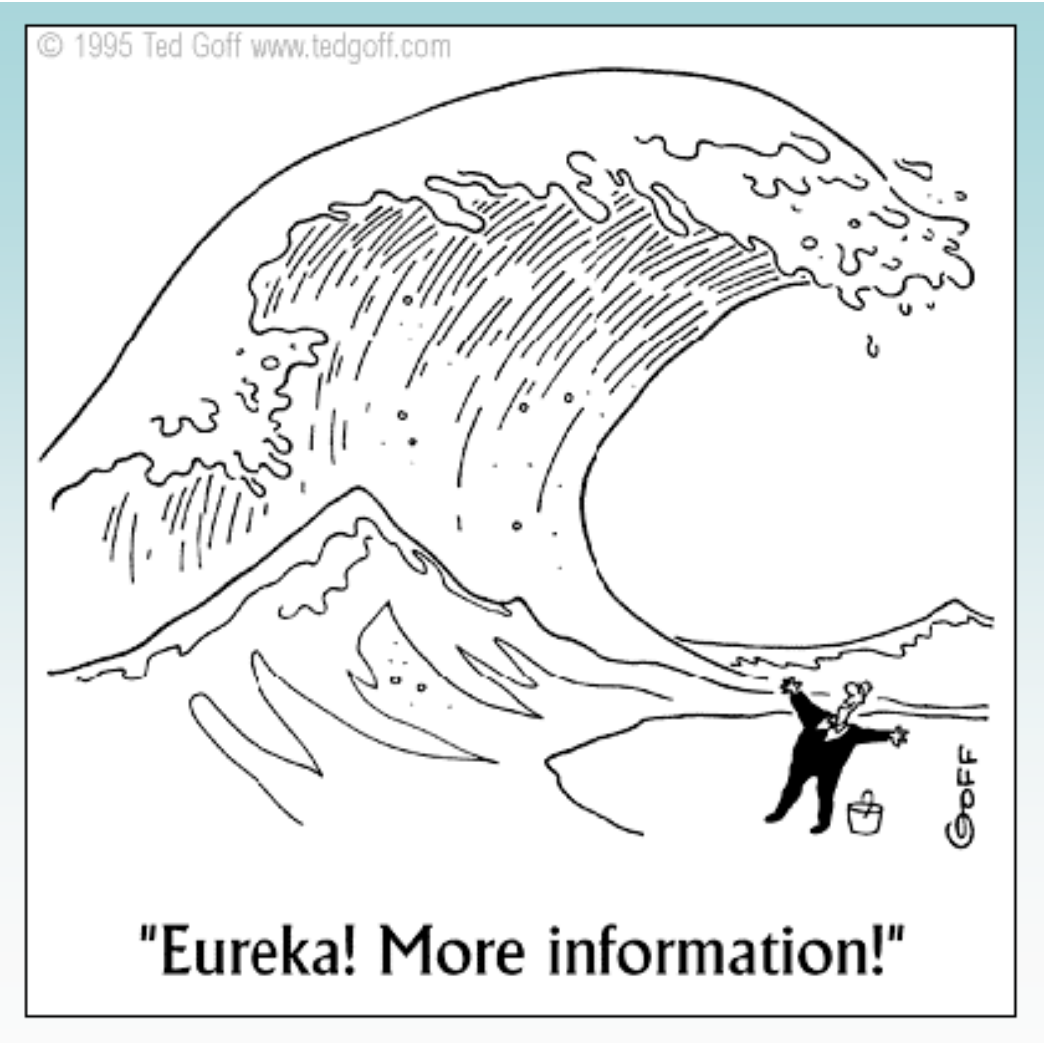
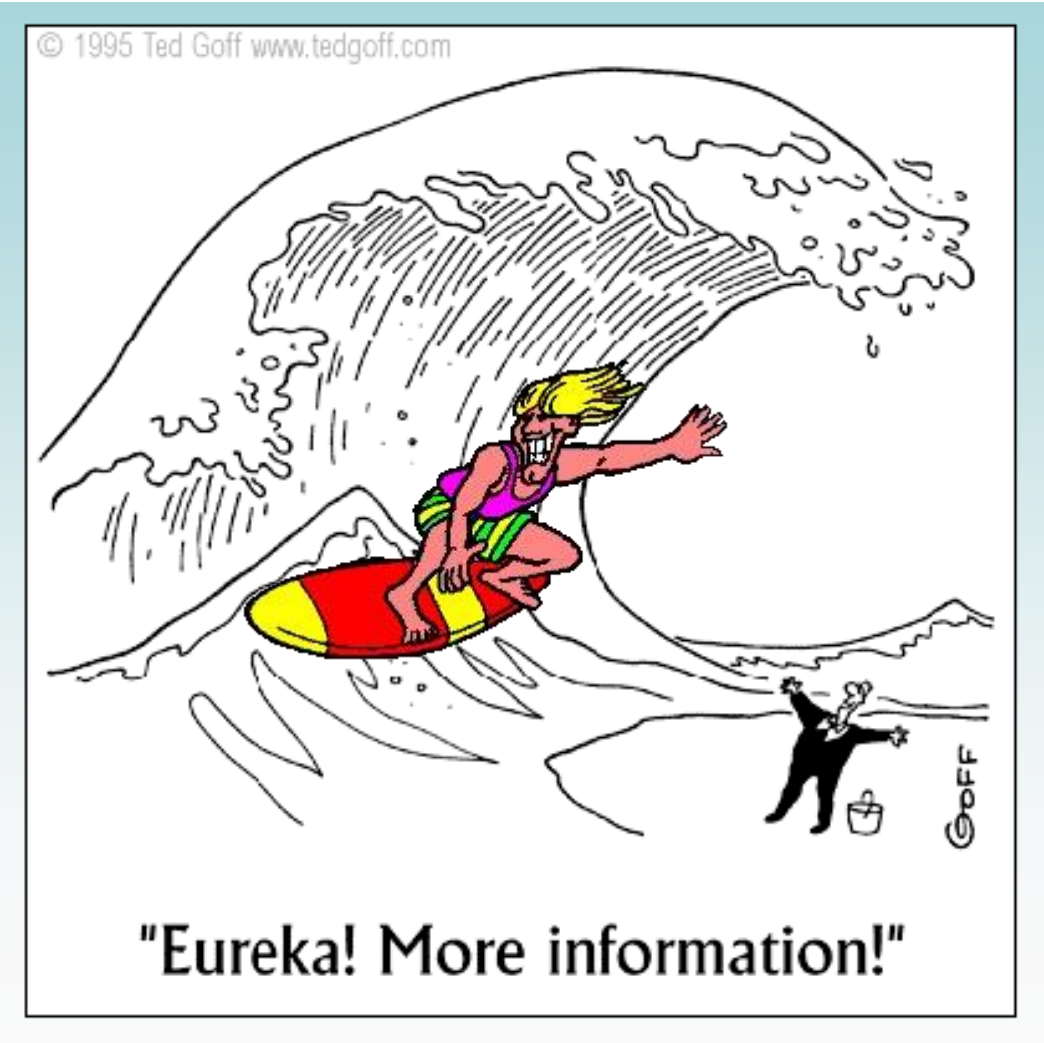
Improving health and reducing inequities worldwide

The challenge

- Health care providers, consumers, researchers, and policy makers are inundated with unmanageable amounts of information.
- It is unlikely that all will have the time, skills and resources to find, appraise and interpret this evidence and to incorporate it into health care decisions.
- Systematic reviews respond to this challenge by identifying, appraising and synthesizing research-based evidence and presenting it in an accessible format.

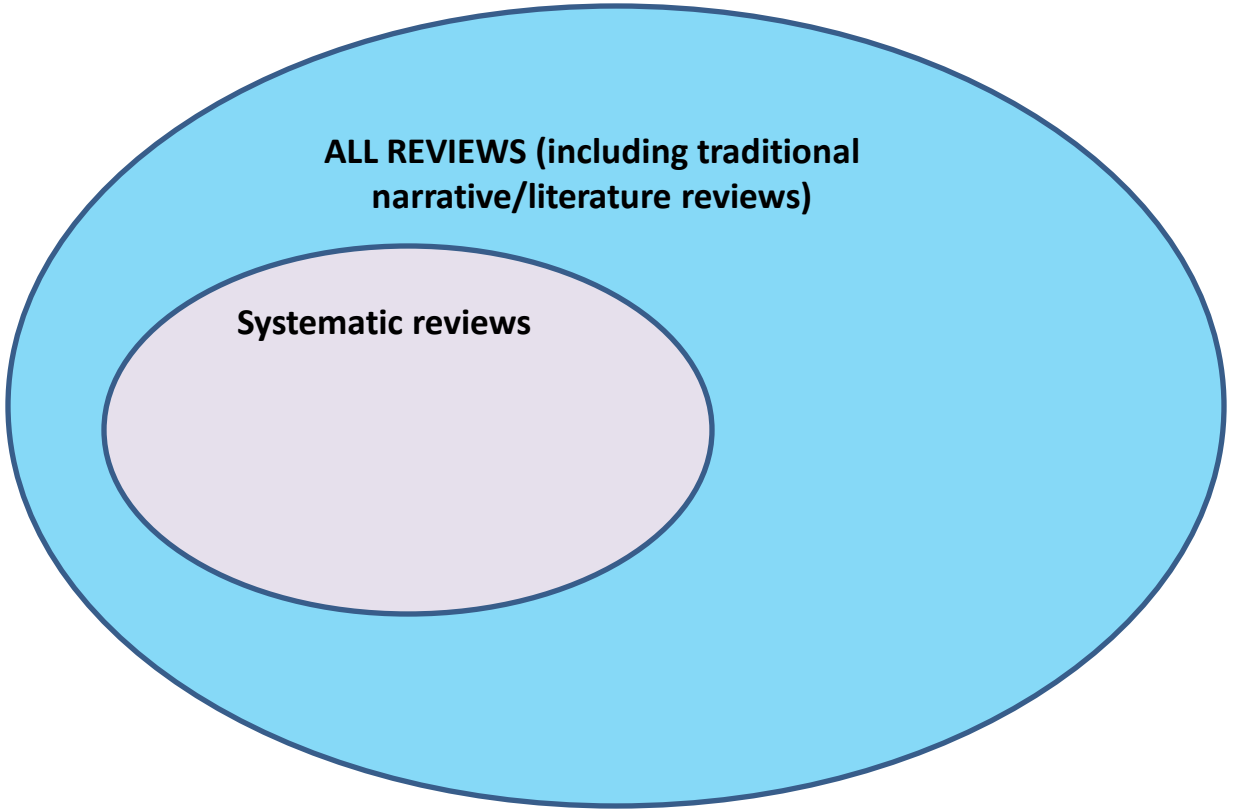


PubMed alone indexes >9,500 new papers **each week**



Systematic reviews synthesize research evidence, making it accessible and more useful

Types of literature reviews



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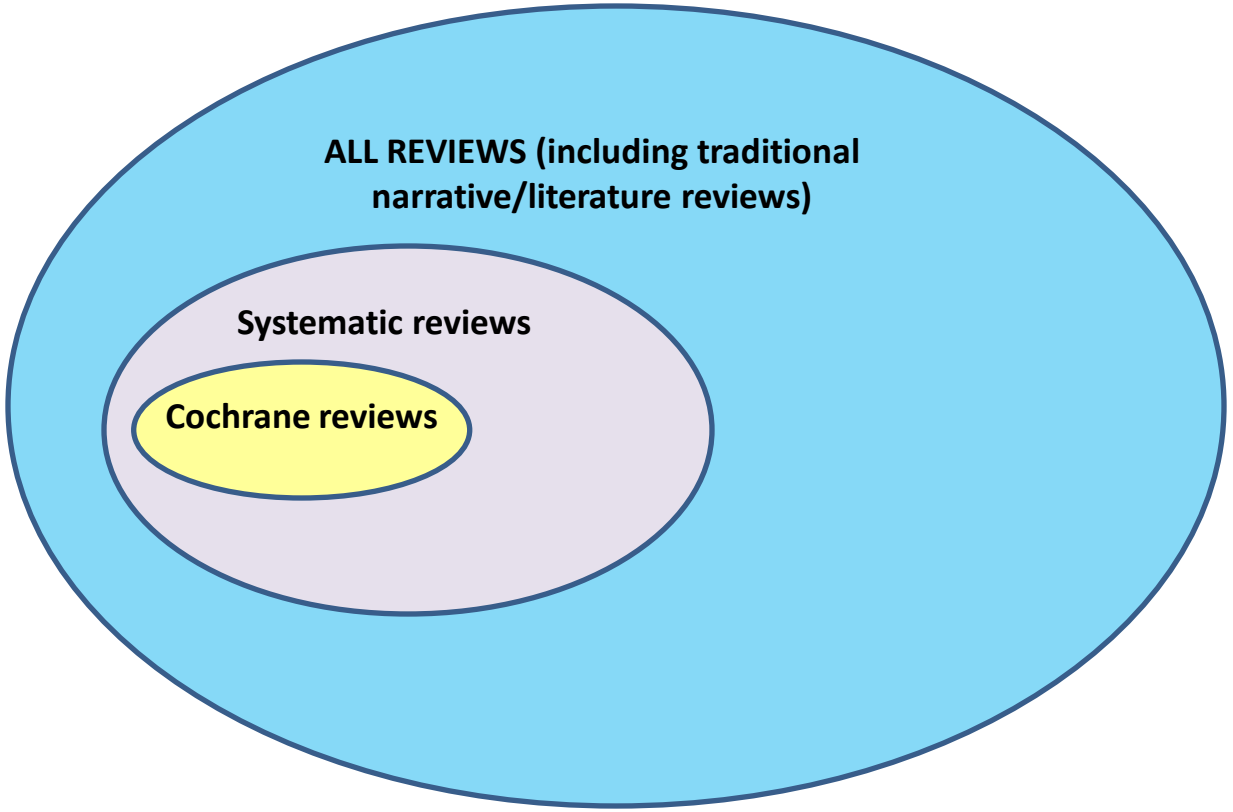

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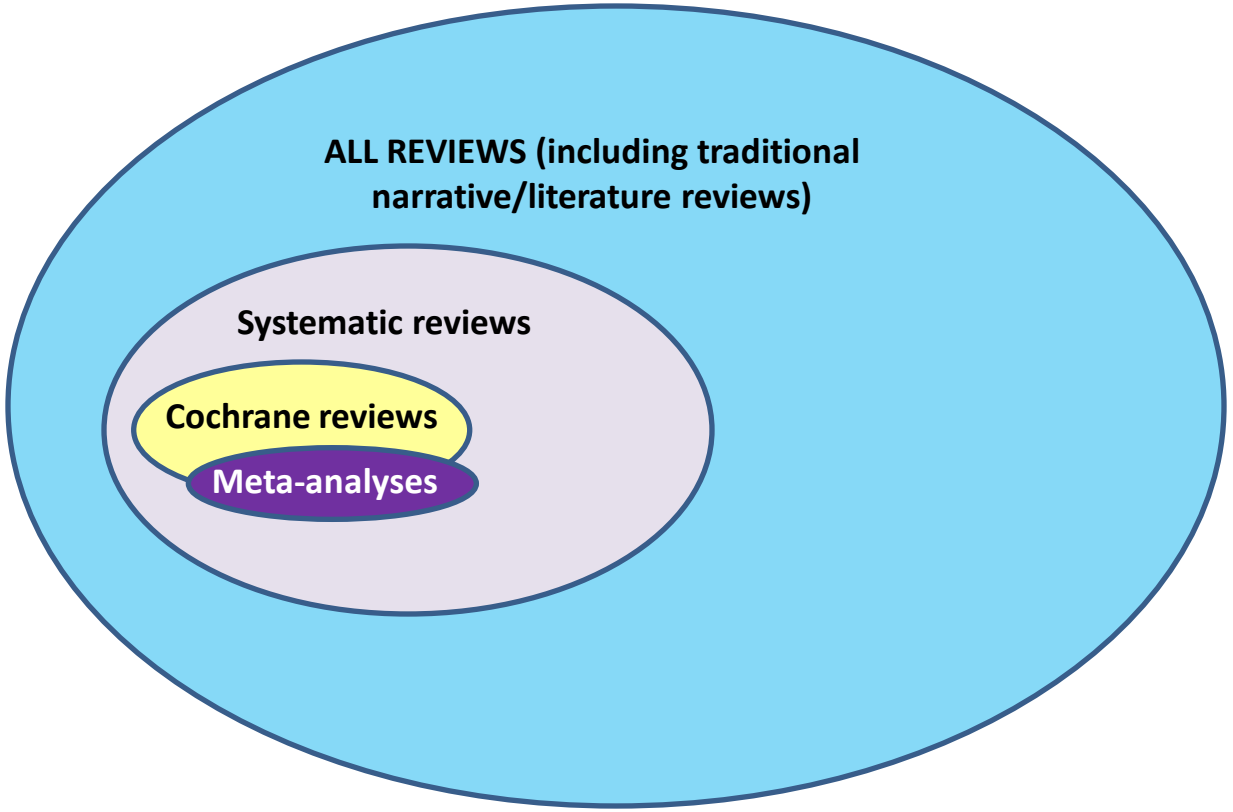
Types of literature reviews



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Narrative / literature reviews

- Usually written by experts in the field
- Use informal and subjective methods to collect and interpret information
- Usually narrative summaries of the evidence

What is a systematic review?

- Collates all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question.
- Uses explicit, systematic methods that are selected with a view to minimizing bias
- Many systematic reviews contain meta-analyses. By combining data (as appropriate), meta-analyses can provide more precise estimates of intervention effects

Who benefits from systematic reviews?

- Clinicians/practitioners
  - Current knowledge to assist with decision-making
- Researchers
  - Reduced duplication
  - Identify research gaps
- Community/patients
  - Recipients of evidence-based interventions
- Funders
  - Identify research gaps/priorities
- Policy makers
  - Current knowledge to assist with policy formulation

Systematic review

Structured, systematic process involving several steps :

1. Conceptualize the review
2. Formulate the question; prepare protocol
3. Comprehensive search
4. Unbiased selection and abstraction process
5. Critical appraisal of data
6. Synthesis of data (may include meta-analysis) and presenting results
7. Interpretation of results; conclusions

All steps are described explicitly in the review.

Key characteristics of rigorous systematic reviews

- Clearly stated objectives
- Pre-defined eligibility criteria for studies
- Explicit, reproducible methodology
- Systematic search that attempts to identify **all** eligible studies
- Assesses validity of study findings through risk of bias assessment
- Systematic presentation, and synthesis, of the characteristics and findings of the included studies

Systematic vs. Narrative reviews

SYSTEMATIC:

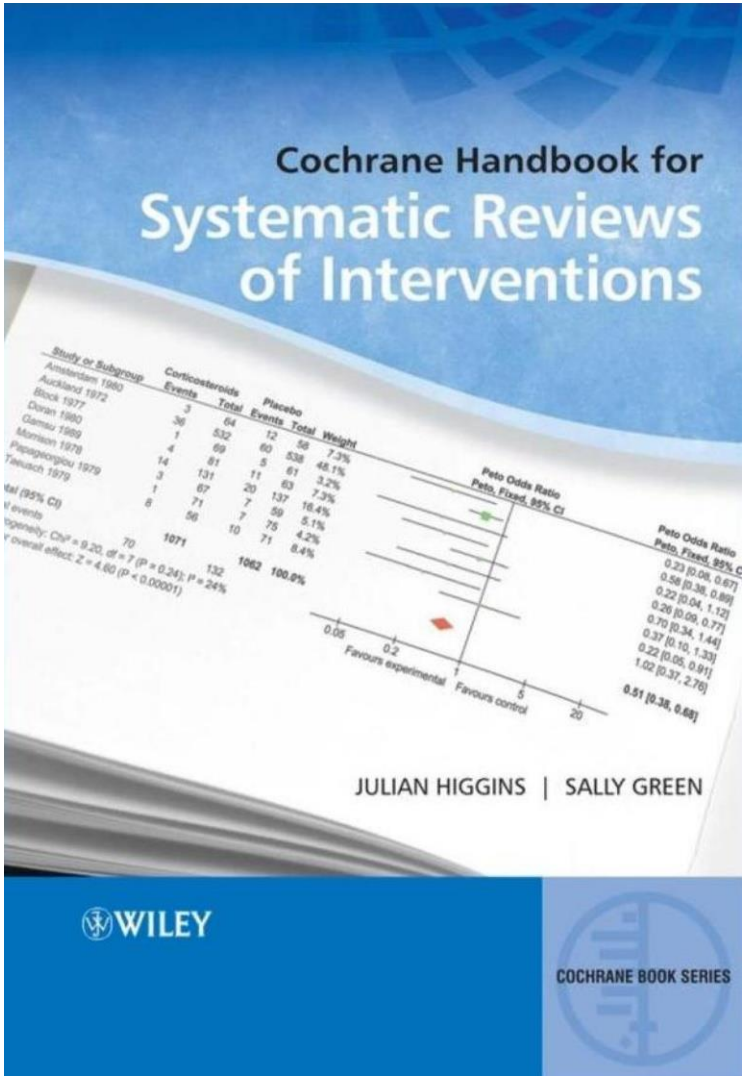
- Scientific approach to a review article
- Inclusion/exclusion criteria determined at outset
- Comprehensive search for relevant articles, multiple (i.e. all available) databases
- Explicit methods of appraisal and synthesis
- Meta-analysis may be used to combine data

NARRATIVE:

- Depend on authors' inclination
- Author gets to pick any criteria
- Search any databases, perhaps only PubMed
- Methods not usually specified in much (if any) detail
- Narrative summary and conclusions
- Can't replicate review

How are Cochrane reviews different from other systematic reviews?

- Cochrane reviews follow rigorous guidance of the Cochrane Handbook (other reviews may be more ad hoc or loose in methods)
- Cochrane reviews are kept up-to-date as new evidence emerges, updated every two years
- Cochrane reviews (and protocols for these reviews) are published in the Cochrane Database of Systematic Reviews (**CDSR**), the key component of The Cochrane Library.
- **Bottom line: High degree of rigor is <u>mandatory</u> in Cochrane reviews!**

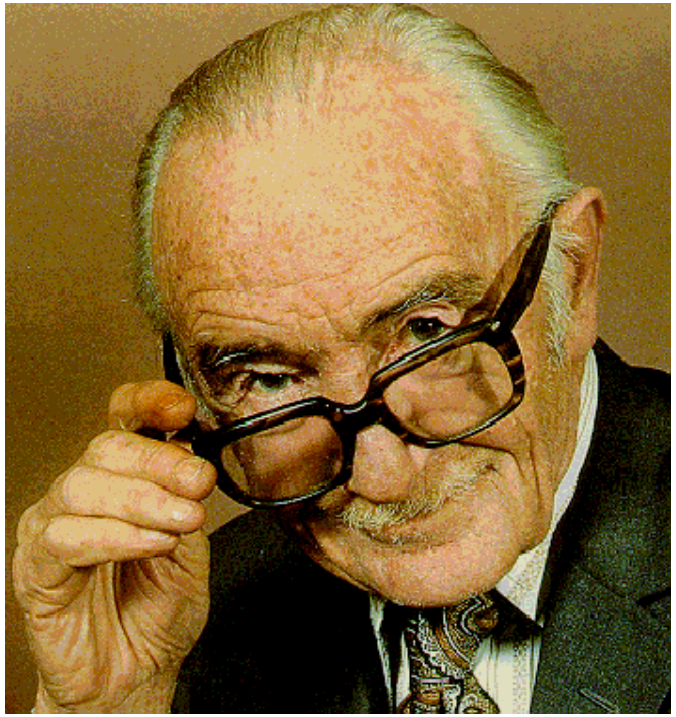


The Cochrane Collaboration

- Named in honor of British epidemiologist Archie Cochrane (1909-1988)

In 1979:

"It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomised controlled trials."



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The Cochrane Collaboration

- The Cochrane Collaboration is a global independent network of health practitioners, researchers, patient advocates and others.
- Established 1993. International and multidisciplinary focus: >30,000 contributors from >120 countries
- The Collaboration works together to produce credible, accessible health information that is free from commercial sponsorship and other conflicts of interest.
- Internationally recognized as the benchmark for high quality information about the efficacy of healthcare interventions

Mission

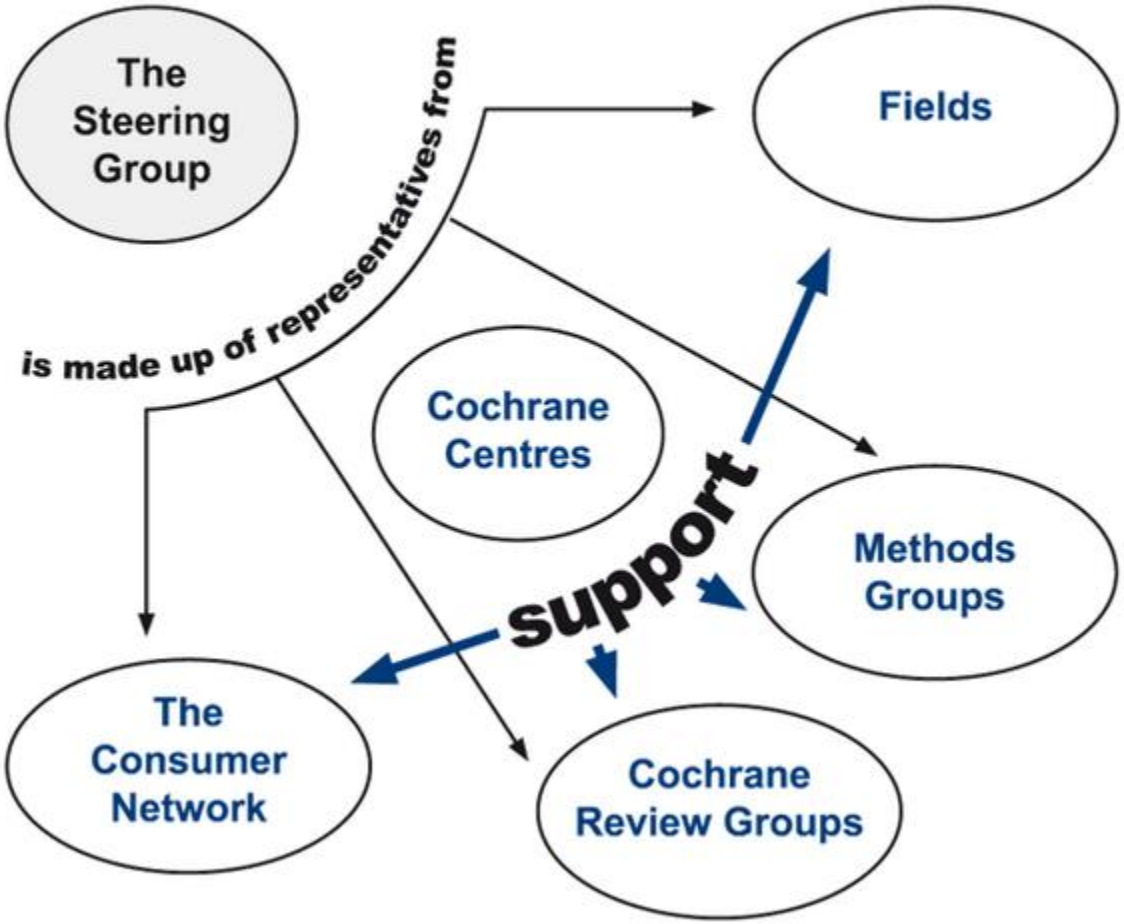
- The Cochrane Collaboration is an **international** organisation that aims to help people make **well-informed decisions** about health care by preparing, maintaining and promoting the accessibility of **systematic reviews** of the effects of healthcare interventions.

The Cochrane Library

- What is it?
  - ***Cochrane Database of Systematic Reviews***
  - **Cochrane Central Register of Controlled Trials ("CENTRAL")**
  - Other (non-Cochrane) systematic reviews
  - Health Technology Assessments
  - Economic Studies
  - Methods studies

- Reliable evidence about
  - Treatment
  - Diagnosis and screening
  - Health promotion
  - Organization of care
  - Anything you can do to someone to influence their state of health

How the Cochrane Collaboration is organized



Cochrane Collaborative Review Groups (CRGs)

- 53 CRGs, each focused around an area of health care, e.g. HIV/AIDS, Acute Respiratory Infections, Heart, Wounds, Breast Cancer, Occupational Health, STIs, Infectious Diseases, and many others
- Editorial bases of CRGs facilitate review process with volunteer authors from around the world
- Most CRGs based in the UK and Canada; others are in Australia, Denmark, Germany, New Zealand and a couple of other countries. Three CRGs based in USA.

Cochrane Review Group personnel (typically)

- Coordinating Editor
- Managing Editor
- Domain Editors
  - e.g. with HIV/AIDS Group, we have Editors for behavioral prevention, biomedical prevention, antiretroviral therapy, opportunistic infections & cancers, and organization of care
- Trials Search Coordinator
- Statistical Editor
- Methods Editor
- Perhaps others

Getting involved

Authors may be motivated to conduct Cochrane systematic reviews for many reasons.

- To resolve conflicting evidence
- To address questions of clinical uncertainty
- To explore variations in practice
- To highlight a need for further research
- The overarching aim in preparing a review is to help people make well-informed decisions about health care.

Getting involved

- Before beginning work, your proposed Cochrane Review title must be registered with a CRG
- Each of the 53 CRGs is coordinated by an editorial team who edit and publish protocols and completed reviews in the Cochrane Library
- Unlike other journals, your Cochrane Review Group will provide support and advice throughout the review process.

Systematic review

1. **Conceptualize the review**
2. Formulate the question; prepare protocol
3. Comprehensive search
4. Unbiased selection and abstraction process
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Getting started in Cochrane: Thinking about a topic

- Visit the web sites of CRGs most relevant to your research interests
- Some CRGs maintain a list on their web sites of “high priority reviews” that are needed. In other words, Cochrane reviews, not yet spoken for, that await an interested and committed team of authors.
- If you see a topic that interests you, formulate and propose a title to the CRG.

Getting started in Cochrane: Thinking about a topic

- Even if they don't have such a list, each CRG shows all its existing reviews (whether completed or in progress) on its web site
- See if you can perceive a "gap" amid these titles, in an area that interests you
- Formulate and propose a title to the CRG

Example: A few of the Cochrane Heart Group's existing reviews and protocols. Within each sub-topic, you might perceive "a review that isn't there" – i.e. a title that ought to be there, but isn't. You might then propose this "missing" title.

By subtopic:

- A. Cardiovascular Disease: Primary Prevention (38)
  - Prevention (38)
    - A.1 Drugs (12)
      - A.1.1 Antiplatelets (1)
        - Aspirin for primary prevention of coronary heart disease (protocol stage)
      - A.1.2 Lipid Lowering (7)
        - Statins for the primary prevention of cardiovascular disease
        - Interventions to improve adherence to lipid lowering medication
        - Lipid lowering efficacy of atorvastatin
        - Lipid lowering efficacy of rosuvastatin (protocol stage)
        - Fibrates for primary prevention of cardiovascular disease events (protocol stage)
        - Fibrates for secondary prevention of cardiovascular disease and stroke (protocol stage)
        - Chronotherapy versus conventional statins therapy for the treatment of hyperlipidaemia (protocol stage)
      - A.1.3 Other (4)
        - Hormone therapy for preventing cardiovascular disease in post-menopausal women
        - Co-enzyme Q10 supplementation for the primary prevention of cardiovascular disease (protocol stage)
        - Homocysteine-lowering interventions for preventing cardiovascular events
        - Fixed-dose combination therapy for the prevention of cardiovascular disease (protocol stage)
    - A.2 Lifestyle (19)
      - A.2.1 Dietary (7)
        - Dietary advice for reducing cardiovascular risk
        - 'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease
        - Green and black tea for the primary prevention of cardiovascular disease
        - Increased consumption of fruit and vegetables for the primary prevention of cardiovascular diseases
        - Interventions for increasing fruit and vegetable consumption in children aged 5 years and under
        - Reduced or modified dietary fat for preventing cardiovascular disease
        - Omega 3 fatty acids for prevention and treatment of cardiovascular disease
      - A.2.2 Exercise (8)
      - A.2.3 Other lifestyle interventions (4)

Systematic review

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Formulate the "PICO question"

Precise statement of the research question, using PICO framework: Population, Intervention, Comparator, Outcomes

P: A description of the **p**opulation

I: An **i**ntervention or interventions

C: An explicit **c**omparison

O: Relevant **o**utcomes

- Example: "In adults, adolescents and children with HIV infection, living in resource-limited settings, what interventions (compared to standard care) are efficacious for improving patient retention in antiretroviral therapy (ART) programs?"

The PICO(T) question

Problem, population	**Intervention**	**Comparison**	**Outcome**	**Types of studies**
Adults, adolescents and children with HIV infection, on antiretroviral therapy, living in resource-limited settings	▪ Home-based care ▪ Directly-observed therapy ▪ Incentives ▪ Other interventions ?	Standard care	▪ Retention in care after ART initiation ▪ Mortality ▪ Morbidity ▪ Transfer out ▪ Loss to follow-up ▪ Adherence to ART ▪ Viral suppression	▪ RCTs ▪ Observational studies, if they have comparators

Develop a review title to propose

Cochrane review titles are generally formulated in several kinds of ways:

- INTERVENTION for HEALTH PROBLEM
  - Example: “Antiretroviral therapy for preventing mother-to-child HIV transmission”
- INTERVENTION A vs. INTERVENTION B for HEALTH PROBLEM
  - Example: “Efavirenz or nevirapine in combination therapy for initial treatment of HIV infection”
- INTERVENTION for HEALTH PROBLEM in POPULATION GROUP and/or SETTING
  - Example: “Interventions for improving retention in antiretroviral therapy programs in people with HIV infection in resource-limited settings”

Register title

- The next step in the review process is to propose and agree on a review title with the appropriate CRG.
- Each CRG's web site provides a title proposal form
- It may take a few iterations, back and forth with the CRG, before the title is agreed.
- If agreed, the CRG will register your title.

Getting started in Cochrane: Assembling a team

- Cochrane reviews are always conducted by two or more authors.
- Review teams must include **expertise in the topic area being reviewed** and include (or have access to) **expertise in systematic review methodology**, including **statistical expertise**.
- First-time review authors are encouraged to participate in Cochrane Collaboration workshops and other training events.
  - Extensive training materials also available online for Cochrane review authors who have registered titles with a relevant Cochrane review group

Get the *Cochrane Handbook for Systematic Reviews of Interventions*!

- It is available in large online bookstores, e.g. Amazon.com, for around $40
- It is also available online for free: http://handbook.cochrane.org
- It is also available within the "Help" menu of Review Manager (RevMan), Cochrane's free software for conducting reviews

Download RevMan

- Cochrane protocols and reviews are conducted with RevMan
- RevMan is available at no cost from http://tech.cochrane.org/revman/download
- Combines word-processing functions with statistical/meta-analytic functions
- Quite easy to use
- Interfaces with Cochrane's "Archie" collaborative online database/workspace

Preparing a protocol

- You and your team will prepare a protocol for the review, and will submit it to the CRG.
- A Cochrane review protocol is the *a priori* work-plan for the review itself.
- The CRG will put the protocol through internal and external peer review, and will send you the comments
- After your revisions, the CRG will publish your protocol in the CDSR.

The protocol

- Background
- Review objectives
- Describe selection criteria
- Describe proposed search methods and strategy in detail
  - Important first to obtain guidance from specialist research librarian
- Describe how you will systematically apply selection criteria
  - In duplicate, reproducible, transparent
- Describe how you will assess risk of bias in included studies
- Describe how you will analyze results, using meta-analysis if appropriate and possible
  - How you will investigate heterogeneity, reporting bias
  - How you will perform sensitivity analyses, if needed

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials (RCTs) conducted in resource-limited settings.
- Non-randomised studies (with comparators) conducted in resource-limited settings.

Types of participants

- Adults, adolescents or children with HIV infection, living in resource-limited settings.

Types of interventions

- Any intervention for people with HIV infection having an outcome of retention in care after ART initiation
  - Comparator: Standard of care

Types of interventions to be excluded:

- Interventions concerned with retention in care between HIV diagnosis and ART initiation.
- Decentralisation of care and task-shifting interventions. These interventions are covered in existing Cochrane reviews (Kredo 2012a, Kredo 2012b).

Types of outcome measures

Primary outcomes

- Retention in care after ART initiation where retention is defined by a patient who is still on HIV treatment (assessed at clinically appropriate intervals, e.g. 6, 12, 24, 36, 48, 60 months) and has not (1) died, (2) transferred out, (3) stopped treatment, or (4) been lost-to follow-up.¬
- A patient retained in care after ART initiation shall also be defined as someone who has been seen in the clinic at least 6 months later because the WHO recommends an HIV viral load test at 6 months after initiating ART, as well as a CD4 count every 6 months (WHO 2013).

Secondary outcomes

- Mortality
- Morbidity
- Transfer out
- Loss to follow-up
- Adherence to ART
- Viral suppression

We will formulate a comprehensive and exhaustive search strategy in an attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press and in progress). Full details of the Cochrane HIV/AIDS Review Group methods and the journals hand-searched are published in the section on Collaborative Review Groups in The Cochrane Library.

Journal and trial databases

We will search the following electronic databases, in the period from 1 January 1996 to the search date:

- CENTRAL (Cochrane Central Register of Controlled Trials)
- PsycINFO
- PubMed
- Web of Science / Web of Social Science
- World Health Organization (WHO) Global Health Library, which includes references from AIM (AFRO), LILACS (AMRO/PAHO), IMEMR (EMRO), IMSEAR (SEARO), and WPRIM (WPRO).

Along with appropriate MeSH terms and relevant keywords, we will use the Cochrane Highly Sensitive Search Strategy for identifying reports of randomised controlled trials in MEDLINE (Higgins 2008), and the Cochrane HIV/AIDS Group's validated strategies for identifying references relevant to HIV infection and AIDS. The search strategy will be iterative, in that references of included studies will be searched for additional references. All languages will be included.

See Appendix 2 for our PubMed search strategy, which will be modified and adapted as needed for use in the other databases.

Conference databases

We will search conference abstract archives on the web sites of the Conference on Retroviruses and Opportunistic Infections (CROI), the International AIDS Conference (IAC), and the International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (IAS), for abstracts presented at all conferences from 1996 through 2013.

Searching other resources

In addition to searching electronic databases, we will contact individual researchers, experts working in the field and authors of major trials to address whether any relevant manuscripts are in preparation or in press.¬The references of published articles found in the above databases will be searched for additional pertinent materials.

We will search WHO's International Clinical Trials Registry Platform (ICTRP) to identify ongoing trials.

Types of study designs

- Randomized controlled trials
- Quasi-randomized trials
- Prospective cohort studies
- Retrospective cohort studies
- Controlled before and after studies
- Uncontrolled before and after studies
- Interrupted time series
- Qualitative research (usually to augment the review's quantitative research)

Systematic review

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2. Formulate the question; prepare protocol
3. **Comprehensive search**
4. Unbiased selection and abstraction process
5. Critical appraisal of data
6. Synthesis of data (may include meta-analysis) and presenting results
7. Interpretation of results; conclusions

The real work begins: Comprehensive searches

- After your protocol has been accepted and published in the CDSR, you can begin your searches.
- Most CRGs will conduct some searches for you, usually of PubMed, Embase and the CRG's Specialized Register (which feeds into CENTRAL). Trials search coordinators will work with you to refine/adapt your search strategies for each of these databases.
- It will be up to you to conduct searches of other relevant databases and sources to which you have access. Research librarians can help you with strategies and access.

Search strategies

Develop strategy by thinking of concepts, e.g. “HIV terms” AND “retention in care terms” AND “developing country terms.” Research librarian (and Cochrane trials search coordinator) can help.

Retention, attrition, loss to follow-up, LTFU, defaulting, loss to care, loss to program etc.

HIV, AIDS, HIV/AIDS, human immunodeficiency virus, acquired immunodeficiency syndrome, antiretroviral, anti-retroviral etc.

Resource-limited, resource-constrained, developing countries, low-and middle-income countries, LMIC, etc.

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Search strategies

- Searches should seek high sensitivity, which may result in relatively low precision (i.e. there could be many search results)
- Wide variety of search terms should be combined (in Boolean approach) with “OR”, within each concept. All known variations of terms, alternate spellings (e.g. UK spellings), acronyms etc.
- Both free-text **and** subject headings should be used to the degree possible, e.g. NLM’s Medical Subject Headings (MeSH)
- Also include Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE/PubMed

Example of a PubMed search strategy

#5	**Search #1 AND #2 AND #3 AND #4**
#4	Search (HAART[tiab] OR ART[tiab] OR cART[tiab] OR antiretroviral[tiab] OR anti-retroviral[tiab] OR anti-viral[tiab] OR antiviral[tiab] OR "Antiretroviral Therapy, Highly Active"[Mesh])
#3	Search (HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tiab] OR hiv-1[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab]OR human immune deficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*) AND(deficiency virus[tiab])) OR acquired immunodeficiency syndromes[tiab] OR acquired immune deficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*) AND (deficiency syndrome[tiab])) or "sexually transmitted diseases, viral"[mh]) OR HIV[tiab] OR HIV/AIDS[tiab] OR HIV-infected[tiab] OR HIV[title] OR HIV/AIDS[title] OR HIV-infected[title]
#2	Search randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[MeSH] OR random allocation[MeSH] OR double-blind method[MeSH] OR single-blind method[MeSH] OR clinical trial[pt] OR clinical trials[MeSH] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR random*[tw] OR research design[mh:noexp] OR prospective studies[MeSH] OR control*[tw] OR volunteer*[tw]) OR observational[tw] OR non-random*[tw] OR nonrandom*[tw] OR before after study[tw] OR time series[tw] OR cohort*[tw] OR cross-section*[tw] OR prospective*[tw] OR retrospective*[tw] OR research design[mh:noexp] OR follow-up studies[MeSH] OR longitud*[tw] OR evaluat*[tiab] OR pre-post[tw] OR (pre-test[tw] AND post-test[tw]) NOT (animals[MeSH] NOT human[MeSH])
#1	Search (retention[tiab] OR retain*[tiab] OR "lost to follow-up"[tiab] OR "loss to follow-up"[tiab] OR ("loss*"[tiab] AND "follow up"[tiab]) OR LTFU[tiab] OR attrition[tiab] OR "loss to care"[tiab] OR "lost to care"[tiab] OR "loss to program*"[tiab] OR "lost to program*"[tiab] OR default*[tiab] OR engage*[tiab] OR disengage*[tiab])

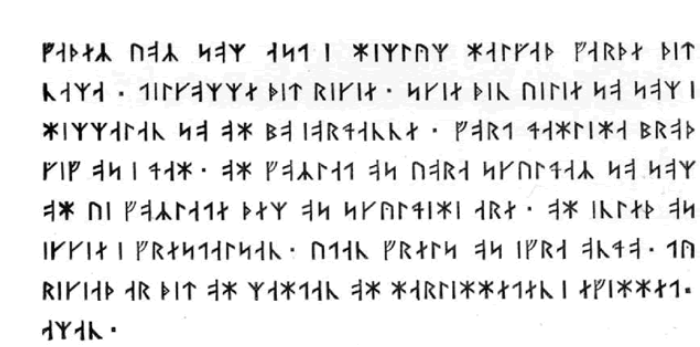
Commonly-used databases

- PubMed
- Embase
- Central
- Web of Science
- Scopus
- PsycINFO
- WHO Global Index Medicus
- Literatura Latino-americana e do Caribe em Ciências da Saúde (LILACS)
- Any others to which you have access, if they are relevant to your review topic!

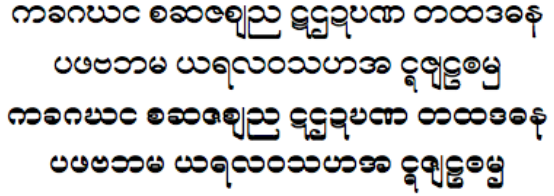
Librarians are your friends!

Other sources

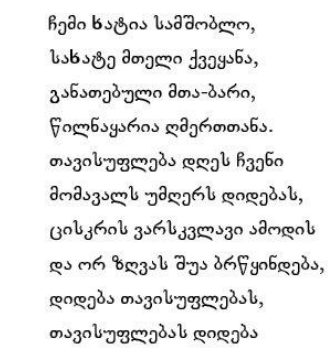
- Hand searching of key journals and conference proceedings
- Scanning bibliographies/reference lists of primary studies and reviews
- Contacting researchers/agencies/academic institutions
- Neglecting certain sources may result in reviews being biased

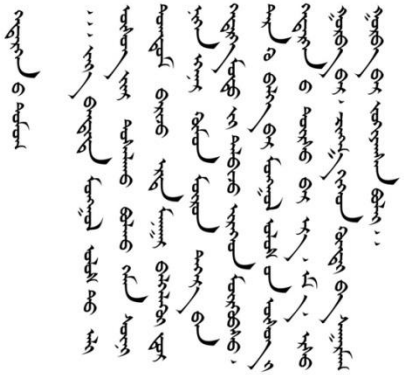


No limits!



- Studies published in any language must be eligible.
  - But what happens if we need to decide the eligibility of (and/or collect data from) an article we can’t even read?
  - The CRG will try very hard to find someone who can translate at least the key points.





Search results…

Systematic review

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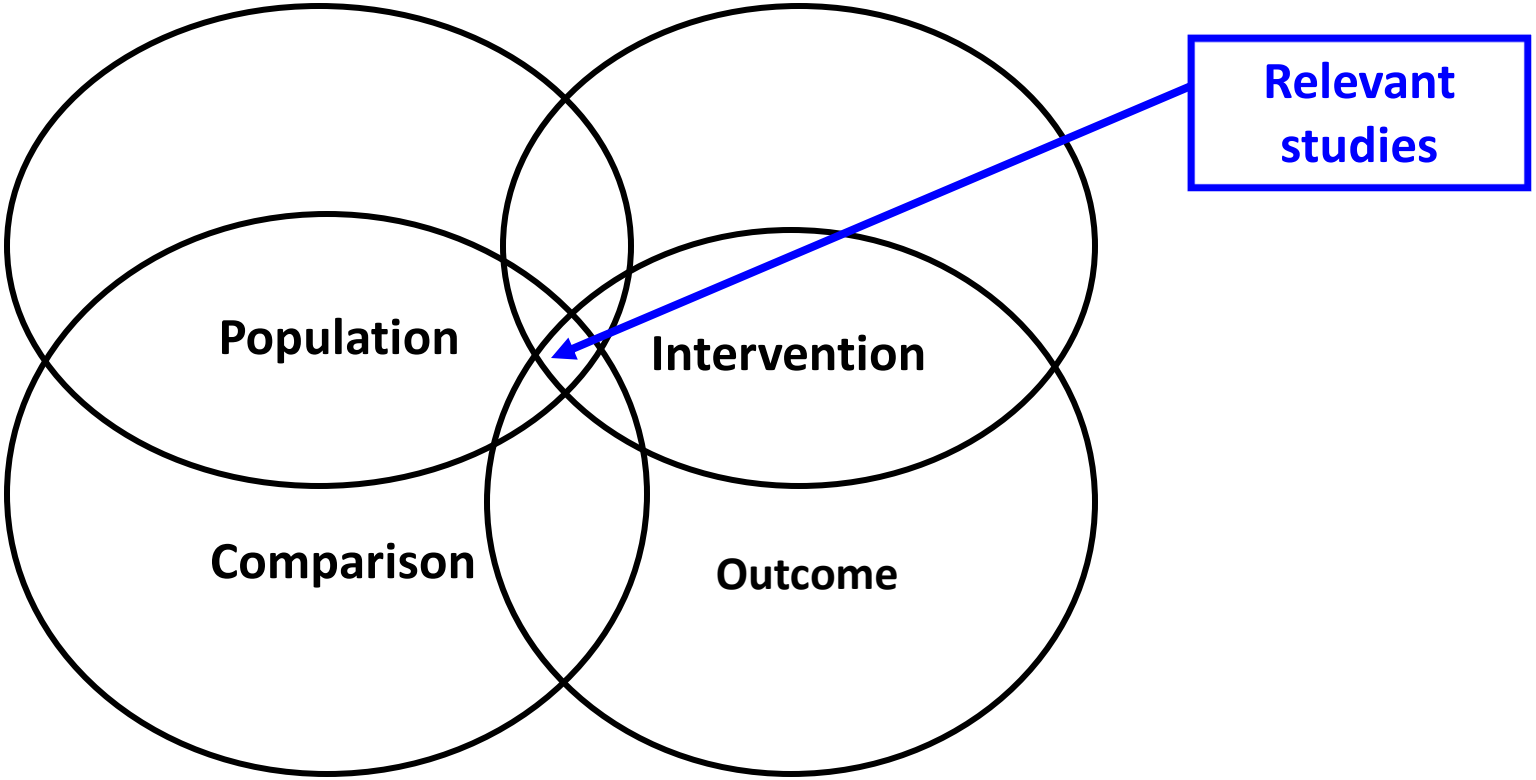
Working with search results

- After the searches have been done, you will likely have several files containing results from the respective databases
- Import all results into a citation-management software (e.g. EndNote or RefWorks)
- Remove duplicate references.
- One author may first (optionally) skim through the references by title, removing those that are clearly irrelevant

Selecting studies

- Two or more authors should then begin the process of INDEPENDENTLY screening titles and abstracts.
  - If there is any doubt of a study's eligibility, obtain the full-text article for closer examination
  - Select final studies for inclusion in the review.
  - A neutral party could serve as an arbiter in case of disagreement.
  - Keep track of the numbers at every stage of screening! You will need these for the flow-chart of your screening process.

How PICO informs study selection



Collecting data

- Collection of data from study reports should also be done by at least two people, working independently.
- Cochrane reviews have studies, rather than reports, as the unit of interest. Multiple reports of the same study need to be linked together.
- Data collection forms should be designed carefully to target the objectives of the review, and should be pre-piloted for each review
- The Handbook (and all CRGs) have suggestions for helping with the design and use of data collection forms.
- Relevant data must be entered in RevMan

Data collection forms

- Elements of standardized data collection forms may include:
  - Research design
  - Sample size
  - Time period over which data were collected
  - Characteristics of the intervention
  - Characteristics of the study population
  - Outcomes assessed
  - Findings
  - Data necessary to assess risk of bias in each study

Example of data collection form

"Community-based approaches to improve adherence to antiretroviral therapy"

A	B	C	D	E	F	G	H	I
Study	**DESIGN**	**POPULATION & SETTING**	**TYPE of INTERVENTION**	**COMPARATOR**	**MORTALITY**	**MORBIDITY**	**ADHERENCE**	**REDUCED VIRAL LOAD ON ART @ 3, 6, 12, 24 mo**
Chang 2011	Cluster-randomized trial. Sub-study of Chang 2010. Randomized 2:3 to PHWs receiving mHealth support intervention or not.	Adults (n=970), either on ART or starting ART during the trial. ~67% ART-naïve. Uganda. ~67% female.	PHWs used mobile phones to call and text higher level providers with patient-specific	Peer health worker intervention without mobile phone support.	At 26 months. I:37/446. C: 53/524.	not reported	At 26 months: Adherence (<95%, pill count): I: 2/401. C: 10/473. Adherence (<100% pill count): I:	VIRAL FAILURE: all patients. At 6 mo: I: 25/203. C: 20/259. At 48 weeks: I: 18/201. C: 24/255.
Futterman 2010	Prospective cohort study.	Pregnant women (n=160) attending two maternity clinics offering PMTCT in South Africa.	Women at intervention site received support of HIV+ mentor mother; also	Standard care.	not reported	not reported	not reported. "Self-reports of adherence to PMTCT practices ≥90%" Footnote, maybe.	not reported
Grimwood 2012	Multicentre cohort study.	ART-naive children (n=3563), 47 public ART facilities n South Africa. Ns: I: n=323. C: n=3240	Patient advocates.	Standard care	N must be back-calculated. At 3 years, I: 3.7%. C: 8.0%.	not reported	not reported.	not reported
Kabore 2010	Multicentre cohort study.	Adults initiating ART (n=587) at 4 sites in Botswana, Lesotho, Namibia, South Africa.	Integrated community-based services /participatory action.	Standard care.	not reported	not reported	At 12 months: Receiving home-based care and/or food support: Adherence (<95%, pill count): I: 287/429. C:	not reported

Additional outcomes assessed, risk of bias details etc.

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Systematic review

1. Conceptualize the review
2. Formulate the question; prepare protocol
3. Comprehensive search
4. Unbiased selection and abstraction process
5. **Critical appraisal of data**
6. Synthesis of data (may include meta-analysis) and presenting results
7. Interpretation of results; conclusions

Assessing the risk of bias in included studies

- Problems with the design and execution of individual studies of healthcare interventions raise questions about the validity of their findings
- An assessment of the validity of studies included in a Cochrane review should emphasize the risk of bias in their results, i.e. the risk that they will overestimate or underestimate the true intervention effect
- Cochrane Collaboration recommends a specific tool for assessing risk of bias in each included study

Risk of bias vs. “quality”

- “Assessment of methodological quality” often used in systematic review methods: Suggests an investigation of the extent to which study authors conducted their research to highest standards.
- Key consideration in a Cochrane review is the extent to which results of included studies should be **believed**. Assessing risk of bias targets this question squarely.
- A study may be performed to the highest possible standards yet still have an important risk of bias.
  - e.g. it is often impractical or impossible to blind participants or study personnel to intervention group.

Risk of bias

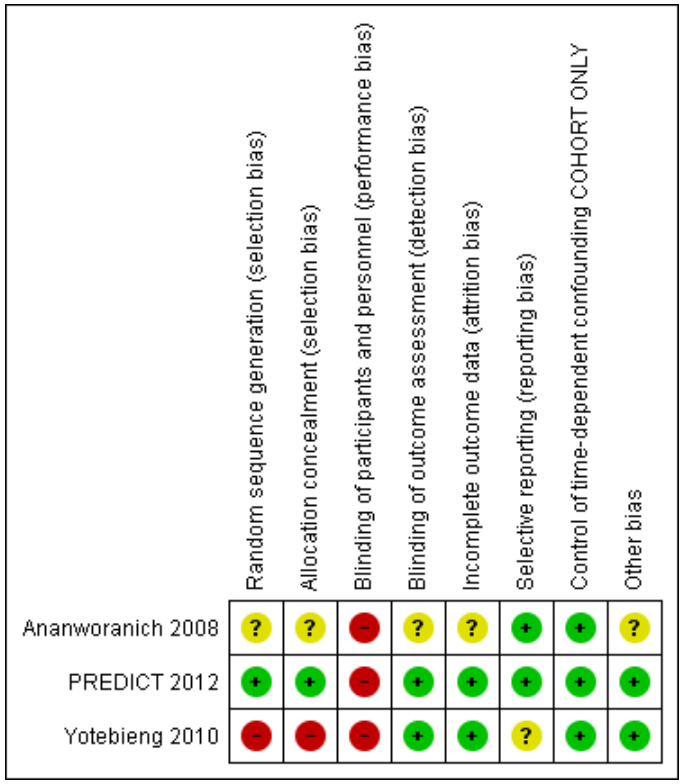
- Cochrane tool: Judgment (and a support for the judgment) for each entry in a “Risk of bias” table, where each entry addresses a specific feature of the study
- Key features in a Cochrane “Risk of bias” table are:
  - sequence generation (selection bias)
  - allocation concealment (selection bias)
  - blinding of participants and personnel (performance bias)
  - blinding of outcome assessment (detection bias)
  - incomplete outcome data (attrition bias)
  - selective outcome reporting (reporting bias)
  - other potential sources of bias.
- Handbook provides detailed guidance in making these judgments

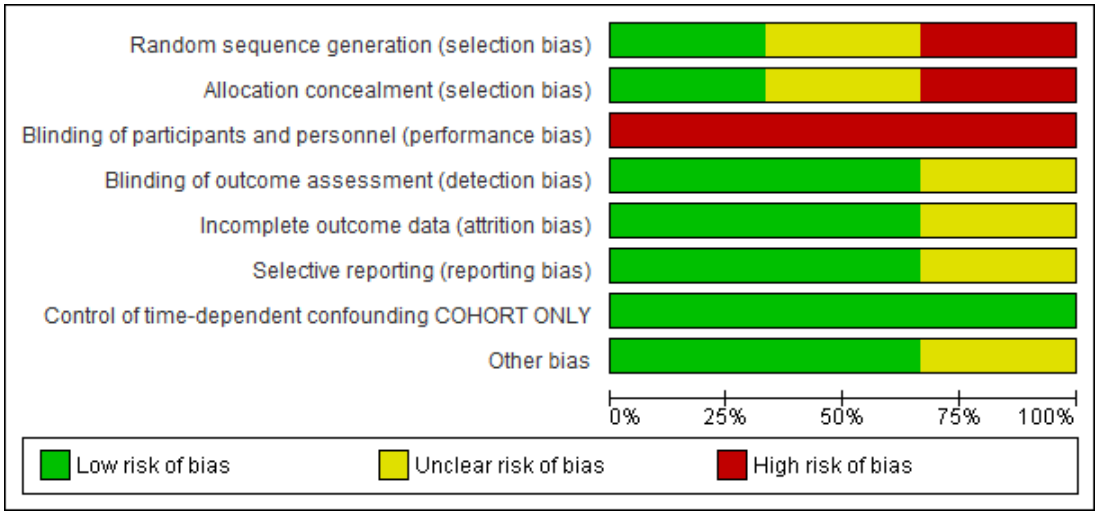
RANDOM SEQUENCE GENERATION **Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.**	
Criteria for a judgment of 'Low risk' of bias.	The investigators describe a random component in the sequence generation process such as: • Referring to a random number table; • Using a computer random number generator; • Coin tossing; • Shuffling cards or envelopes; • Throwing dice; • Drawing of lots; • Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgment of 'High risk' of bias.	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: • Sequence generated by odd or even date of birth; • Sequence generated by some rule based on date (or day) of admission; • Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: • Allocation by judgement of the clinician; • Allocation by preference of the participant; • Allocation based on the results of a laboratory test or a series of tests; • Allocation by availability of the intervention.
Criteria for the judgment of 'Unclear risk' of bias.	Insufficient information about the sequence generation process to permit judgment of 'Low risk' or 'High risk'.

Risk of bias assessment (one trial)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation program using SAS 9.1. The randomisation employed minimization by research site and history of nevirapine exposure.
Allocation concealment (selection bias)	Low risk	The process was done centrally at a trial coordinating centre in Bangkok and assignment was communicated to the site investigator via fax.
Blinding of participants and personnel (performance bias)	High risk	Caregivers and personnel were not blinded as the study was open-label. This may introduce performance bias.
Blinding of outcome assessment (detection bias)	Low risk	An independent committee blinded to assignment, CD4 and ART status, reviewed outcomes of CDC category B and C endpoints and hospitalizations. Other outcomes may have been susceptible to detection bias but we judged this to be of low risk.
Incomplete outcome data (attrition bias)	Low risk	In the IMMEDIATE group, 7/150 (4.6%) were lost-to-follow-up and in the DEFERRED group, 3/150 (2%) were lost-to-follow-up. This represents a low attrition rate.
Selective reporting (reporting bias)	Low risk	We compared the trial report with the entry for NCT00234091 on www.clinicaltrials.gov. There was no selective reporting.
Control of time-dependent confounding COHORT ONLY	Low risk	Not applicable due to the nature of randomisation which eliminates the need to control for confounding.
Other bias	Low risk	The trial was funded by government organizations. The drugs were supplied by pharmaceutical companies which had no role in the study design, analysis or manuscript preparation. The trial was not stopped early. For these reasons we judged the risk of bias to be low for other forms of bias.

Risk of bias summary figures (all trials in review)





Systematic review

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Meta-analysis

- Meta-analysis is the statistical combination of results from two or more individual studies.
- Meta-analysis yields an overall statistic (with its confidence interval) that summarizes effect of the intervention, compared to control
- Potential advantages of meta-analyses include
  - increase in power
  - improvement in precision
  - ability to answer questions not posed by individual studies
  - opportunity to settle controversies arising from conflicting claims

Meta-analysis

- What comparisons should be made?
- What study results should be used in each comparison?
- Are the results of studies similar within each comparison?
- What is the best summary of effect for each comparison?

Meta-analyses shouldn't always be done

"…it is always appropriate and desirable to systematically review a body of data, but it may sometimes be inappropriate, or even misleading, to statistically pool results from separate studies. Indeed, it is our impression that reviewers often find it hard to resist the temptation of combining studies even when such meta-analysis is questionable or clearly inappropriate."

Egger et al. Systematic reviews in health care. London: BMJ Books, 2001:5

When NOT to do meta-analyses

- Too much heterogeneity among studies: Meta-analysis may be meaningless. Genuine differences in effects may be obscured.
- Meta-analyses of studies that are at risk of bias may be seriously misleading.
- Meta-analyses in the presence of serious publication and/or reporting biases are likely to produce an inappropriate summary.

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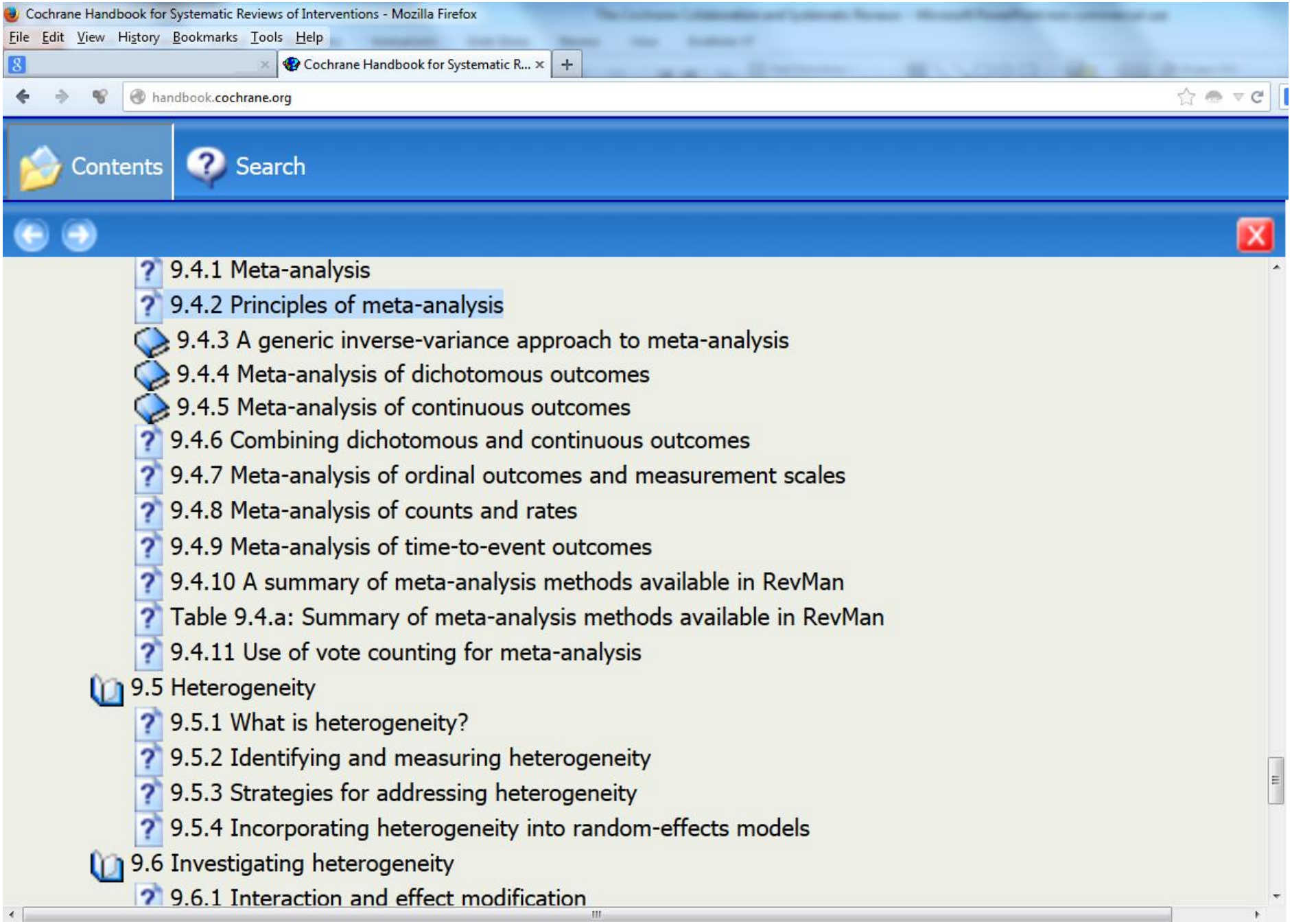
Meta-analysis methods

- Choice of summary statistic
  - Dichotomous data
    - Usually use risk ratio or odds ratio; other possibilities available
  - Continuous data
    - Results can be pooled directly if measured on the same scale, or converted to a common metric if measured on different scales

Meta-analysis methods

- Two statistical models for pooling results
  - Fixed effects – assumes differences in results across studies are due to random error
  - Random effects – assumes underlying effects may vary across studies
- Random effects models incorporate heterogeneity
- The two models will produce different estimates in the presence of heterogeneity


Cochrane Handbook for Systematic Reviews of Interventions - Mozilla Firefox
File Edit View History Bookmarks Tools Help
Cochrane Handbook for Systematic R...
handbook.cochrane.org
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9.4.5 Meta-analysis of continuous outcomes
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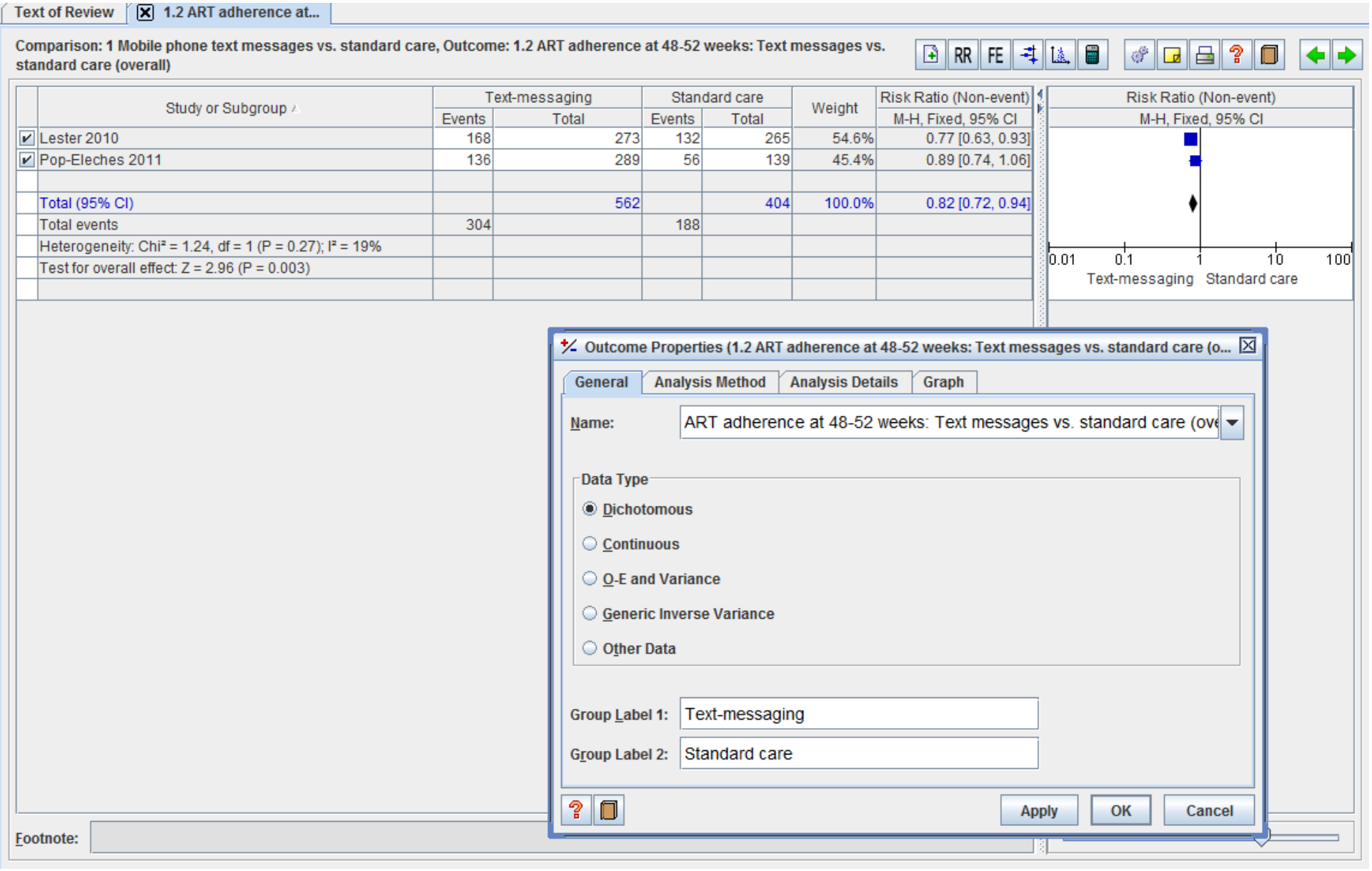
Meta-analysis (simple example)



Other analyses that can be useful in meta-analysis

Sensitivity analysis

- Does not calculate effect estimate for "removed" group
- May not be pre-specified

Subgroup analysis

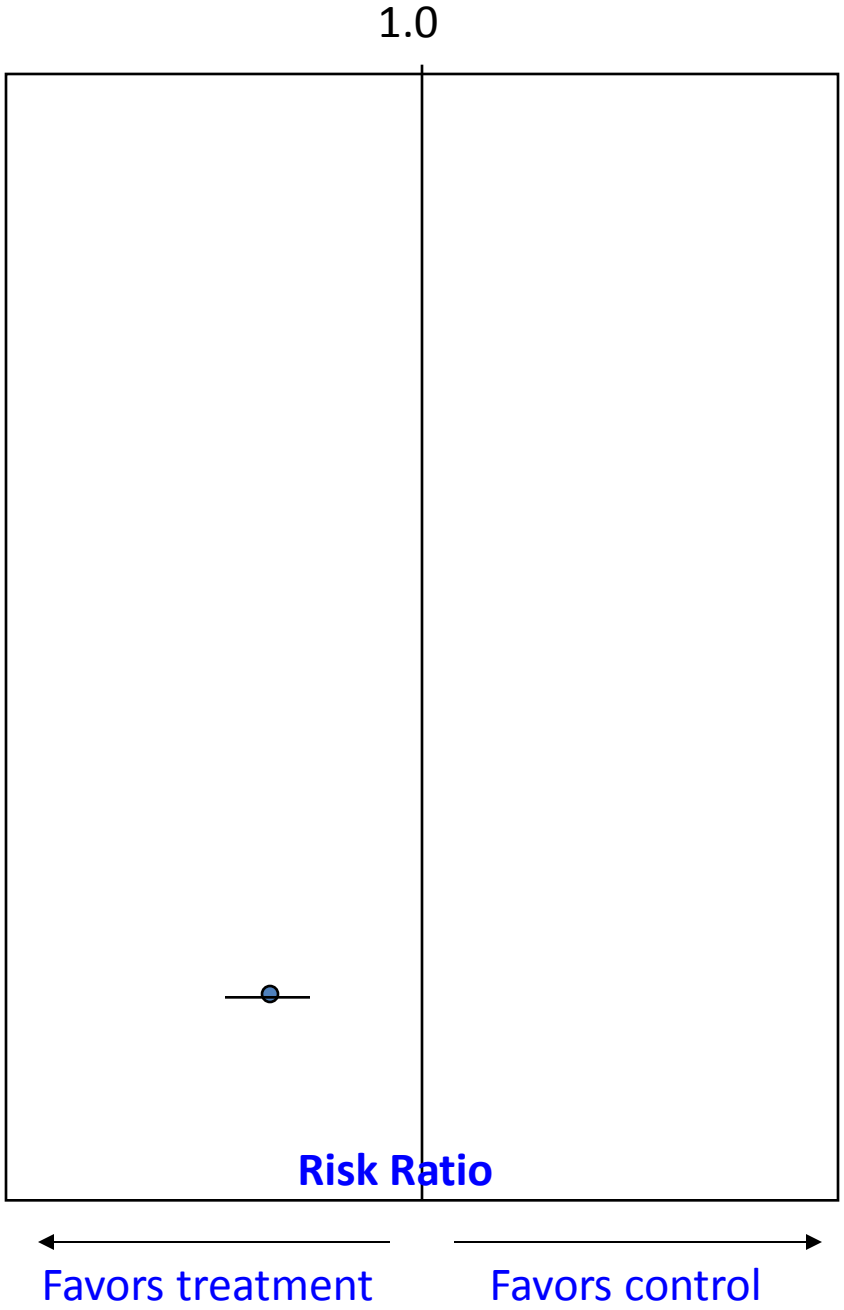
- Effect estimates calculated for each group
- Formal statistical comparisons made between groups
- Must be pre-specified in protocol

Sensitivity analysis

REPEAT the primary meta-analysis using different decision criteria.

- Changing the inclusion criteria (e.g. if they include a numerical value)
- Setting risk of bias cut-offs
- Excluding unpublished studies

Sensitivity analysis



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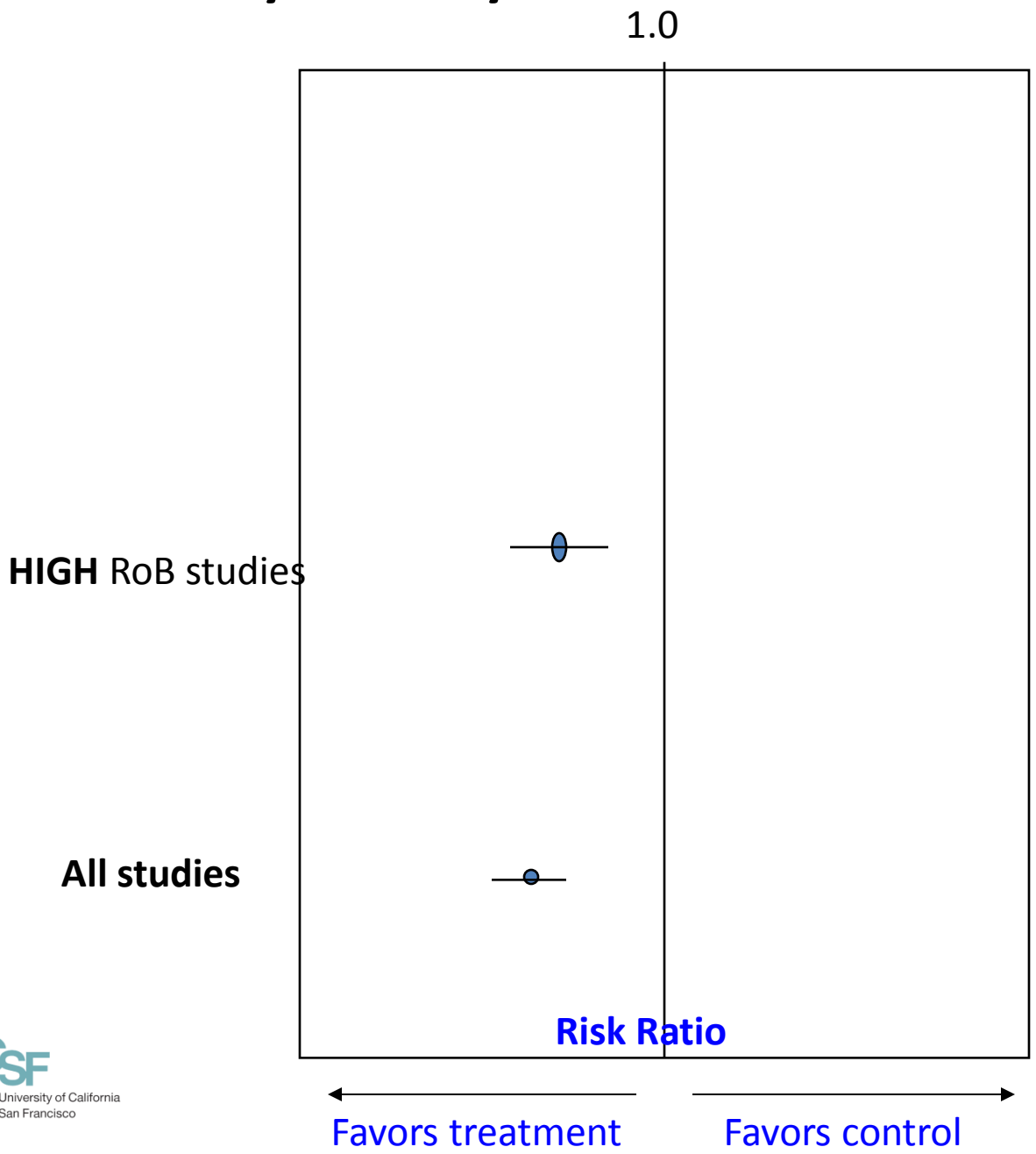
Sensitivity analysis



REMOVE studies at LOW risk of bias

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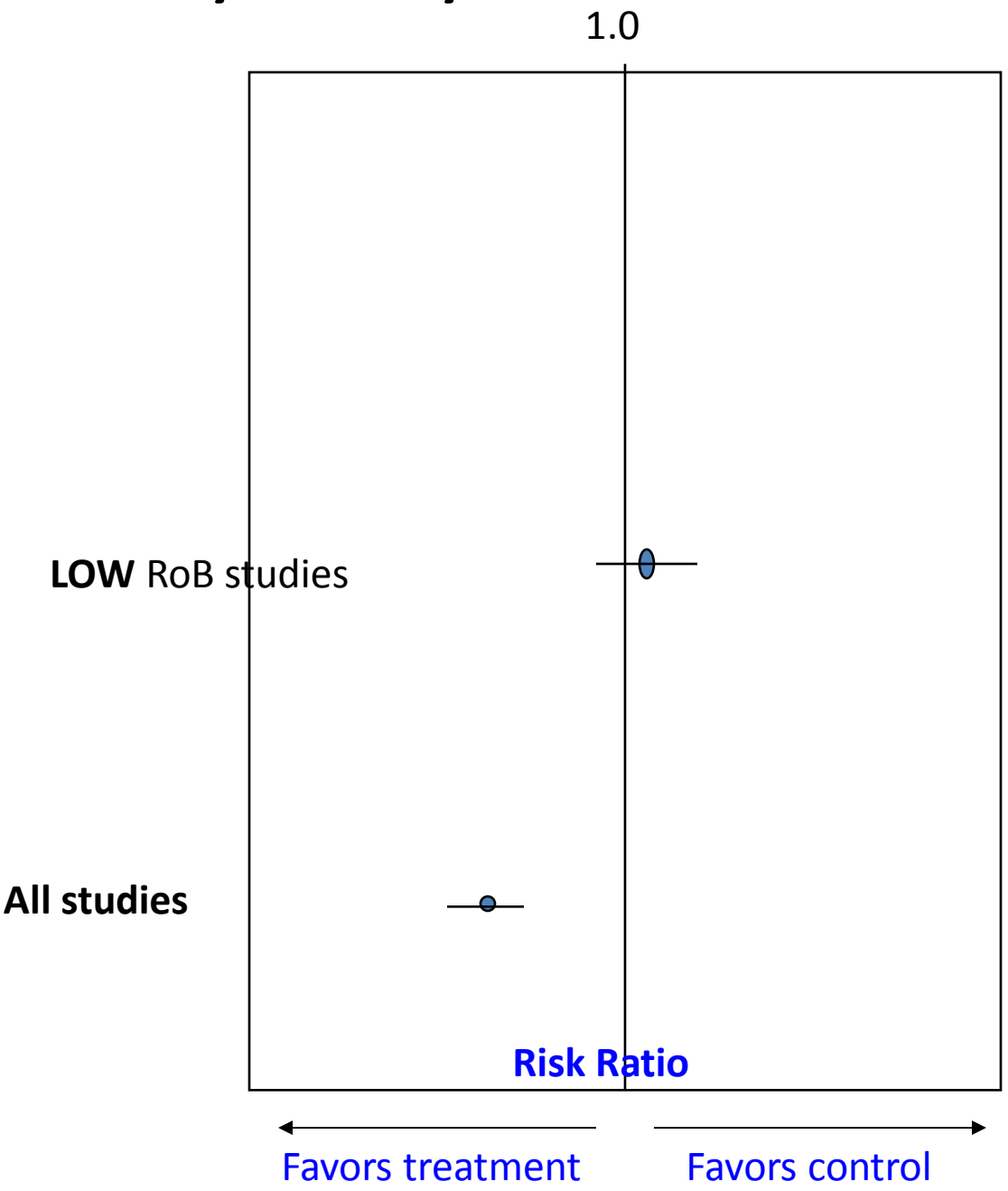
Sensitivity analysis



REMOVE studies at HIGH risk of bias

Results section

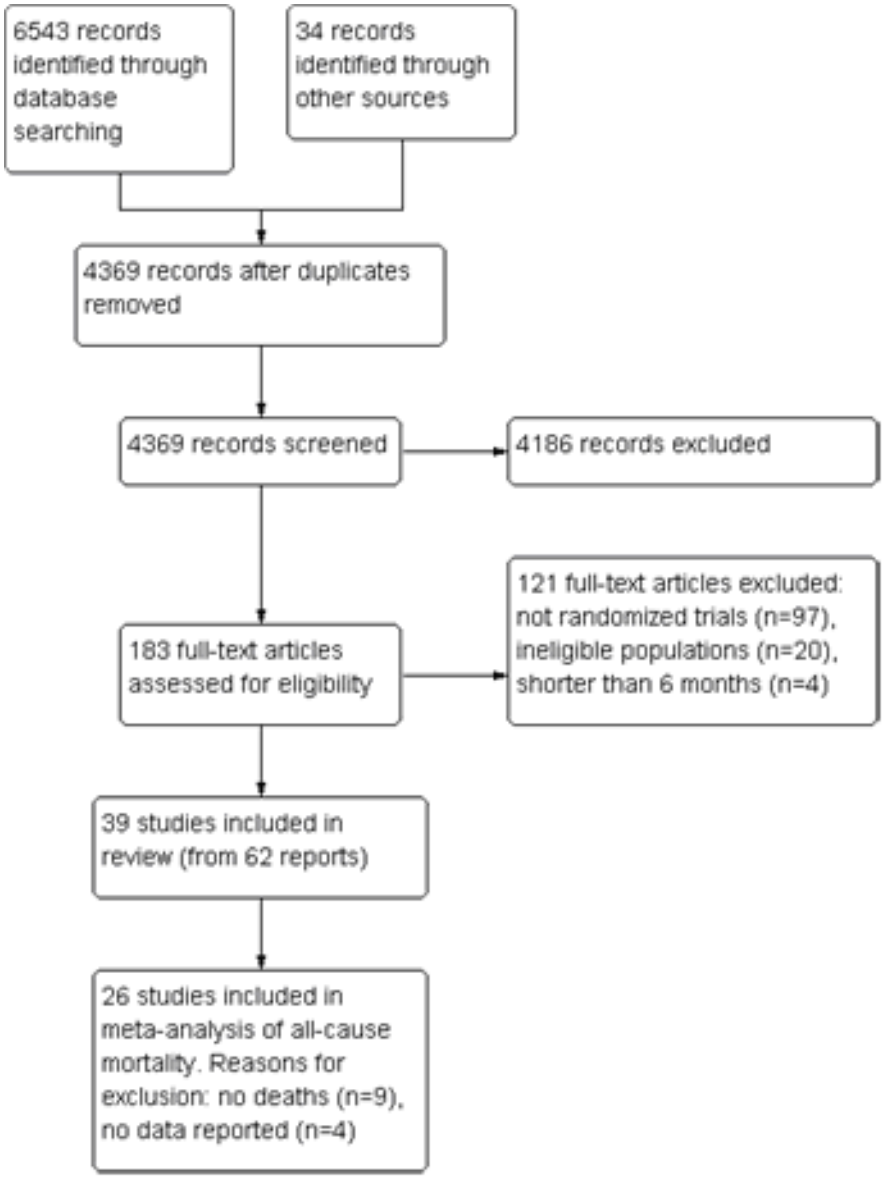
- Results section of a review should summarize findings in a clear and logical order, and should explicitly address the objectives of the review.
- Variety of tables and figures available to present information in a more convenient format:
  - "Characteristics of included studies" tables (including "Risk of bias" tables).
  - "Data and analyses" (the full set of data tables and forest plots).
  - Figures
  - "Summary of findings" tables (including evidence quality)
  - Additional tables

Results of the search

- Described narratively, but also with “PRISMA” flow diagram
  - number of unique records identified by the searches;
  - number of records excluded after preliminary screening (e.g. of titles and abstracts);
  - number of records retrieved in full text;
  - number of records or studies excluded after assessment of the full text, with brief reasons;
  - number of studies meeting eligibility criteria for the review
  - number of studies contributing to the main outcome

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Medicine 2009; 6: e1000100.

PRISMA flow diagram



"Characteristics of included studies" (table)

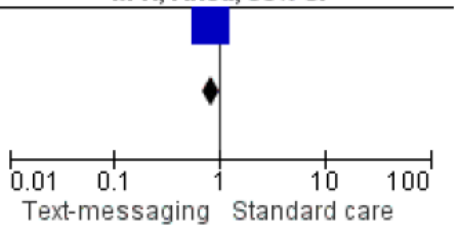
- **Methods**: Detailed description of study design
- **Participants**: setting; relevant details of health status of participants; age; sex; country. Sufficient information should be provided to allow users of the review to determine the applicability of the study to their population, and to allow exploration of differences in participants across studies.
- **Intervention**: a clear list of the intervention groups included in the study
- **Outcomes**: a clear list of outcomes and time-points from the study that are considered in the review

Forest plots

Figure 4 (Analysis 1.1)

Study or Subgroup	Text-messaging Events	Total	Standard care Events	Total	Weight	Risk Ratio (Non-event) M-H, Fixed, 95% CI
Lester 2010	156	273	128	265	100.0%	0.83 [0.69, 0.99]
Total (95% CI)		**273**		**265**	**100.0%**	**0.83 [0.69, 0.99]**
Total events	156		128			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.05 (P = 0.04)



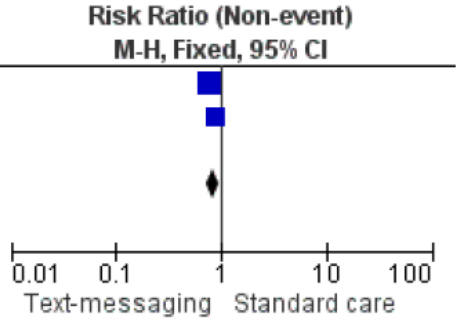
Caption

Forest plot of comparison: 1 Mobile phone text messages vs. standard care, outcome: 1.1 Viral load suppression at 52 weeks.

Figure 5 (Analysis 1.2)

Study or Subgroup	Text-messaging Events	Total	Standard care Events	Total	Weight	Risk Ratio (Non-event) M-H, Fixed, 95% CI
Lester 2010	168	273	132	265	54.6%	0.77 [0.63, 0.93]
Pop-Eleches 2011	136	289	56	139	45.4%	0.89 [0.74, 1.06]
Total (95% CI)		**562**		**404**	**100.0%**	**0.82 [0.72, 0.94]**
Total events	304		188			

Heterogeneity: $Chi^2 = 1.24$, df = 1 (P = 0.27); $I^2 = 19\%$
Test for overall effect: Z = 2.96 (P = 0.003)



Caption

Forest plot of comparison: 1 Mobile phone text messages vs. control, outcome: 1.1 ART adherence at 48-52 weeks: Text messages vs. standard care (overall).

Summary of findings table

- GRADE methodology for assessing evidence quality
- Summary of findings tables present the main findings of a review in a transparent and simple tabular format
- Provide key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the main outcomes

*Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schunemann HJ, GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336(7650):924-6.

About the “Grades of Recommendation Assessment, Development and Evaluation” (GRADE) approach (briefly)

- GRADE ranks the quality of evidence on four levels: "high," "moderate," "low" and "very low."
  - Evidence from RCTs starts at "high," but can be downgraded based on study limitations, inconsistency of results, indirectness of evidence, imprecision or for reporting bias.
  - Evidence from observational studies starts at "low," but can be upgraded if the magnitude of treatment effect is very large, if there is a significant dose-response relation, or if all possible confounders would decrease the magnitude of an apparent treatment effect.
  - Evidence from observational studies can also be downgraded.
- GRADE now used extensively in guideline development

Summary of findings table

Mobile phone text messages (comparing different intervals and lengths) for promoting adherence to antiretroviral therapy in patients with HIV infection

Patient or population: Patients with HIV infection, on ART
Settings: Kenya
Intervention: Mobile phone text messages (comparing different intervals and lengths)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Mobile phone text messages (comparing different intervals and lengths)				
ART adherence at 48 weeks: Short weekly messages vs. long weekly messages	**527 per 1000**	**516 per 1000** (369 to 733)	**RR 0.98** (0.7 to 1.39)	147 (1 study)	⊕⊕⊖⊖ **low** [1]	
ART adherence at 48 weeks: Weekly vs. daily messages (overall)	**408 per 1000**	**323 per 1000** (261 to 404)	**RR 0.79** (0.64 to 0.99)	289 (1 study)	⊕⊕⊖⊖ **low** [1]	
ART adherence at 48 weeks: Short vs. long messages (overall)	**473 per 1000**	**477 per 1000** (383 to 591)	**RR 1.01** (0.81 to 1.25)	289 (1 study)	⊕⊕⊖⊖ **low** [1]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes

[1] Very few events.

Presenting results in the text

If there are meta-analyses:

- Results section should be organized to follow the order of comparisons and outcomes specified in the protocol, so that it explicitly addresses the objectives of the review.
- Text should present the overall results in a logical and systematic way:
  - Should not rely too heavily on tables or figures, or constantly refer to them to get a clear picture of the review findings.
  - Rather, tables should be used as an additional resource that might provide further details.

Presenting results in the text

If there are not meta-analyses:

- "Big picture" narrative assessment of the evidence
  - Also describe why meta-analysis was not appropriate
- Organize the studies into groupings or clusters (e.g. by intervention type, population groups, setting etc.)
- Descriptive paragraph about the results of each study

Might there still be studies out there that we missed???

- You can test for reporting bias.

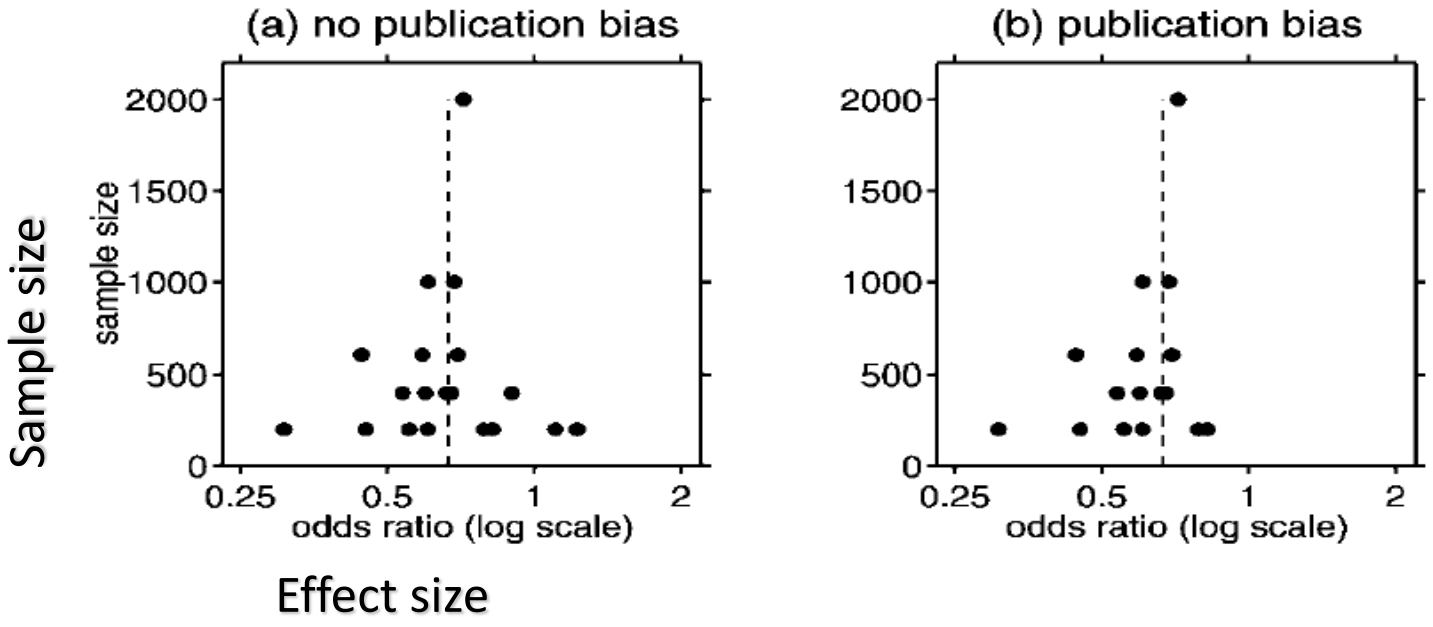
Reporting bias

- Reporting biases arise when dissemination of research findings is influenced by the nature and direction of results
- There is convincing evidence that studies with significant, positive findings are more likely to be:
  - Published
  - Published in English
  - Published rapidly
  - Published in a non-obscure journal

Reporting bias: a few common types

- Depending on nature & direction of results:
  - Publication bias: Publication or non-publication
  - Time-lag bias: Rapid or delayed publication
  - Language bias: Publication in a particular language (usually not English)
  - Outcome reporting bias: Selective reporting of some study outcomes
    - This one is done in the risk of bias assessment

Funnel plots



No publication bias = symmetrical inverted funnel

Effect size vs. sample size

i.e. Smaller studies without statistically significant effects remain unpublished, gap in bottom corner of graph

Could be other reasons for asymmetry besides bias; can be tested

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Drawing conclusions

- Authors' conclusions from a Cochrane review are divided into **implications for practice** and implications for **research**.
- Useful to consider:
  - Quality of evidence for key outcomes (GRADE methodology)
  - Applicability

Issues in applicability

- Biologic variation
  - Males, females, adults, children etc.
- Variation in context and culture
  - Health systems, rural/urban, socioeconomic
- Variation in adherence
  - Feasibility, difference between results in RCT and results in real life
- Variation in values and preferences
  - Trade-offs: adverse effects, potential for harm, costs

Implications for practice

- Authors of Cochrane reviews should not make recommendations.
- Authors may highlight different actions that might be consistent with particular patterns of values and preferences. Other factors that might influence a decision should also be highlighted.
- Example from a review showing clinical implications for situations where there are important trade-offs between desirable and undesirable effects of the intervention:
  - "The decision for a patient with cancer to start heparin therapy for survival benefit should balance the benefits and downsides and integrate the patient's values and preferences. Patients with a high preference for survival prolongation (even though that prolongation may be short) and limited aversion to bleeding who do not consider heparin therapy a burden may opt to use heparin, while those with aversion to bleeding and the related burden of heparin therapy may not."

Akl EA, Kamath G, Kim SY, Yosuico V, Barba M, Terrenato I, Sperati F, Schünemann HJ. Oral anticoagulation for prolonging survival in patients with cancer. Cochrane Database Syst Rev 2007 Apr 18;2:CD006466.

Implications for research

- Should comment on the need for further research, and the nature of the further research that would be most desirable.
- In particular, explicitly pointing out gaps
- Example from a review in which there had been two trials of an intervention in adults, in a low-income country:
  - "There is a need for large RCTs of this intervention in adolescent populations, and in persons who care for children and infants with HIV. In contrast to the usual situation, there is a need for large RCTs of this intervention in high-income countries, as well as in middle-income countries. There is also a need for more evidence concerning the intervention's acceptability, and other qualitative concerns, including culture-specific data on message-content and message-length."

Horvath T, Azman H, Kennedy GE, Rutherford GW. Mobile phone text messaging for promoting adherence to antiretroviral therapy in patients with HIV infection. Cochrane Database Syst Rev. 2012 Mar 14;3:CD009756.

When you finish your review

- Submit draft review to CRG; they will put it through internal and external peer review
- In due course, your review will be published in the CDSR
- As with a publication in any major peer-reviewed journal, your review will appear in PubMed search results as well as those of other bibliographic databases

That's it, in a nut-shell!

- Naturally, I haven't covered every aspect of systematic reviews, or of the Cochrane Collaboration
- This presentation should provide sufficient information for you to understand the need for systematic reviews, and what the process would entail should you wish to conduct one
- One area in particular that I haven't covered is Cochrane reviews of diagnostic test accuracy (DTA)
  - Fairly new initiative
  - Methodology still being developed and fine-tuned
  - Some Cochrane Review Groups don't have these reviews

Outside of Cochrane?

- I have focused on Cochrane reviews of **interventions**
- What if you wanted to do a review epidemiologic associations, correlations, risk factors etc.?
  - What if you simply wanted to do a review outside of Cochrane?
- PROSPERO online protocol registry at University of York: http://crd.york.ac.uk
  - Closely follow Cochrane methods, and it will likely be a fine review

The Cochrane Collaboration is also a “community”

22nd COCHRANE COLLOQUIUM
Evidence-Informed Public Health: Opportunities and Challenges
Hyderabad International Convention Centre
Hyderabad, India
2014
September 21 - 26

South Asian Cochrane Network & Centre
A member of Cochrane's global network
Celebrate Cochrane's 21st Anniversary

- Annual Cochrane Colloquium somewhere interesting in the world
  - September 2014: Hyderabad
  - 2013: Quebec City
  - 2012: Auckland
  - 2011: Madrid
  - 2010: Colorado
  - 2009: Singapore
  - 2008: Freiburg im Breisgau
  - 2007: São Paulo
  - 2006: Dublin
  - etc.
- Other national and regional conferences, training workshops etc.

Some links:

- The Cochrane Collaboration http://www.cochrane.org
- The Cochrane Library http://www.thecochranelibrary.com
- Cochrane Review Groups (CRGs) http://www.cochrane.org/contact/review-groups