Cochrane
Drugs and Alcohol

Cochrane reviews Methodology

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Contents

My contribution to the review

Cochrane Structure and Organization

Cochrane methodology for the production of systematic reviews

My contribution to the alcohol marketing review

Methodological support in the development of the protocol

Methodological support in the conduct of the review:

- Risk of bias assessment
- Data extraction
- Evaluating the quality of the evidence (GRADE)
- Writing the text of the full review : adherence to the MECIR standard of reporting and to the Cochrane methodological and editorial rules

Cochrane

What is Cochrane?

International collaboration founded in 1992.

Involves about 40.000 contributors from more than 130 countries (researchers, clinicians, patients)

Mission: to produce and disseminate **high-quality, relevant, accessible systematic reviews** and other synthesized research evidence to improve quality of health care

Acknowledged as one of the world's leading organizations in the health sector, with a reputation for producing high-quality, credible information to inform health decision making; Cochrane reviews are used by many guidelines producers and by wide range of stakeholders in diverse products and activities

Strategy to 2020

It defines the organization's direction for the next years and provides the framework for strategic decision making to further improve their products and their relevance for health care decision making

The Strategy to 2020 is based around **achieving four key goals:**

GOAL 1: Producing evidence

- Investing in quality (**increasing quality**)
- Making reviews more relevant for decision makers: **prioritization (topics clinically relevant)**
- Increase efficiency: **shorten the time for publication**
- New review questions: more diagnosis, prognosis, qualitative and economic

Strategy to 2020

GOAL 2: Making our evidence accessible

To make Cochrane evidence accessible and useful to everybody, everywhere in the world.

Open access

- Since February 2013, all new Cochrane Reviews became free to access for all readers 12 months after publication
- all the reviews will be free by 2020

Translation

- We will translate key content into at least the five other official languages of the World Health Organization (Spanish, French, Russian, Chinese and Arabic)

Strategy to 2020

GOAL 3: Advocating for evidence

- Increase **media coverage**
- make **Cochrane the 'go-to' place for evidence** to inform health decision making by **offering a range of evidence-informed products and resources**, and by making Cochrane Library more easy to browse

GOAL 4: Building an effective & sustainable organisation

- Create an **online learning** environment
- Organizing **training program** for editors and new contributors
- Greater involvement of **low income countries** contributors

Independency

Cochrane does not accept commercial or conflicted funding. This is vital to generate authoritative and reliable information, working freely, unconstrained by commercial and financial interests.

Primary authors of the reviews and co-ordinator editors must be free from any conflict of interest

Review groups

52 composed by reviewers who make Cochrane reviews

Each Cochrane Review Group focuses on a specific topic area and is led by a Co-ordinating Editor(s) and an editorial team including a Managing Editor and Trials Search Co-ordinator.

The Cochrane Review Groups provide authors with methodological and editorial support to prepare Cochrane Reviews, and manage the editorial process, including peer review.

Methods groups

Through continuous research they provide methodological advice to Cochrane on how validity, precision and applicability of Cochrane reviews can be improved and to ensure that they meet the highest standards of quality.

They provide training, peer review and specialist advice, contribute to software developments, and conduct methodological research

The **16** Methods Groups tackle a wide variety of issues ranging from statistical methods to information retrieval (e.g. : diagnostic tests, inclusion of NRS, priority setting, prognosis, economics, qualitative data, etc)

Cochrane

What are systematic reviews?

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

- a clearly stated set of objectives with pre-defined eligibility criteria for studies;
- an explicit, reproducible methodology;
- a systematic search that attempts to identify all studies that would meet the eligibility criteria;
- an assessment of the validity of the findings of the included studies, through the assessment of risk of bias;
- a systematic presentation, and synthesis, of the characteristics and findings of the included studies

Trusted evidence (Cochrane Handbook. Higgins J, Green S)
Informed decisions.
Better health.

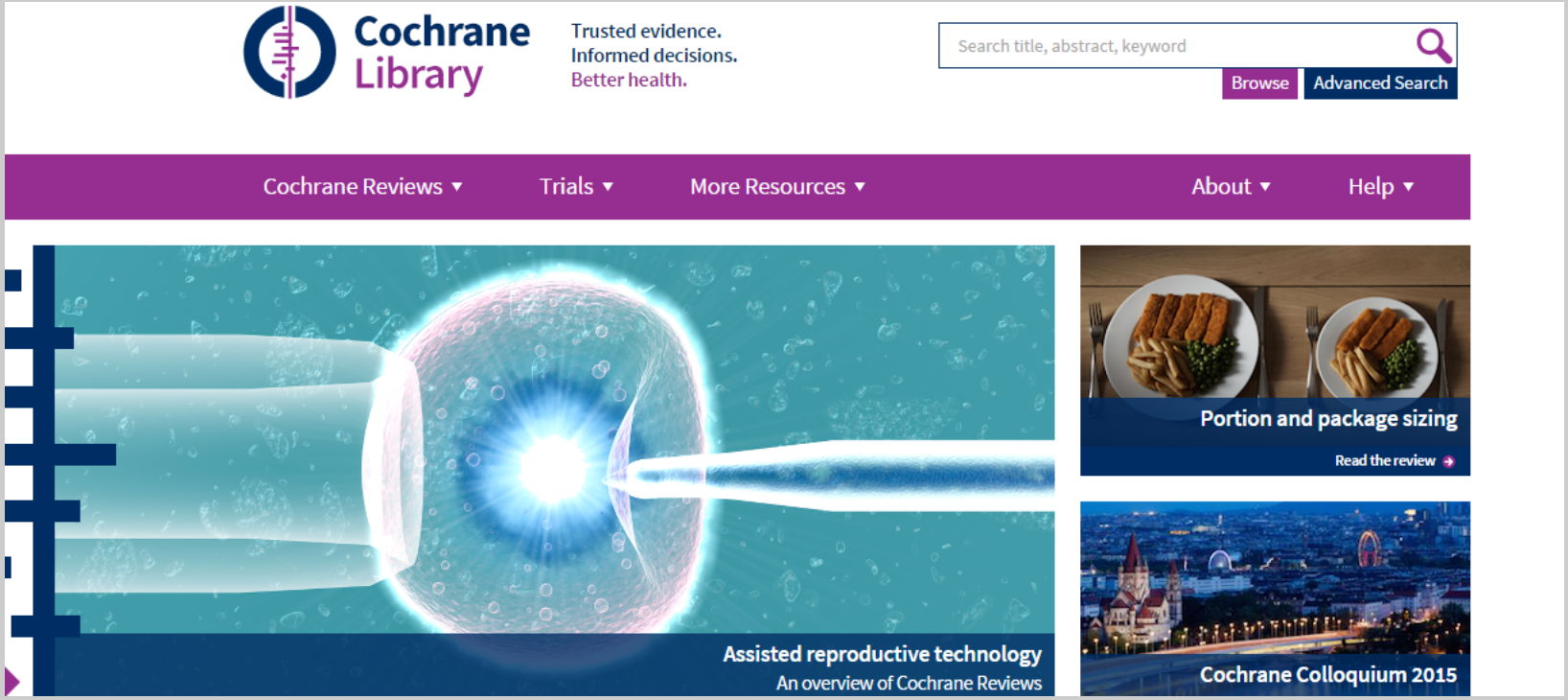
What are Cochrane reviews ?

Cochrane Reviews are systematic reviews of primary research in human health care and health policy, and are internationally **recognized as the highest standard in evidence-based health care resources**. They investigate the effects of interventions for **prevention, treatment, and rehabilitation**. They also assess the **accuracy of a diagnostic test** for a given condition in a specific patient group and setting.

Cochrane

Where you can find Cochrane reviews? Cochrane Library

http://www.cochranelibrary.com/



Which are the differences ?

Publication of the **protocol** before undergoing the review

Only **one review** for each clinical question

Regularly **updated** every two years

Very **comprehensive bibliographic search** of primary studies without language and date restriction and search also for unpublished studies

Strong rigor on **methodology** and **quality of conduct**

Transparency and high quality of reporting

Severe **editorial process** to guarantee high quality reviews

Plain language summary for lay people

What is a protocol?

Detailed description of the review aim and methods:

Objective of the review

Inclusion criteria of primary studies (PICO)

Bibliographic search strategy

Methods for study selection and data extraction

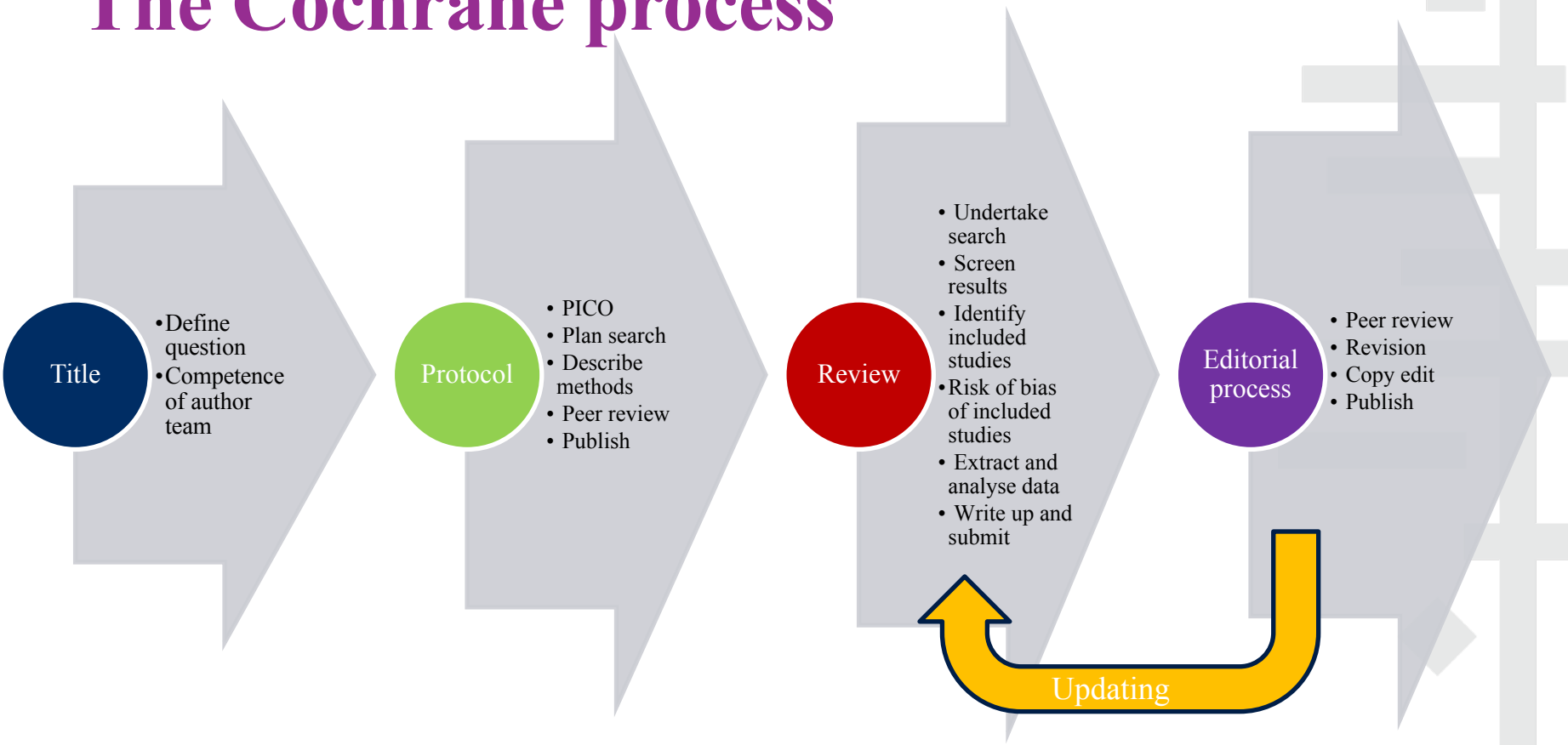
Criteria for assessing risk of bias

Method used to analyze and pool the data (meta-analysis)

Method used to assess the quality / certainty of the evidence

- **To increase validity by minimizing the risk of selection and reporting bias of the review**

The Cochrane process



Severe editorial process to guarantee high quality reviews

Cochrane groups internal review (methods): Quality advisor, statistician, managing editor

External referees for content and clinical relevance

Central Editorial Unit: assess reviews considered of highest clinical relevance and a random sample of all the other reviews

Complete editorial process performed both at the protocol stage and at the full review stage

Update

Only one review for each clinical question: to avoid duplication of the effort

Regularly updated every two years: relevant clinical question; new trials continue to be published on the topic

Withdrawn reviews: no more relevant clinical question (treatment no more used or superseded); important flaws discovered after publication

Stable reviews : robust results about effectiveness or ineffectiveness, no more trials expected to be published; question still relevant for clinical practice

Rigor on methodology and quality of conduct
Transparency and high quality of reporting

Cochrane Handbook: authors must follow the methods reported in the handbook; handbook regularly updated

RevMan: Cochrane reviews must be done only using the RevMan software; both for writing the text and for undergoing risk of bias assessment and statistical analyses.

Fixed format: fixed headings and subheadings for each section; fixed format of tables and figures

Rigor on methodology and quality of conduct
Transparency and high quality of reporting

MECIR (Methodological Expectations of Cochrane Intervention Reviews): document containing standards for both conduct and reporting; detailed guidance on what and how do /report in each phase/section of the review;

Mandatory items: means that a new review will not be published if this is not done/reported

Highly desirable items: means that this should generally be done, but that there are justifiable exceptions

To be used by authors when undergo the review and write the draft and by the quality advisor to check quality of conduct and reporting

Standards for **reporting**

Section of the review	**N items**	**mandatory**
Title and authors	2	1
Abstracts	16	14
Background and objectives	7	5
Inclusion criteria	6	6
Searching for studies	6	5
Data collection and analysis	16	13
Results- description of studies	17	13
risk of bias	3	2
Effects of interventions	24	12
Discussion	2	1
Conclusions	2	2
Total:	**101**	**69**

MECIR

R13	Abstract, Main results: adverse effects	**Mandatory**
Ensure that any findings related to adverse effects are reported. If adverse effects data were sought, but availability of data was limited, this should be reported.	The Abstract of the review should aim to reflect a balanced summary of the benefits and harms of the intervention. See *Handbook* 11.8	
R14	Abstract, Main results: format of numerical results	**Mandatory**
Present summaries of statistical analyses in the same way as they are reported in the review and in a standard way, ensuring that readers will understand the direction of benefit and the measurement scale used, and that confidence intervals are included where appropriate.	The standard format for reporting the results of statistical analysis includes an indication of the summary measure, point estimate and confidence interval, e.g. odds ratio 0.75 (95% confidence interval 0.62 to 0.89).	

Objective – inclusion criteria

The review question must specify the types of population (participants), types of interventions (and comparisons), and the types of outcomes that are of interest.

The acronym PICO (Participants, Interventions, Comparisons and Outcomes) must be used

- **Methods**
- **Criteria for considering studies for this review**
- ***Types of studies***
- ***Types of participants***
- ***Types of interventions***
- ***Types of outcome measures***
- Primary outcomes
- Secondary outcomes

Bibliographic search

Very sensitive and comprehensive

At least three databases (Medline, Embase, CENTRAL, subject specific database)

Reference list of existing reviews and included studies

Search for ongoing and unpublished studies (national and international trials registers, Subject-specific trials registers, Conference abstracts, contact with authors)

No language restriction (studies in languages other than English should be translated)

No date restriction

It is the responsibility of each CRG to support review authors, and most CRGs employ a Trials Search Coordinator to design search strategies and run the searches

Bibliographic search

Both free-text and subject headings should be used (for example Medical Subject Headings (MeSH) and EMTREE).

Limiting to RCTs: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE combined in AND with the keywords related to patients and intervention (PICO)

Including non-randomised studies (NRS): same strategy for PICO **without filter for RCTs or any other filter**

Study selection

Two phases process:

1. **Screening of titles and abstracts**: at least two authors independently; disagreement resolved by discussion

Potentially relevant studies acquired in full text

2. Full text evaluation for final inclusion: at least two authors independently; disagreement resolved by discussion

Complete the PRISMA flow diagram

Report reasons for exclusion for studies read in full (Table of excluded studies)

Data extraction

Use a pre-specified data collection form which has been piloted

Populate a table of 'Characteristics of included studies', one for each study (details of participants, interventions and comparators, outcomes and study design.)

Extract outcomes data (two authors independently or at least checked by a second reviewer)

Characteristics of included studies table

Carroll 1991

Methods	Randomised controlled trial
Participants	**Country**: USA **Participants**: cocaine abusers (DSM-III) **N** – 42 **Age**: 27 years old (mean age) **Sex**: males 74% Ethnicity: white 76.2% **Marital status**: married 17.5% **Education level**: 13 years (mean) **Employment**: employed 65% **Setting**: outpatients **History**: • Route: 33.3% freebase, 50% intranasal • Psychostimulant use: – 4 g per week, for approximately 40 months • Other drugs: 31% of participants also report regular use of other substances (alcohol 87.5%, marijuana 37.5%) • Psychiatric comorbidity: depressive disorders (19%), antisocial personality disorders (26%)
Interventions	1. CBT (RP), n – 21 2. Interpersonal therapy (IPT), n – 21 **Duration of intervention**: both interventions consisted of individual sessions of 50-60 min once a week for 3 months **Duration of follow-up**: 3 months
Outcomes	• Dropouts • Use of cocaine for at least 3 consecutive weeks at any point of treatment • Use of cocaine for at least 3 consecutive weeks at endpoint of study
Notes	**Funding source**: National Institute on Drug Abuse Grant DA 04299 **Conflict of interest**: not stated

Assessment of Risk of bias of primary studies

- Assessment of the internal validity of each study results, for randomized trials, the Cochrane 'Risk of bias' tool must be used
- Done at study level and then summarized across all the studies

Risk of bias of RCTs

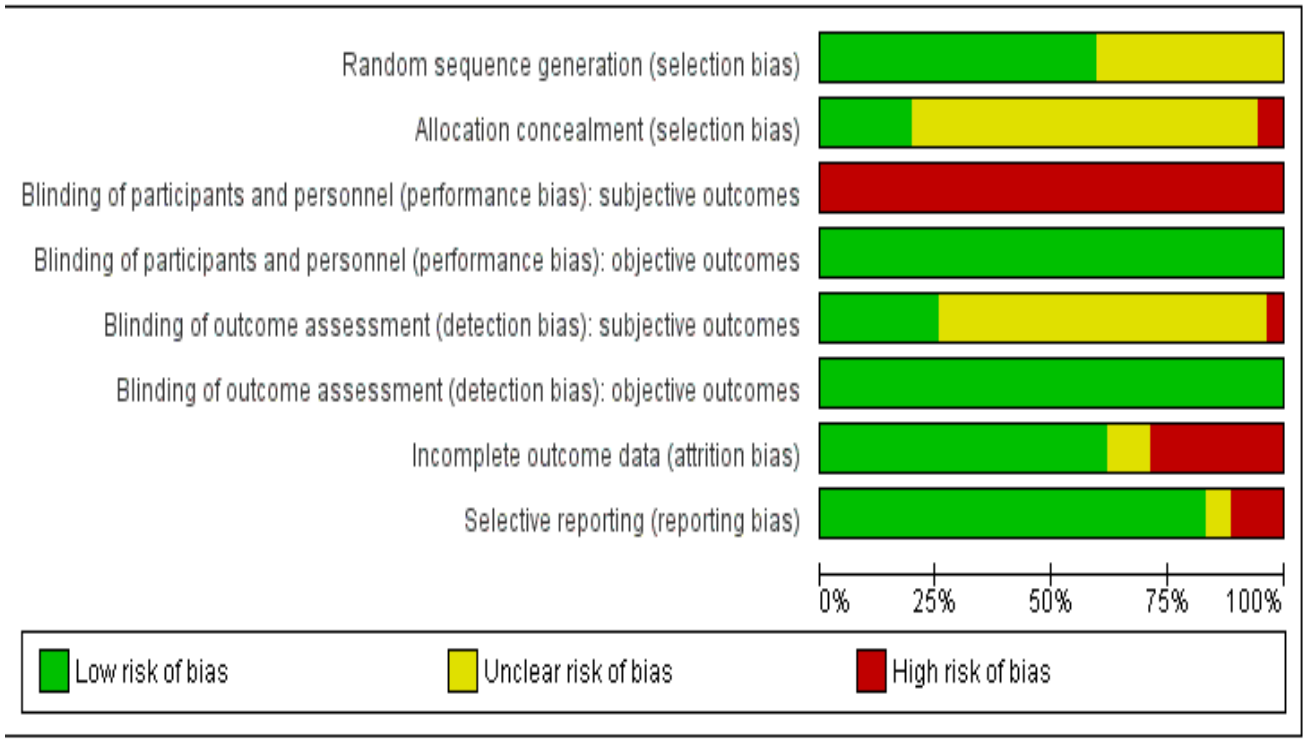
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk of bias High risk of bias Unclear risk of bias	
Allocation concealment (selection bias)	Low risk of bias High risk of bias Unclear risk of bias	
Blinding of participants and personnel (performance bias)	Low risk of bias High risk of bias Unclear risk of bias	
Blinding of outcome assessment (detection bias)	Low risk of bias High risk of bias Unclear risk of bias	
Incomplete outcome data (attrition bias)	Low risk of bias High risk of bias Unclear risk of bias	
Selective reporting (reporting bias)	Low risk of bias High risk of bias **Unclear risk of bias**	

Risk of bias ***R***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not reported
Allocation concealment (selection bias)	Unclear risk	Information not reported
Blinding of participants and personnel (performance bias) subjective outcomes	High risk	Blinding of participants and personnel impossible for the types of intervention
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) subjective outcomes	Low risk	Quote: "to maintain a single blind for psychotherapy, the clinical evaluator saw subjects in a office physically separated from the office in which therapy was conducted and instructed subjects not to disclose details of their therapist or treatment"
Blinding of outcome assessment (detection bias) objective outcomes	Low risk	Quote: " to maintain a single blind for psychotherapy, the clinical evaluator saw subjects in a office physically separated from the office in which therapy was conducted and instructed subjects not to disclose details of their therapist or treatment"
Incomplete outcome data (attrition bias) All outcomes except retention in treatment	Low risk	4% dropout
Selective reporting (reporting bias)	Low risk	All the declared outcomes in the Methods section were reported in the ResultsAll the declared outcomes in the Methods section were reported in the Results

Risk of bias of RCTs

⊟ Figure 2



Caption

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Risk of bias of non-randomised studies

No strict rules

1.For experimental and controlled studies, and for prospective cohort studies, the six domains in the standard 'Risk of bias' tool could usefully be assessed, whether allocation is randomized or not.

Than further domains could be added (e.g. comparability of groups at baseline for confounding and prognostic factors, adjustment for confounding performed)

Risk of bias of non-randomised studies

2.ROBINS-I: Risk Of Bias In Non-randomized Studies - of Interventions

developed by members of the Cochrane Bias Methods Group and the Cochrane Non-Randomised Studies Methods Group

Sterne JAC et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions BMJ 2016; 355:i4919

To evaluate risk of bias of NRS that **compare the health effect of two or more interventions** (i.e. effectiveness, not aetiology, prognosis, risk factor)

Not yet mandatory; very complex and time consuming

For cohort studies, case control, cross sectional

Risk of bias of non-randomised studies

Interrupted time series (ITS) studies : criteria developed by the Effective Practice and Organization of Care (EPOC) Group (www.epoc.cochrane.org);

Uncontrolled case series: no suggested check list; not useful study design to assess efficacy or causal relationship

Data synthesis

Clinical heterogeneity: Undertake a meta-analysis only if participants, interventions, comparisons and outcomes are judged to be sufficiently similar to ensure an answer that is clinically meaningful.

Statistical heterogeneity: random versus fixed effect model; exploration for heterogeneity by subgroup analysis

Robustness of the results: consider sensitivity analysis (impact of imputed data and high risk of bias studies)

Do not pool RCTs and NRS results together

Quality/certainty of the evidence (GRADE approach)

Extensive evaluation of the evidence considering not only the estimate of the effect and risk of bias but also other relevant domains to make a final judgment abut the confidence in the overall estimate when we have to generalize from the samples analyzed in the retrieved studies to the general population that is the target of the review .

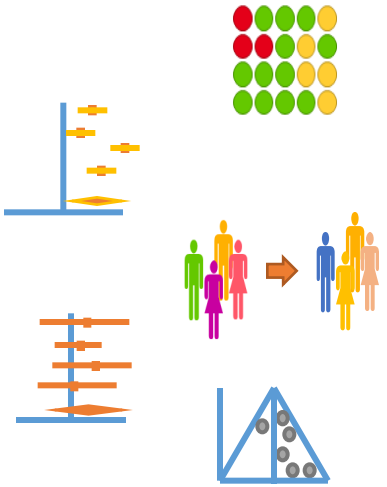
GRADE working group: born in 2000; now involves about 200 members who meet regularly twice a year. Elaborated a new method for grading the evidence and the strength of the recommendations of clinical practice guidelines. To be used by guidelines producers and systematic review authors.

Mandatory since 2016 to include the Summary of findings in a Cochrane review

Quality/certainty of evidence assessment based on GRADE approach

- **RCTs ⊕⊕⊕⊕**
- **observational studies ⊕⊕◯◯**

- **5 factors that can lower quality**
  1. limitations in detailed study design and execution *(risk of bias criteria)*
  2. Inconsistency *(or heterogeneity)*
  3. Indirectness *(PICO and applicability)*
  4. Imprecision
  5. Publication bias



- **3 factors can increase quality**
  1. large magnitude of effect
  2. opposing plausible residual bias or confounding
  3. dose-response gradient

GRADE Domains: downgrade the evidence

- **Inconsistency (heterogeneity) between studies results:** Point estimates vary widely across studies; Confidence intervals (CIs) minimal or no overlap; statistical test for heterogeneity P< 0,10; The $\mathbf{I^2}$: 60 e 90% :substantial, 75 e 100% : considerable)
- **Directness of Evidence (generalizability, transferability, applicability):** differences between PICO and available evidence in populations/patients , interventions ,outcomes
- **Publication bias**: find only small "positive" studies, mainly if sponsored by industry Funnel plot showing asimmetry
- **Imprecision of the overall estimate**: Wide confidence intervals. Small number of events. Small sample size

GRADE Domains: upgrade the evidence

- Only for observational studies
- **Large magnitude of effect** (RRR 50%/RR 2) or very large **(**RRR 80%/RR 5); modeling studies suggests that confounding alone is unlikely to explain associations with a RR greater than 2 (or less than 0.5), and very unlikely to explain associations with an RR greater than 5 (or less than 0.2)
- **Dose response relation**
- **Residual confounding** not adjusted for that could increase the association e.g.: effect of condom use on HIV infection among men who have sex with men RR: 0.34 [0.21, 0.54] (RRR: 66%) in favor of condom use vs no condom use. Condom users were more likely to have more partners (but studies did not adjust for this confounding factor). Considering the number of partners would, if anything, strengthen the effect estimate in favor of condom use.

Quality (certainty) of evidence assessment based on GRADE approach

Symbol	Quality	Interpretation
⊕⊕⊕⊕	High	We are very confident that the true effect lies close to that of the estimate of the effect
⊕⊕⊕◯	Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⊕⊕◯◯	Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⊕◯◯◯	Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Quality (certainty) of evidence assessment based on GRADE approach

- Assessment done at the **outcome level** – no at study level – across all the studies.
- For the most relevant primary outcomes (up to seven)
- **One SoF for each comparison** (up to four)

Summary of findings table

Summary of finding: antibiotics for acute otitis media in children

Antibiotics compared with placebo for acute otitis media in children

Patient or population: Children with acute otitis media
Setting: High- and middle-income countries
Intervention: Antibiotics
Comparison: Placebo

	Estimated risks (95% CI)				
	Control risk[a]	Intervention risk			
Outcomes	Placebo	Antibiotics	Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)
Pain at 24h	367 per 1,000	330 per 1,000 (286–382)	RR 0.9 (0.78–1.04)	1229 (5)	⊕⊕⊕⊕ High
Pain at 2–7 d	257 per 1,000	185 per 1,000 (159–213)	RR 0.72 (0.62–0.83)	2791 (10)	⊕⊕⊕⊕ High
Hearing, inferred from the surrogate outcome abnormal tympanometry—1 mo	350 per 1,000	311 per 1,000 (262–375)	RR 0.89 (0.75–1.07)	927 (4)	⊕⊕⊕◯ Moderate[b]
Hearing, inferred from the surrogate outcome abnormal tympanometry—3 mo	234 per 1,000	227 per 1,000 (178–290)	RR 0.97 (0.76–1.24)	808 (3)	⊕⊕⊕◯ Moderate[b]
Vomiting, diarrhea, or rash	113 per 1,000	156 per 1,000 (123–199)	RR 1.38 (1.09–1.76)	1,401 (5)	⊕⊕⊕◯ Moderate[c]

Plain Language for lay people

Summary of the review written in plain language able to be understood by lay people without knowledge of technical terminology (400 to 700 words)

Title: rewritten in plain language

Whci is the review question?: objective

What was studied in the review?: background

What are the main results?: study characteristics, funding source, effect of treatment without figures

Search date: currency of the review

Quality of the evidence: (based on GRADE approach)

Key messages: conclusions