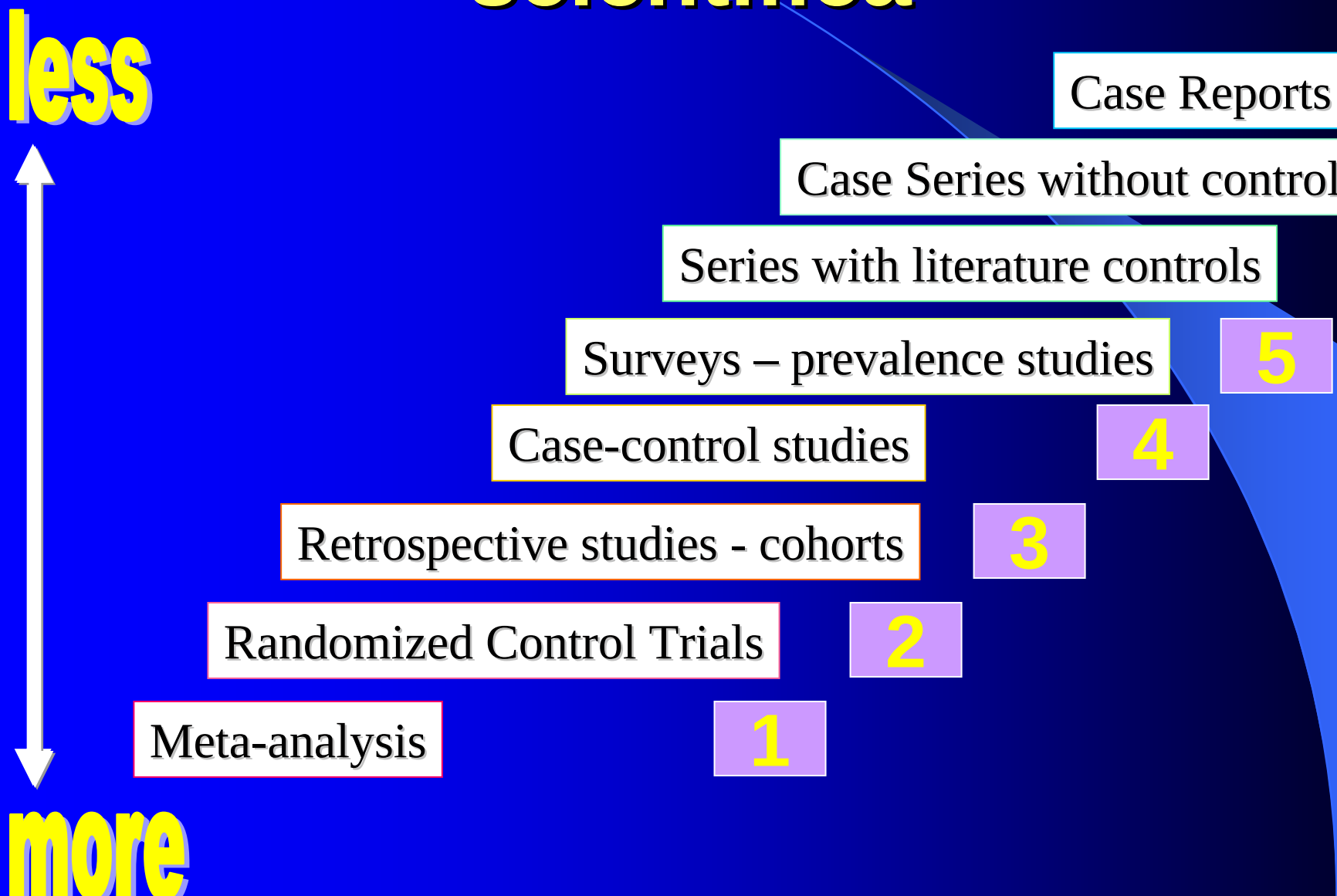
Corso di perfezionamento
"EBM e metodologia delle revisioni sistematiche di studi di efficacia"

Struttura e Qualita' delle Revisioni Sistematiche di Letteratura

federica vigna-taglianti

La gerarchia dell'evidenza scientifica



What is a systematic review?

- **A review of the evidence on a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant primary research, and to extract and analyse data from the studies that are included in the review***

*Undertaking Systematic Reviews of Research on Effectiveness. CRD's Guidance for those Carrying Out or Commissioning Reviews. CRD Report Number 4 (2nd Edition). NHS Centre for Reviews and Dissemination, University of York. March 2001.

Systematic vs. Narrative reviews

- Scientific approach to a review article
- Criteria determined at outset
- Comprehensive search for relevant articles
- Explicit methods of appraisal and synthesis
- Meta-analysis may be used to combine data

- Depend on authors' inclination (bias)
- Author gets to pick any criteria
- Search any databases

- Methods not usually specified
- Vote count or narrative summary
- Can't replicate review

Advantages of systematic reviews

- Reduce bias
- Replicability
- Resolve controversy between conflicting studies
- Identify gaps in current research
- Provide reliable basis for decision making

Limitations

- Results may still be inconclusive
- There may be no trials/evidence
- The trials may be of poor quality
- The intervention may be too complex to be tested by a trial
- Practice does not change just because you have the evidence of effect/effectiveness

Sources of systematic reviews

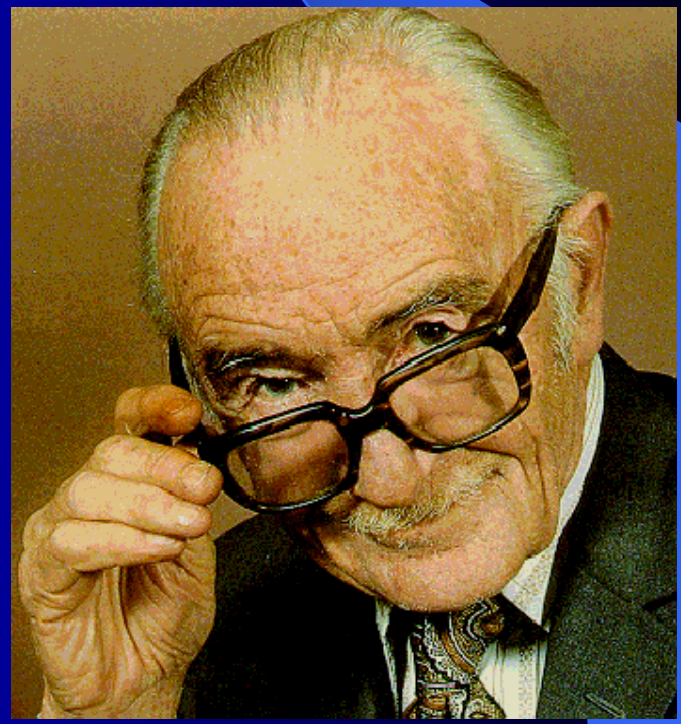
- Cochrane Collaboration
- Guide to Community Preventive Services (The Guide), US
- The Effective Public Health Practice Project, Canada
- Health Development Agency, UK
- The Evidence for Policy and Practice Information and Co-ordinating Centre (EPPI-Centre), UK
- Centre for Reviews and Dissemination, UK
- The Campbell Collaboration

Cochrane Collaboration

Named in honour of Archie Cochrane, a British researcher

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"



Cochrane Collaboration

International non-profit organisation that prepares, maintains, and disseminates systematic up-to-date reviews of health care interventions

The Cochrane Library

- The Cochrane Database of Systematic Reviews
- The Database of Abstracts of Reviews of Effectiveness
- The Cochrane Controlled Trials Register
- The Cochrane Methodology Register

Pubblicate ad oggi (Issue 4/2008):

- **Reviews = 3625**
- **Protocols = 1921**

www.cochrane.org

To conduct a systematic reviews

- Topic of relevance or interest
- Team of co-authors
- Training and support
- Access to/understanding of stakeholders or likely users
- Funding and time (at least 6 months)
- Access to databases of published and unpublished literature
- Statistical software, if appropriate
- Bibliographic software

Review manuals

- Cochrane Collaboration Reviewers' Handbook
- Cochrane Collaboration Open Learning Materials
- NHS Centre for Reviews and Dissemination Guidance for those Carrying Out or Commissioning Reviews
- The Methods of the Community Guide
- A Schema for Evaluating Evidence on Public Health Interventions
- EPPI-Centre Reviewers' Manual

Centro Cochrane Italiano - Risorse per i revisori - Microsoft Internet Explorer

File Modifica Visualizza Preferiti Strumenti ?

Indietro Cerca Preferiti

Indirizzo http://www.cochrane.it/it/authors.html Vai Collegamenti

Questo web site Cerca A-Z Indice Assistenza

Altri gruppi Cochrane >

MARIO NEGRI ISTITUTO DI RICERCHE FARMACOLOGICHE

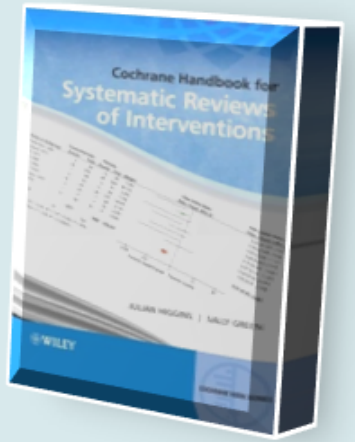
A CENTRE OF THE COCHRANE COLLABORATION®

Centro Cochrane Italiano

Risorse per i revisori

English français norsk

La nuova guida per la preparazione delle Cochrane Reviews. Regolarmente aggiornata, contiene la metodologia per gli autori di revisioni sistematiche. È disponibile in versione on-line sul sito www.cochrane.org



Cochrane Handbook for Systematic Reviews of Interventions è il documento

Internet

start Centro Cochrane Itali... Disco rimovibile (F:) IT 15.50

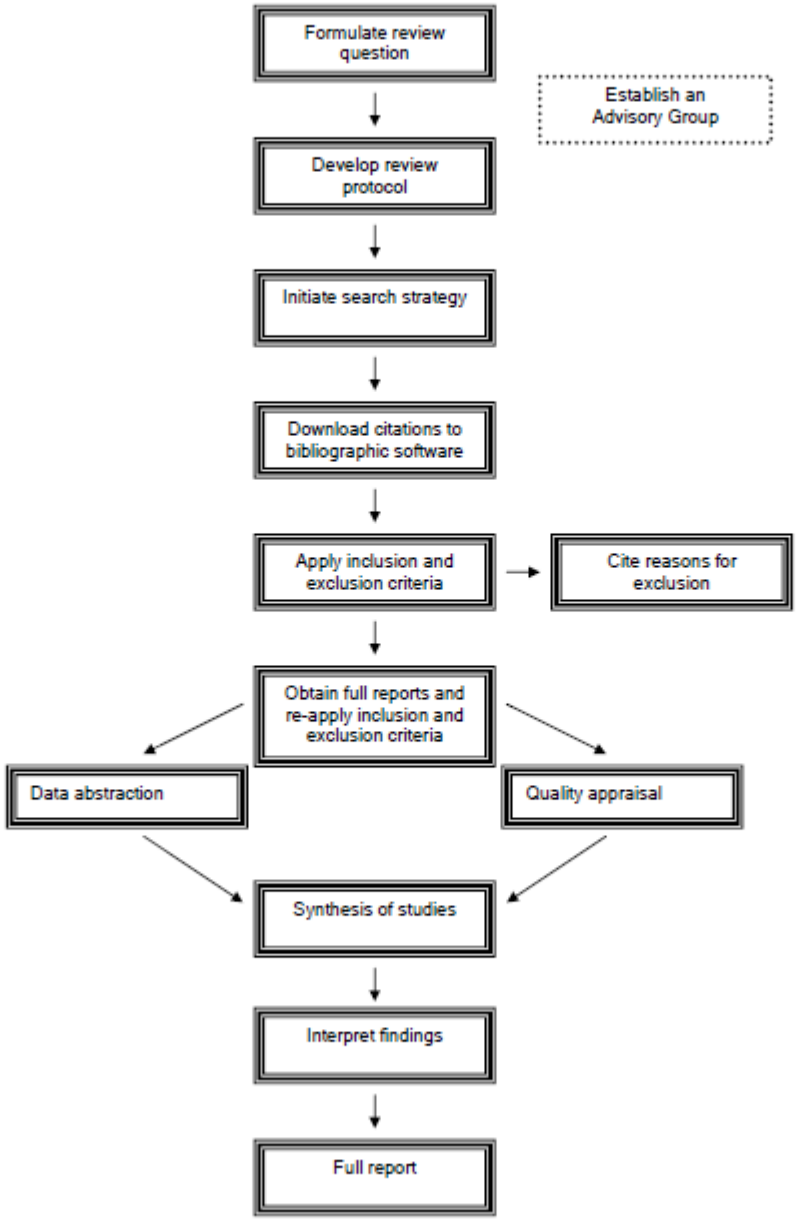


Figure One. Flow chart of a systematic review

Writing your protocol

1) Background

- Why is it important?
- How important is the problem?
- Is there uncertainty?
- What is the reasoning as to why the intervention(s) might work? (include theoretical frameworks)
- Other similar reviews?

Writing your protocol

2) Objectives

- What are the questions/hypotheses?

3) Selection criteria

- PICO(T)
  - Population(s)
  - Intervention(s)
  - Comparison(s)
  - Outcomes (Primary / Secondary)
  - Types of studies

Writing your protocol / review

4) Planned search strategy

- Databases and terms

5) Planned data extraction

- Processes and outcomes?
- More than one reviewer?
- Planned quality appraisal (incl. checklists)

6) Method of synthesis

- Tabulate
- Narrative/qualitative synthesis or meta-analysis

1.Systematic review process

1. **Well formulated question**
2. **Comprehensive data search**
3. **Unbiased selection and abstraction process**
4. **Critical appraisal of data**
5. **Synthesis of data**
6. **Interpretation of results**

Importance of research question

A clearly framed question will guide:

- **the reader**
  - **in their initial assessment of relevance**
- **the reviewer**
  - **on how to collect studies**
  - **on how to check whether studies are eligible**
  - **on how to conduct the analysis**

Answerable questions

EFFECTIVENESS

A description of the **populations** — P

An identified **intervention** — I

An explicit **comparison** — C

Relevant **outcomes** — O

A PICO question ?

A time-consuming question:

What is the best strategy to prevent smoking in young people?

An answerable question

Are mass media (or school-based or community-based) interventions effective in preventing smoking in young people?

Choose to look at mass media interventions ……..

The PICO(T) chart

Problem, population	Intervention	Comparison	Outcome	Types of studies
Young people under 25 years of age	a) Television b) Radio c) Newspapers d) Bill boards e) Posters f) Leaflets g) Booklets	a) School-based interventions b) No intervention	a) objective measures of smoking (saliva thiocyanate levels, alveolar CO) b) self-reported smoking behaviour c) Intermediate measures (intentions, attitude, knowledge, skills) d) Media reach	a) RCT b) Controlled before and after studies c) Time series designs

Types of study designs

- Randomised controlled trial
- Quasi-randomised/pseudo-randomised controlled trial/controlled clinical trial
- Controlled before and after study/cohort analytic (pre and post-test)/concurrently controlled comparative study
- Uncontrolled before and after study/cohort study
- Interrupted time series
- Qualitative research

2. Systematic review process

1. Well formulated question
2. **Comprehensive data search**
3. Unbiased selection and abstraction process
4. Critical appraisal of data
5. Synthesis of data
6. Interpretation of results

A good search

- ✓ Clear research question
- ✓ Comprehensive search
  - All domains, no language restriction, unpublished and published literature, up-to-date
- ✓ Document the search (replicability)

Electronic searching

- Database choice should match area of interest:
  - Medical: Medline, EMBASE, CINAHL
  - Social Science: PsycINFO, Social Science Citation Index, Sociological Abstracts
  - Educational: ERIC
  - Other: AGRIS (agricultural), SPORTSDiscus (sports), EconLit (economics)
  - Other registers: CENTRAL (Cochrane), BiblioMap (EPPI-Centre), HealthPromis (HDA)

Components of electronic searching

1. Describe each PICO component
2. Start with primary concept
3. Find synonyms
   a) Identify MeSH / descriptors / subject headings
   b) Add textwords
4. Add other components of PICO question to narrow citations *(may use study filter)*
5. Use search strategy in other databases (may need adapting)

Different bibliographic databases

- Databases use different types of controlled vocabulary
  - Same citations indexed differently on different databases
  - Medline and EMBASE use a different indexing system for study type
  - PsycINFO and ERIC do not have specific terms to identify study types

Need to develop search strategy for each database

Unpublished literature

- Only 30-80% of all known published trials are identifiable in Medline (depending on topic)
- Only 25% of all medical journals in Medline
- Non-English language articles are under-represented in Medline (and developing countries)
- Publication bias – tendency for investigators to submit manuscripts and of editors to accept them, based on strength and direction of results (Olsen 2001)

Unpublished literature

- Hand searching of key journals and conference proceedings
- Scanning bibliographies/reference lists of primary studies and reviews
- Contacting individuals/agencies/ academic institutions

Neglecting certain sources may result in reviews being biased

3. Systematic review process

1. Well formulated question
2. Comprehensive data search
3. **Unbiased selection and abstraction process**
4. Critical appraisal of data
5. Synthesis of data
6. Interpretation of results

Details to collect

- Publication details
- Study design
- Population details (n, characteristics)
- Intervention details
- Theoretical framework
- Provider
- Setting
- Target group

- Study details (date, follow-up)
- Consumer involvement
- Process measures – adherence, exposure, training, etc
- Context details
- Outcomes and findings

Selection and abstraction

- Separate evaluation and data abstraction by two reviewers
- Inconsistencies decided by a third author

4. Systematic review process

1. Well formulated question
2. Comprehensive data search
3. Unbiased selection and abstraction process
4. **Critical appraisal of data**
5. Synthesis of data
6. Interpretation of results

Critical appraisal

The process of systematically examining research evidence to assess its validity, results and relevance before using it to inform a decision.

Alison Hill, Critical Appraisal Skills Programme, Institute of Health Sciences, Oxford http://www.evidence-based-medicine.co.uk

Why appraise validity?

- Not all published and unpublished literature is of satisfactory methodological rigour
  - Just because it is in a journal does not mean it is sound!
  - Onus is on you to assess validity!
- Quality may be used as an explanation for differences in study results
- Guide the interpretation of findings and aid in determining the strength of inferences

Why appraise validity?

- Poor quality affects trial results by exaggerating intervention effect:
  - Inadequate allocation concealment exaggerated treatment effects by 35-41% (Moher 1998, Schulz 1995)
  - Lack of blinding of subjects exaggerated treatment effect by 17% (Schulz 1995)
  - Open outcome assessment exaggerated treatment effect by 35% (Juni 1999, Moher 1998)

Bias / quality criteria

1. Selection bias
2. Allocation bias
3. Blinding (detection bias)
4. Withdrawals and drop-outs
5. Statistical analysis / confounding

1. Selection bias

Recruiting study population

- **Differences in the way patients are accepted or rejected for a trial, and the way in which interventions are assigned to individuals**
- **Difficult in public health studies**

2. Allocation bias

Randomisation (coin-toss, computer)

↓

Allocation schedule

↓

Allocation

→ Intervention

→ Control

Alternate, days of week, record number

↓

Allocation

→ Intervention

→ Control

Allocation bias

Need comparable groups

Randomisation = similar groups at baseline

Allocation schedule should not be administered by person who is responsible for the study to prevent manipulation

Allocation bias

Reduced by:

- ✓ centralised randomisation
- ✓ on-site computer system with group assignments in a locked file
- ✓ sequentially numbered, sealed, opaque envelopes
- ✓ any statement that provides reassurance that the person who generated the allocation scheme did not administer it
- ✗ Not: alternation, dates of birth, day of week.

3. Blinding outcome assessors

Detection bias –

- **Blinding of outcome assessors to prevent systematic differences between groups in the outcome assessment**

4. Withdrawals from study

Attrition bias -

- **Systematic differences between groups in losses of participants from the study**
  - **Look at withdrawals, drop-outs**

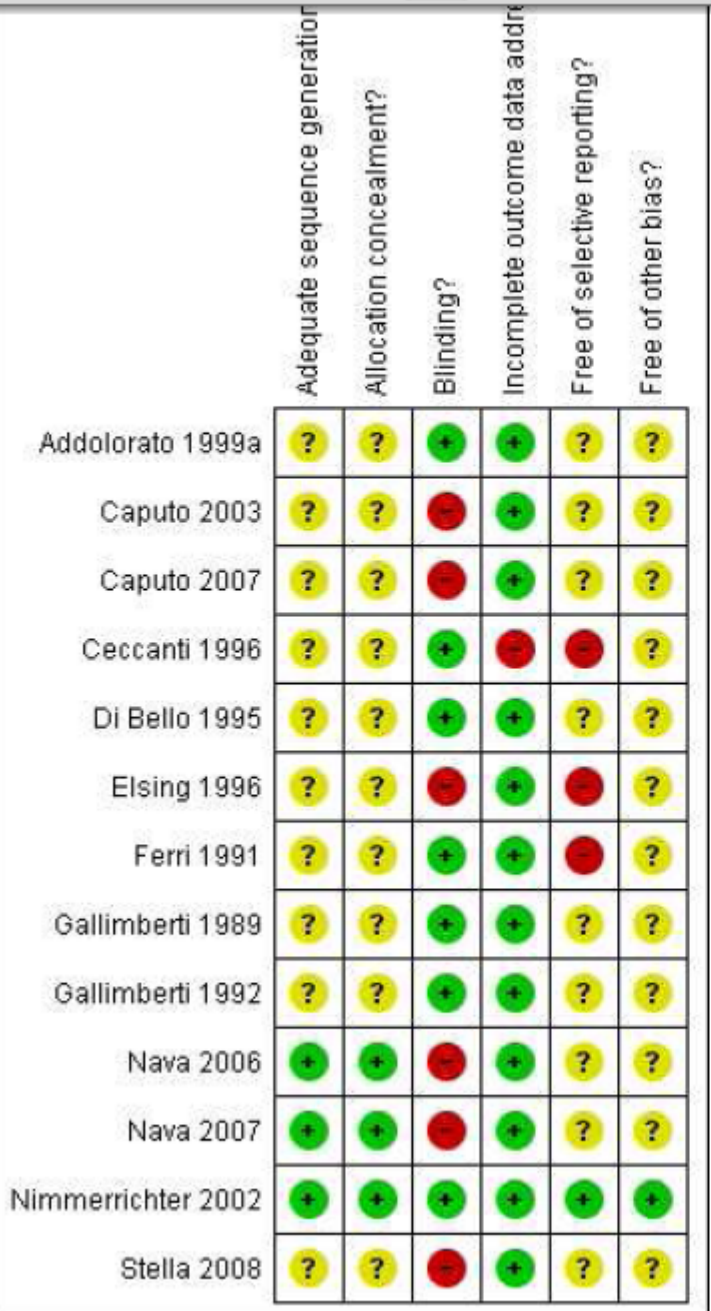
Risk of bias tables

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Unclear	"All the subjects were randomly divided into two groups of treatment"
Allocation concealment?	Unclear	not reported
Blinding?	Yes	"The whole study was performed on a single-blind design; in particular, investigators who performed CIWA-Ar, STAI, and Zung tests at the different times of treatment did not know which drug was being administered to the patients"
Incomplete outcome data addressed?	Yes	Attrition at 18 days: - GHB group: 13.3% - diazepam group: 26.6%
Free of selective reporting?	Unclear	study protocol not mentioned
Free of other bias?	Unclear	"The two groups of patients were well matched in terms of age, gender, demographic characteristics, alcohol consumption, and duration of addiction. Total CIWA-Ar, STAI-y1, and SDS Zung tests score also did not differ between groups at baseline."

Caputo 2003

Methods	RCT. Open randomized study. The 35 patients were randomly assigned to the two groups of treatment.



Summary of risk of bias evaluation

5. Statistical analysis

- Power / sample size calculation
  - Appropriate sample size determination
- Intention-to-treat
- Confounding
- Unit of analysis (Cluster studies allocate by school/community etc but generally analyse at individual level… unit of analysis errors.. overestimation of effect)

Confounding

Need similar groups at baseline

Determine which factors could confound the association of the intervention and outcome

Non-randomised studies – can never adjust for unknown confounding factors (and difficulties in measuring known confounding factors)

If confounding is likely – adjusted for in analysis

5. Systematic review process

1. Well formulated question
2. Comprehensive data search
3. Unbiased selection and abstraction process
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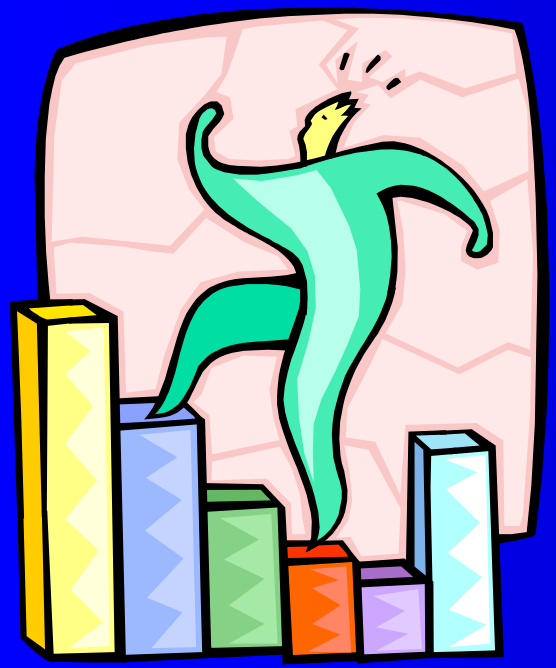
Steps



1. Table of study data
2. Check for heterogeneity
    a. No – meta-analysis
    b. Yes – identify factors, subgroup analysis or narrative synthesis
3. Sensitivity analyses
4. Explore publication bias

Step 1

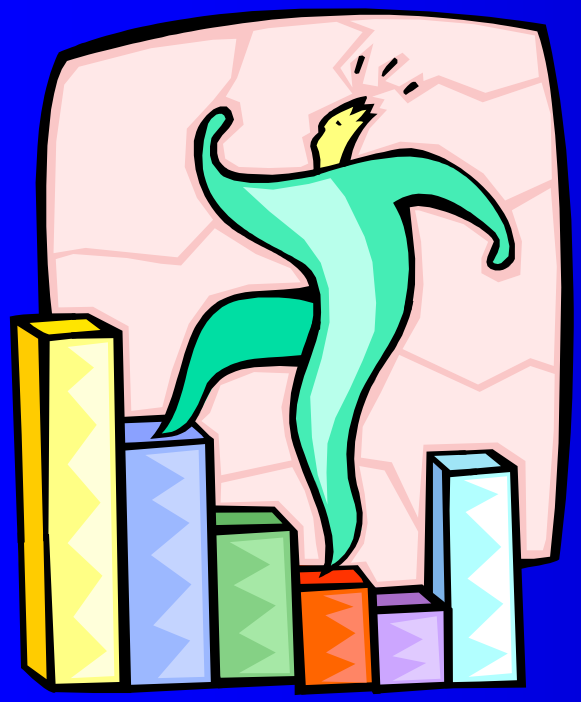
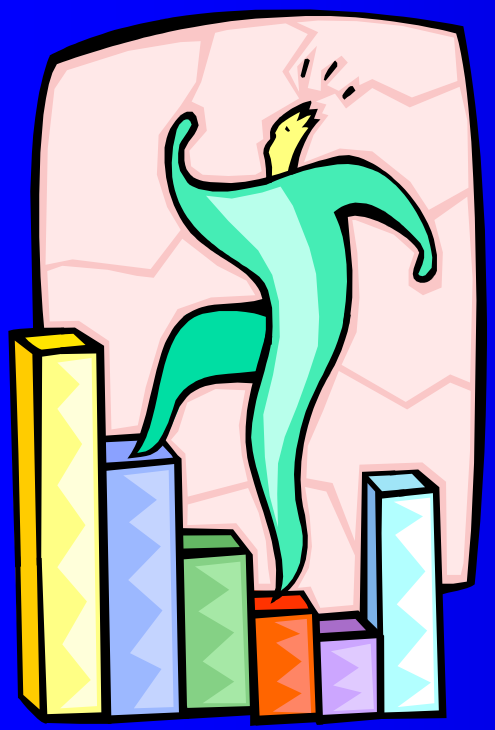


Table of study data

- Year
- Setting
- Population details (including any baseline differences)
- Study design
- Intervention details (including theory)
- Control group details
- Results
- Study quality

Step 2



Check for heterogeneity

- **Are the results consistent?**

Yes

Meta-analysis

No

Narrative synthesis

or subgroup analysis

Explain causes of heterogeneity

Not all systematic reviews are meta-analyses

"…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."

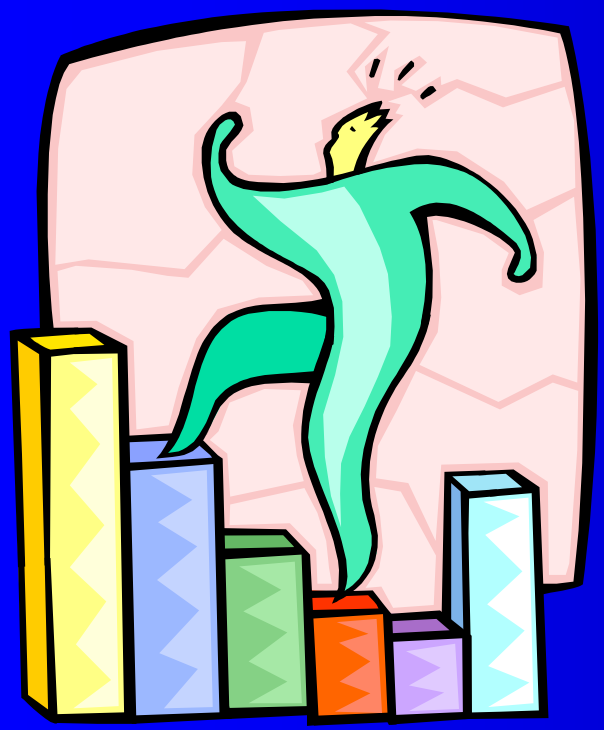
Egger et al. Systematic reviews in health care. London: BMJ Books, 2001:5

Step 3

Sensitivity analysis

- How sensitive are the results of the analysis to changes in the way it was done?
  - Changing inclusion criteria for types of studies
  - Including or excluding studies where there is ambiguity
  - Reanalysing the data imputing using a reasonable range of values for missing data
  - Reanalysing the data using different statistical approaches

Step 4



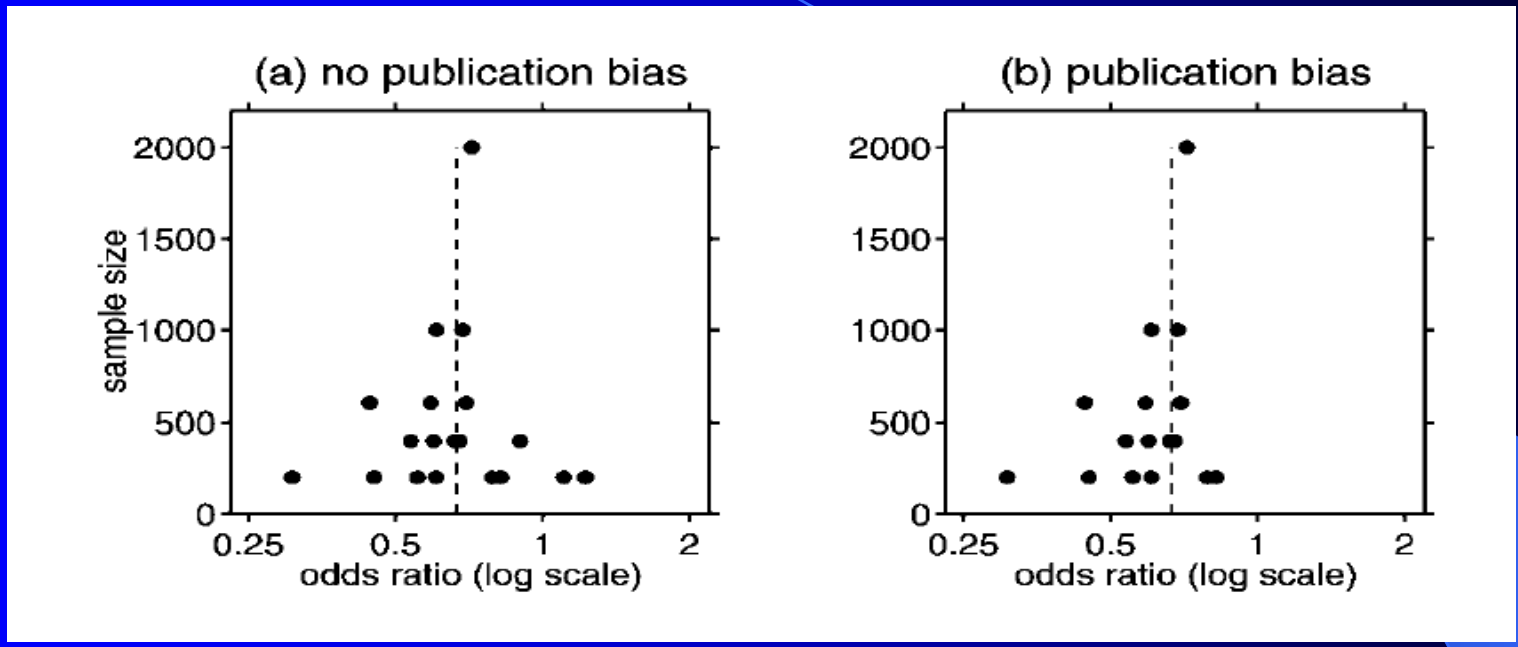
Explore publication bias

- **Is there a possibility I have missed some studies?**

Publication bias

- Funnel plot
- Studies with significant results are more likely to be
  - Published
  - Published in English
  - Cited by others

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

6. Systematic review process

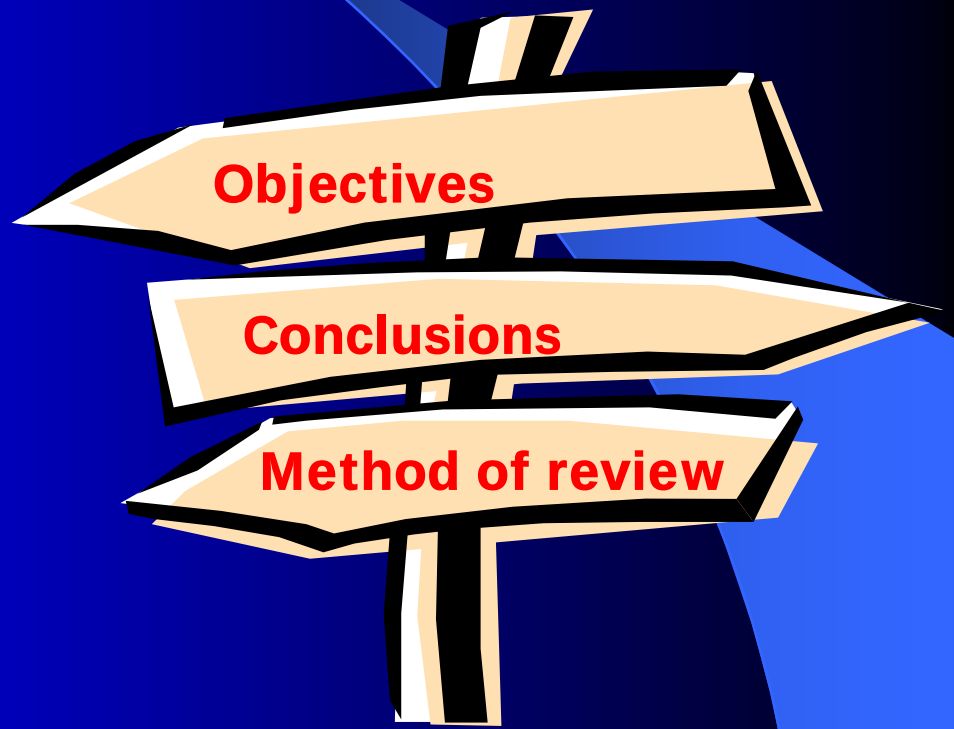
1. Well formulated question
2. Comprehensive data search
3. Unbiased selection and abstraction process
4. Critical appraisal of data
5. Synthesis of data
6. **Interpretation of results**

Interpretation, conclusions and recommendations

- **VERY IMPORTANT!**

  Many people prefer to go directly to the conclusions before looking at the rest of the review

  Conclusions must reflect findings in review



Issues to consider

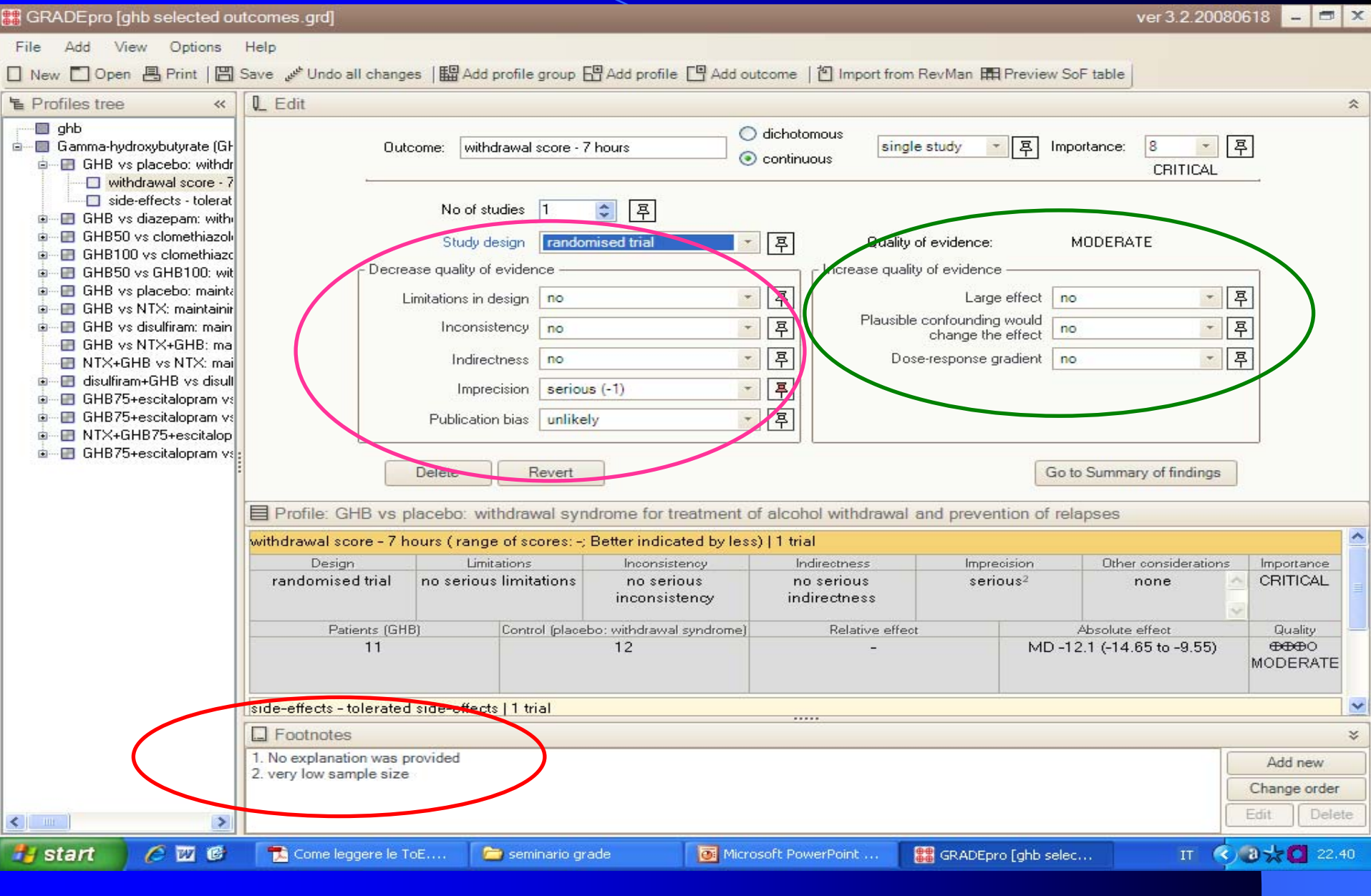
Conclusions should be based on:

- Strength of evidence
- Biases/limitations of review
- Applicability and sustainability of results
- Trade-offs between benefits and harms
- Implications for public health and future research

Strength and biases

- Strength
  - How good is the quality of evidence?
  - How large are the effects?
  - Consistent results?
- Biases / limitations of review
  - Comprehensive search?
  - Quality assessment?
  - Appropriate analysis?
  - Publication bias?

GRADE quality of evidence



Summary of findings tables

6 GHB 50mg vs placebo: maintaining abstinence

GHB 50mg compared to placebo for alcohol dependent patients

Patient or population: alcohol dependent patients

Settings:

Intervention: GHB 50mg

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	GHB 50mg				
abstinence - 6 months	Medium risk population		RR 1.33 (0.58 to 3.07)	17 (1)	⊕⊕⊕⊖ moderate [1]	
	500 per 1000	665 per 1000 (290 to 1535)				
relapse to heavy drinking - 6 months	Medium risk population		RR 0.44 (0.05 to 4.02)	17 (1)	⊕⊕⊕⊖ moderate [1]	
	250 per	110 per 1000 (13 to 1005)				

Applicability

- Applicability – relates to:
  - Study population characteristics
  - Validity of the studies
  - Relevant outcomes (incl. efficiency), interventions, comparisons
  - Integrity of intervention – details of intervention (provider, adherence, medium, setting, access, infrastructure)
  - Maintenance of intervention/sustainability

Qualità di una revisione

- ✓ **QUOROM**

  qualità del reporting

- ✓ **QUOROM modificato (FVT)**

  qualità della revisione

- ✓ **PRISMA**

  qualità del reporting, aggiornata

QUOROM

Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement

David Moher, Deborah J. Cook, Susan Eastwood, Ingram Olkin, Drummond Rennie, Donna F. Stroup, for the QUOROM Group*

University of Ottawa, Thomas C Chalmers Centre for Systematic Reviews, Ottawa (D Moher MSc); McMaster University, Hamilton (D J Cook MD), Ontario, Canada; University of California, San Francisco (S Eastwood ELS(D)); Stanford University, Stanford, CA (I Olkin PhD); *JAMA*, Chicago, IL (D Rennie PhD); and Centers for Disease Control and Prevention, Atlanta, GA, USA (D F Stroup PhD)

Correspondence to: Dr David Moher, Thomas C Chalmers Centre for Systematic Reviews, Children's Hospital of Eastern Ontario Research Institute, 401 Smyth Road, Ottawa, Ontario K1H 8L1, Canada (E-mail: dmoher@uottawa.ca)

Background: The Quality of Reporting of Meta-analyses (QUOROM) conference was convened to address standards for improving the quality of reporting of meta-analyses of clinical randomised controlled trials (RCTs).

Methods: The QUOROM group consisted of 30 clinical epidemiologists, clinicians, statisticians, editors, and researchers. In conference, the group was asked to identify items they thought should be included in a checklist of standards. Whenever possible, checklist items were guided by research evidence suggesting that failure to adhere to the item proposed could lead to biased results. A modified Delphi technique was used in assessing candidate items.

Findings: The conference resulted in the QUOROM statement, a checklist, and a flow diagram. The checklist describes our preferred way to present the abstract, introduction, methods, results, and discussion sections of a report of a meta-analysis. It is organised into 21 headings and subheadings regarding searches, selection, validity assessment, data abstraction, study characteristics, and quantitative data synthesis, and in the results with 'trial flow', study characteristics, and quantitative data synthesis; research documentation was identified for eight of the 18 items. The flow diagram provides information about both the numbers of RCTs identified, included, and excluded and the reasons for exclusion of trials.

Interpretation: We hope this report will generate further thought about ways to improve the quality of reports of meta-analyses of RCTs and that interested readers, reviewers, researchers, and editors will use the QUOROM statement and generate ideas for its improvement.

*Other members listed at end of paper

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Introduction

Health-care providers and other decision-makers now have, among their information resources, a form of clinical report called the meta-analysis[1–4], a review in which bias has been reduced by the systematic identification, appraisal, synthesis, and, if relevant, statistical aggregation of all relevant studies on a specific topic according to a predetermined and explicit method[3]. The number of published meta-analyses has increased substantially in the past decade[5]. These integrative articles can be helpful for clinical decisions, and they may also serve as the policy foundation for evidence-based practice guidelines, economic evaluations, and future research agendas. The value of meta-analysis is evident in the work of the international Cochrane Collaboration[6,7], the primary purpose of which is to generate and disseminate high-quality systematic reviews of health-care interventions.

Like any research enterprise, particularly one that is observational, the meta-analysis of evidence can be flawed. Accordingly, the process by which meta-analyses are carried out has undergone scrutiny. A 1987 survey of 86 English-language meta-analyses[8] assessed each publication on 23 items from six content areas judged important in the conduct and reporting of a meta-analysis of randomised trials: study design, combinability, control of bias, statistical

Heading	Subheading	Descriptor	Reported? (Y/N)	Page number
Title		Identify the report as a meta-analysis (or systematic review) of RCTs[26]		
Abstract		Use a structured format[27]		
		Describe		
	Objectives	The clinical question explicitly		
	Data sources	The databases (i.e. list) and other information sources		
	Review methods	The selection criteria (i.e. population, intervention, outcome, and study design); methods for validity assessment, data abstraction, and study characteristics, and quantitative data synthesis in sufficient detail to permit replication		
	Results	Characteristics of the RCTs included and excluded; qualitative and quantitative findings (i.e. point estimates and confidence intervals); and subgroup analyses		
	Conclusion	The main results		
		Describe		
Introduction		The explicit clinical problem, biological rationale for the intervention, and rationale for review		
Methods	Searching	The information sources, in detail[28] (e.g. databases, registers, personal files, expert informants, agencies, hand-searching), and any restrictions (years considered, publication status[29], language of publication[30,31])		
	Selection	The inclusion and exclusion criteria (defining population, intervention, principal outcomes, and study design[32]		
	Validity assessment	The criteria and process used (e.g. masked conditions, quality assessment, and their findings[33–36])		
	Data abstraction	The process or processes used (e.g. completed independently, in duplicate)[30,36]		
	Study characteristics	The type of study design, participants' characteristics, details of intervention, outcome definitions, &c[37], and how clinical heterogeneity was assessed		
	Quantitative data synthesis	The principal measure of effect (e.g. relative risk), method of combining results (statistical testing and confidence intervals), handling of missing data; how statistical heterogeneity was assessed[38]; a rationale for any a-priori sensitivity and subgroup analyses; and any assessment of publication bias[39]		
Results	Trial flow	Provide a meta-analysis profile summarizing trial flow (see figure)		
	Study characteristics	Present descriptive data for each trial (e.g. age, sample size, intervention, dose, duration, follow-up period)		
	Quantitative data synthesis	Report agreement on the selection and validity assessment; present simple summary results (for each treatment group in each trial, for each primary outcome); present data needed to calculate effect sizes and confidence intervals in intention-to-treat analyses (e.g. 2 × 2 tables of counts, means and SDs, proportions)		
Discussion		Summarize key findings; discuss clinical inferences based on internal and external validity; interpret the results in light of the totality of available evidence; describe potential biases in the review process (e.g. publication bias); and suggest a future research agenda		

Quality of reporting of meta-analyses

OPEN ACCESS Freely available online

PLoS MEDICINE

Guidelines and Guidance

Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

David Moher[1,2]*, Alessandro Liberati[3,4], Jennifer Tetzlaff[1], Douglas G. Altman[5], The PRISMA Group[¶]

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Introduction

Systematic reviews and meta-analyses have become increasingly important in health care. Clinicians read them to keep up to date with their field [1,2], and they are often used as a starting point for developing clinical practice guidelines. Granting agencies may require a systematic review to ensure there is justification for further research [3], and some health care journals are moving in this direction [4]. As with all research, the value of a systematic review depends on what was done, what was found, and the clarity of reporting. As with other publications, the reporting quality of systematic reviews varies, limiting readers' ability to assess the strengths and weaknesses of those reviews.

Several early studies evaluated the quality of review reports. In 1987, Mulrow examined 50 review articles published in four leading medical journals in 1985 and 1986 and found that none met all eight explicit scientific criteria, such as a quality assessment of included studies [5]. In 1987, Sacks and colleagues [6] evaluated the adequacy of reporting of 83 meta-analyses on 23 characteristics in six domains. Reporting was generally poor; between one and 14 characteristics were adequately reported (mean = 7.7; standard deviation = 2.7). A 1996 update of this study found little improvement [7].

clinicians, medical editors, and a consumer. The objective of the Ottawa meeting was to revise and expand the QUOROM checklist and flow diagram, as needed.

The executive committee completed the following tasks, prior to the meeting: a systematic review of studies examining the quality of reporting of systematic reviews, and a comprehensive literature search to identify methodological and other articles that might inform the meeting, especially in relation to modifying checklist items. An international survey of review authors, consumers, and groups commissioning or using systematic reviews and meta-analyses was completed, including the International Network of Agencies for Health Technology Assessment (INAHTA) and the Guidelines International Network (GIN). The survey aimed to ascertain views of QUOROM, including the merits of the existing checklist items. The results of these activities were presented during the meeting and are summarized on the PRISMA Web site (http://www.prisma-statement.org/).

Only items deemed essential were retained or added to the checklist. Some additional items are nevertheless desirable, and review authors should include these, if relevant [10]. For example, it is useful to indicate whether the systematic review is an update [11] of a previous review, and to describe any changes in

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

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

For more information, visit: www.prisma-statement.org.

QUOROM modificato

A score was provided for each quality criterion

Total score: 50

- **title 2.5**
- **abstract 5**
- **introduction 2.5**
- **objectives 5**
- **methods 15**
- **results 13**
- **discussion 7**

Heading	Descriptor	Weight	Value
Title		2.5	
review	Identify the report as a meta-analysis or systematic review	1	1
study design	Identify the kind of studies included (RCT, etc)	0.75	0.75
intervention	Identify the intervention	0.75	0.75
Abstract		5	
format	Use a structured format	0.50	0.50
objectives	Describe the intervention/studied relationship Describe the comparison Describe the outcome	1	0.35 0.35 0.30
data sources	Describe databases and other sources used Describe the years covered	1	0.70 0.30
methods	Define the population Define the intervention Define the control group Define the outcomes Define the study design Describe the quality assessment methods Describe the quantitative data synthesis methods	1	0.12 0.12 0.12 0.12 0.12 0.20 0.20
results	Describe number of included studies Describe number of excluded studies Describe quantitative findings Describe subgroups analysis Describe heterogeneity of results	1	0.20 0.20 0.20 0.20 0.20
conclusion	Describe the main conclusion	0.50	0.50
Introduction		2.5	
problem	Describe the clinical problem	0.75	0.75
intervention	Describe biological rationale for the intervention	0.75	0.75
review	Describe rationale for the review	1	1
Objectives		5	
intervention	Definition of experimental intervention/studied relationship	2	2
control	Definition of control intervention	1.5	1.5
outcome	Definition of outcome measures	1.5	1.5

Heading	Descriptor	Weight	Value
Methods		15	
searching	Describe searching strategy	3.5	0.50
	Describe databases and other sources used		0.50
	Describe years covered		0.50
	Describe any language exclusion		0.50
	Use at least two bibliographic sources		0.50
	Update to less than 2 years before publication		0.50
	Include at least two languages		0.50
selection	Describe inclusion criteria	3.5	0.75
	Describe exclusion criteria		0.75
	Define population		0.25
	Define intervention/studied relationship		0.25
	Define control		0.25
	Define outcomes		0.25
	Define study design		0.25
	Use of duplicate assessment		0.75
quality	Description of quality assessment method	3.0	0.75
	List of quality assessment criteria		0.75
	Concealment, blinding, attrition and ITT as quality criteria		0.75
	Use of duplicate assessment		0.75
data abstraction	Description of data abstraction method	2.0	1.00
	Use of duplicate assessment		1.00
quantitative data synthesis	Describe measure of effects	3.0	0.50
	Describe method of combining results		0.50
	Describe handling of publication bias		0.50
	Describe method for assessing heterogeneity		0.50
	Describe a priori sensitivity analysis		0.50
	Describe any subgroup analysis		0.50

Heading	Descriptor	Weight	Value
Results		13.0	
Studies' characteristics	Describe the characteristics of the population	3.5	0.50
	Describe the sample size		0.50
	Describe the intervention		0.50
	Describe the control		0.50
	Describe the study design		0.50
	Describe measured outcomes		0.50
	Describe follow-up period		0.50
excluded studies	List of excluded studies	2.0	1.00
	Description of reasons for exclusion		1.00
quality	Description of quality assessment findings	1.5	1.50
quantitative data synthesis	Present simple summary results	6.0	0.75
	Perform sensitivity analysis		0.75
	Perform subgroup analysis		0.75
	Assess heterogeneity		0.75
	Provide meta-analysis or synthetic table of results		0.75
	Data are included in meta-analysis on ITT basis		0.75
	Combine studies in meta-analysis only if homogeneous		0.75
	Provide funnel plot assessing publication bias		0.75
Discussion		7.0	
results	Summarize key findings	1.5	1.5
validity	Discuss internal quality of the studies	2.0	0.75
	Discuss external validity of the studies/heterogeneity		0.75
	Discuss potential bias in the review process		0.50
interpretation	Interpretation of results	2.5	2.5
recommendations	Suggest future research needed	1	0.50
	Suggest public health/practice recommendations		0.50

Quality classes

7 quality classes were determined according to the scores

class	score
A+	46-50
A-	41-45
B+	36-40
B-	31-35
C+	26-30
C-	21-25
D	0-20

Grazie per l'attenzione.. !!