REVIEW ARTICLES

• Review articles are an attempt to summarize the current state of understanding on a topic.

• They analyze or discuss research previously published by others, rather than reporting new experimental results.

• They come in the form of systematic reviews and literature reviews and are a form of secondary literature.

• Some academic journals likewise specialize in review of a field; they are known as review journals.
INTRODUCTION

- Systematic reviews and meta-analyses
- Double-blind Randomized controlled studies

Cohort
Case-control
Case series
Case reports
Ideas, Editorials, Opinions
Animal research
In vitro (‘test tube’) research
Common problems when using individual trials

- Small size
- Single centre
- Publication bias
- Lack power and prone to chance
- Limited external validity (applicability)
- Need to examine all similar trials
INTRODUCTION

• A systematic review is a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review.

• Systematic reviews of high-quality randomized controlled trials are crucial to evidence-based medicine.
INTRODUCTION

• An understanding of systematic reviews and how to implement them in practice is becoming mandatory for all professionals involved in the delivery of health care.

• Besides health interventions, systematic reviews may concern clinical tests, public health interventions, social interventions, adverse effects, and economic evaluations.
NARRATIVE REVIEW

• *Subjective*: prone to bias and error.

• *Selective* inclusion (or exclusion) of studies that support the author’s view

• Usually *not quantitative*

• Different reviewers reaching *different conclusions* from the same research base

• Readers *cannot* judge the quality, replicate or verify the review
SYSTEMATIC REVIEW

• Clearly stated objectives
• Clearly stated methods
• Extensive (and explicit) search strategy
• Quantitative estimate of treatment effect (meta-analysis) if appropriate and possible
• Clear conclusions based on the evidence
• NB... should be explicit and reproducible
META-ANALYSIS

- In a meta-analysis refers to methods that focus on contrasting and combining results from different studies, in the hope of identifying patterns among study results, sources of disagreement among those results, or discovering other interesting relationships.

- Conceptually, a meta-analysis uses a statistical approach to combine the results from multiple studies in an effort to increase power (over individual studies), improve estimates of the size of the effect and/or to resolve uncertainty when reports disagree.
ADVANTAGES OF META-ANALYSIS

• Results can be generalized to a larger population;
• The precision and accuracy of estimates can be improved as more data is used. This increases the statistical power to detect an effect;
• Inconsistency of results across studies can be quantified and analyzed;
• Hypothesis testing can be applied on summary estimates;
• Moderators can be included to explain variation between studies;
• The presence of publication bias can be investigated.
Reviews
(narrative/literature/traditional)

Systematic reviews

Meta-analysis
Stages of a systematic review

- Planning the review: identifying the need for a review, and documenting the methodology

- Conducting the review: finding, selecting, appraising, extracting and synthesising primary research studies

- Reporting and dissemination: writing up and disseminating the results of the review
PRISMA Statement

• The aim of the PRISMA Statement is to help authors report a wide array of systematic reviews to assess the benefits and harms of a health care intervention.

• PRISMA focuses on ways in which authors can ensure the transparent and complete reporting of systematic reviews and meta-analyses.
Title:

1- Title: Identify the report as a systematic review, meta-analysis, or both.

Abstract

2- Structured summary: 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.
3- **Rationale:** Describe the rationale for the review in the context of what is already known.

4- **Objectives:** Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
5- Protocol and registration: 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.

6- Eligibility criteria: 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.
PRISMA 2009 Checklist- Methods

7- Information sources: 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.

8- Search: Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
9- Study selection: State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).

10- Data collection process: Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
11- *Data items*: List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.

12- *Risk of bias in individual studies*: 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.
13- *Summary measures:* State the principal summary measures (e.g., risk ratio, difference in means).

14- *Synthesis of results:* Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.
15- *Risk of bias across studies*: Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).

16- *Additional analyses*: Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
17- *Study selection:* 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.

18- *Study characteristics:* For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
PRISMA 2009 Checklist - Results

19- Risk of bias within studies: Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).

20- Results of individual studies: 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.
21- *Synthesis of results*: Present results of each meta-analysis done, including confidence intervals and measures of consistency.

22- *Risk of bias across studies*: Present results of any assessment of risk of bias across studies (see Item 15).

23- Additional analysis: Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
24- **Summary of evidence:** 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).

25- **Limitations:** 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).
26- Conclusions: Provide a general interpretation of the results in the context of other evidence, and implications for future research.
27- **Funding**: Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.
Formulating the research question in systematic reviews

Akbar Shafiee, MD, MSc

Tehran University of Medical Sciences
Questions for systematic review

Clinical question

• any aspect of
  o clinical practice
  o service delivery

Review question

• define question
  o patient group
  o intervention
  o comparison
  o outcomes
Question components: PICO(T)

- What types of Participants?
- What types of Interventions?
- What types of Comparisons?
- What types of Outcomes?
- What types of Studies?
Who are the patients?
- Individuals with a specific disease
- Members of a group
- Under a special setting

How do you describe them?
I: Intervention

• A special treatment or intervention
• Exposure to something
• Dosage, route and extent of intervention
C: Comparison

• Not applicable to all questions
• Comparing two different groups
• Comparing a new method/drug with the old/standard one
O: Outcome

- Hard outcomes
  - Death
  - Complication/Adverse effect

- Soft outcomes
  - Quality of life
  - Patients’ satisfaction
S: Studies

- Randomized clinical trials (RCT)
- Cohort
- Case-Control
- Case series
- ...
A PICO question

Time-consuming question:

• What is the best strategy to prevent smoking in young people?
An answerable question

Q. Are mass media (or school-based or community-based) interventions effective in preventing smoking in young people?
<table>
<thead>
<tr>
<th>Problem, population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
<th>Types of studies</th>
</tr>
</thead>
</table>
| smoking, Young people <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, skills, attitude, knowledge)  
d) Media reach | a) RCT  
b) Controlled before and after studies  
c) Time series designs |
To determine whether calcium antagonists reduce the risk of death or dependency after acute ischemic stroke.

The influence of different drugs, dosages, routes of administration, time intervals after stroke and trial design on the risk of poor outcome was investigated.
Calcium antagonists for acute ischemic stroke (Cochrane Review). Horn J, Limburg M.

- **Patients** - Patients with presumed or definite acute ischemic stroke, randomised within 14 days after stroke onset

- **Intervention**: calcium antagonists

- **Comparison**: placebo

- **Outcome**: *Primary outcome*: Poor outcome, defined as death (all cause case fatality) or dependency in daily activities. *Secondary outcomes*: Adverse events

- **Study types**: RCTs
In patients undergoing hip replacement, is the risk of post-operative infection reduced by antimicrobial prophylaxis?

- **Patients**: Patients undergoing hip replacement
- **Intervention**: Antimicrobial prophylaxis
- **Comparison**: Without prophylaxis
- **Outcome**: Post-operative infection
- **Study types**: RCTs
### What types of questions can be asked?

<table>
<thead>
<tr>
<th>Question</th>
<th>Ideal study types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>Frequency/rate (burden of illness)</td>
<td>Cross-sectional study/consecutive sample</td>
</tr>
<tr>
<td>Etiology and risk</td>
<td>Cohort study</td>
</tr>
<tr>
<td>Prediction /prognosis</td>
<td>Cohort study</td>
</tr>
<tr>
<td>Diagnostic accuracy</td>
<td>Random or consecutive sample</td>
</tr>
<tr>
<td>Phenomena</td>
<td>Qualitative research</td>
</tr>
</tbody>
</table>
Any question?
Systematic Searching for Systematic Reviews

Akbar Shafiee MD, MSc

Tehran University of Medical Sciences
Publication bias

The likelihood of finding studies is related to the results of those studies.
Publication bias

Sterling study: 97% of papers published in 4 psychology journals showed statistically significant results at alpha level 5%!

“Journal of Negative results in Biomedicine”

www.jnrbrbm.com/
Two basic questions:

• Where to search for systematic reviews?

• How to search for systematic reviews?
Where to Search

- Bibliographic databases
  - MEDLINE
  - EMBASE

- Citation databases
  - Web of Science
  - Scopus

- Systematic Reviews databases
  - The Cochrane Library
Bibliographic databases

• MEDLINE
  – By US National Library of Medicine
  – Since 1946 onward
  – Over 5,600 journals
  – Over 21,000,000 citations of both clinical and preclinical studies.
  – 700,000 articles added in 2013
  – On 40 languages
  – Subject Coverage: Biomedicine and health
  – +70% of References contain Abstracts
  – Pubmed as a free interface
Results: 5 of 1734
Concurrent intrathecal methotrexate and liposomal cytarabine for leptomeningeal metastasis from solid tumors: a retrospective cohort study.

Comparison of treatment patterns and economic outcomes in metastatic breast cancer patients initiated on trastuzumab versus lapatinib: a retrospective analysis.

Pneumonitis and pulmonary fibrosis associated with breast cancer treatments.

Tiastuzumab-containing regimens for metastatic breast cancer.

A process for assessing the feasibility of a network meta-analysis: a case study of everolimus in combination with hormonal therapy versus chemotherapy for advanced breast cancer.

Results: 5 of 10260
Predicting targeted drug combinations based on Pareto optimal patterns of coexpression network connectivity.

2q36.3 is associated with prognosis for oestrogen receptor-negative breast cancer patients treated with chemotherapy.

Systems analysis of drug-induced receptor tyrosine kinase reprogramming following targeted mono- and combination anti-cancer therapy.

Survival and contralateral breast cancer in CHEK2 1100delC breast cancer patients: impact of adjuvant chemotherapy.

Bibliographic databases

- EMBASE
  - Over 5,000 journals
  - Over 15,000,000 citations
  - On 30 languages
  - Embase.com is Elsevier’s own version of EMBASE

Overlap with MEDLINE estimated 30 to 40% varies according to the topic
Your key resource for biomedical information

With extensive international journal and conference coverage, Embase is a key resource for generating systemic reviews, supporting effective evidence-based medicine and drug and medical device tracking. Embase facilitates the clinical decision-making process and allows you to get to market faster, while still ensuring the required drug safety and pharmacovigilance.

→ Discover Embase

Helping you succeed

The breadth and depth of data is the central reason why information managers, regulatory specialists, clinicians, medical librarians, educators and physicians use Embase to track and retrieve precise information on drugs and diseases, from pre-clinical studies to searches on critical toxicological information.

→ Who uses Embase?

A biomedical database that speaks your language

Embase is a biomedical database with over 28 million indexed records from thousands of peer-reviewed journals and conference proceedings — over 6 million of which can't be found in MEDLINE. What's more, all of the content is fully indexed using the Elsevier Life Science thesaurus Emtree — a hierarchically structured, controlled vocabulary for medicine and related life sciences.

→ Explore Emtree
Systematic Reviews databases

The Cochrane Collaboration

www.cochrane.org
The Cochrane Collaboration

Wiley publishes the Cochrane Library for the Cochrane Collaboration

- **Structure** - established as an international organisation in 1993, registered as a charity in the U.K.

- **Aim** - to help people make well-informed decisions about health care.

- **How** - by preparing and maintaining, and promoting access to, systematic reviews of the effects of healthcare interventions.

- **Publishing Output** – The Cochrane Library
Cochrane Library

www.thecochranelibrary.com

• bringing together articles from MEDLINE and EMBASE

• Advantage is Knowing that the articles listed are all recognized as controlled trials or systematic reviews

• Subject Coverage: Clinical medicine reviews

• Update: Updated quarterly
The Cochrane Collaboration now

- more than 31,000 volunteers in more than 120 countries
- Comprises centres in 14 countries
- 53 topic-based Review groups and about 6000 members.
Some of Cochrane Review Groups

- Cochrane Acute Respiratory Infections Group
- Cochrane HIV/AIDS Group
- Cochrane Infectious Diseases Group
- Cochrane Consumers & Communication Group
- Cochrane Drugs and Alcohol Group
- Cochrane Effective Practice and Organisation of Care Group
- Cochrane Injuries Group
What is the Cochrane Library?

The Cochrane Library is a collection of 6 main databases and 1 additional databases that describe Cochrane as an organization. These are:

1. The Cochrane Database of Systematic Reviews (CDSR)
2. The Database of Reviews of Effects (DARE)
3. The Cochrane Central Register of Controlled Trials (CENTRAL)
4. The Cochrane database of Methodology Reviews (CDMR)
5. Health Technology Assessment Database (HTA)
6. NHS Economic Evaluation Database (NHS EED)
7. THE COCHRANE METHODOLOGY REGISTER (CMR)
Database of abstracts of reviews of effects (DARE)

- Produced by the expert reviewers of the NHS Centre for Reviews and Dissemination (NHS CRD) at the University of York, England
- Contains over 4000 abstracts systematic reviews. Focuses on the effects of interventions in health and social care.
- DARE records cover topics such as diagnosis, prevention, screening, and treatment.
CENTRAL

- Contained just over 710,000 citations (October 2013) Includes citations to reports of controlled trials that might not indexed in MEDLINE, EMBASE or other bibliographic databases
  - published in many languages
  - citations that are available only in conference proceedings or other sources that are difficult to access
# The Cochrane Library Total Records at May 2014

<table>
<thead>
<tr>
<th>Database</th>
<th>Total Records</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Cochrane Database of Systematic Reviews (Cochrane Reviews)</td>
<td>8,332</td>
</tr>
<tr>
<td>Database of Abstracts of Reviews of Effects (DARE)</td>
<td>30,175</td>
</tr>
<tr>
<td>The Cochrane Central Register of Controlled Trials (CENTRAL)</td>
<td>780,942</td>
</tr>
<tr>
<td>The Cochrane Methodology Register (Methodology Register)</td>
<td>15,764</td>
</tr>
<tr>
<td>Health Technology Assessment Database (HTA)</td>
<td>13,616</td>
</tr>
<tr>
<td>NHS Economic Evaluation Database (NHS EED)</td>
<td>15,621</td>
</tr>
<tr>
<td>About The Cochrane Collaboration and the Cochrane Collaborative Review Groups (About)</td>
<td>81</td>
</tr>
</tbody>
</table>
Subject Specific databases

- Cumulative Index to Nursing and Allied Health (CINAHL)
  
  www.cinahl.com
Subject Specific databases

• PsycINFO:

  PsycINFO is an abstract database that provides systematic coverage of the psychological literature from the 1800s to the present.

  [www.apa.org/psycinfo/]
**General Search Engines**

Stand on the shoulders of giants.

Google Scholar provides a simple way to broadly search for scholarly literature. From one place, you can search across many disciplines and sources: articles, theses, books, abstracts and court opinions, from academic publishers, professional societies, online repositories, universities and other web sites. Google Scholar helps you find relevant work across the world of scholarly research.
Trip Database

• Turning Research into Practice (TRIP) database
  (evidence-based healthcare resource)

www.tripdatabase.com
Trip Database; PICO search

PICO Search

PICO is a novel approach of allowing users to conduct a focussed search based on a structured clinical question.

Population:
Type of patient eg. diabetics

Intervention:
Any intervention eg. treatment, diagnostic test

Comparison:
Comparing your intervention with another treatment or

Outcome:
Outcome interest eg. reduced mortality, fewer exacerbations

Search
Citation Indexes

- **Web of Science**
  is also incorporated in Web of Knowledge

- **Scopus**
  - Covers more than 18,000 journals and 1000 conference proceedings
Dissertations and theses databases

- CINAHL, indexes nursing dissertations.
- ProQuest Dissertations & Theses Database
- Great Britain and Ireland Dissertation: www.theses.com
- German dissertations: www.dissonline.de
Grey Literature

• Institute for Scientific and Technical Information (INIST) in France

  Opensigle.inist.fr

  Scholar.google.com
Non-bibliographic database sources

• Handsearching

Is useful for at least two reasons:

1. Not all trial reports are included in electronic bibliographic databases

2. They may not contain relevant search terms in the titles or abstracts to be easily identified as trials

• Conference abstracts or proceedings
Non-bibliographic database sources

• Web searching

Searching pharmaceutical industry web sites in particular their trials registers
Non-bibliographic database sources

• Unpublished and ongoing studies

Some completed studies are never published

An association between “significant” results and publication has been documented across a number of studies
Unpublished and ongoing studies

• Colleagues
• Experts
• Pharmaceutical companies
Any Question?
Conducting a search strategy
Boolean Logics

Shaded areas indicate retrieval

Search Statement

Types of records retrieved

stress AND anxiety
Documents that have both stress AND anxiety

stress OR anxiety
Documents that have either stress OR anxiety

stress NOT anxiety
Documents that have stress but NOT anxiety
Pubmed and Elsevier Searching Tips

* **Truncation**: finds a root word plus all the words made by adding letters to the end of it.
  
  – Behav* finds behave, behavioral, behaviour, etc.

? **Wildcard**: replaces a character anywhere in a word, except the first character.

  – Wom?n finds woman and women
Synonyms & Alternative Spelling

• English and American spellings
  – behaviour and behavior, flavour and flavor, colour and color, psychoanalyse and psychoanalyze

• Plurals
  – horse and horses, woman and women, case and cases

• Root words
  – Transplant and transplants and transplanting, hear and hearing

• Synonyms
  – Aspirin will also search acetylsalicylic acid
Example:

• Free form Question:

Which of the toremifene or tamoxifen are more effective and safer in patients with advanced breast cancer?
### Structured Question

<table>
<thead>
<tr>
<th>The Population</th>
<th>Patients with advanced breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>The interventions</td>
<td>toremifene or tamoxifen</td>
</tr>
<tr>
<td>The Outcomes</td>
<td>Efficacy, safety</td>
</tr>
<tr>
<td>The Study Design</td>
<td>A comparative study that allocates subjects with advanced breast cancer to receive toremifene or tamoxifen and determines the effect of the interventions on the disease (eg RCT)</td>
</tr>
</tbody>
</table>
PubMed; MeSH Database

PubMed comprises more than 22 million citations for biomedical literature from MEDLINE, life science journals, and online books. Citations may include links to full-text content from PubMed Central and publisher web sites.
PRISMA flow diagram

• The flow diagram depicts the flow of information through the different phases of a systematic review. It maps out the number of records identified, included and excluded, and the reasons for exclusions
Critical Appraisal

Arash Jalali
PhD in Biostatistics
Tehran University of Medical Sciences
Systematic Review; Step by step

1. Formulating review questions
2. Searching & selecting studies
3. Study quality assessment
4. Extracting data from studies
5. Data synthesis & Interpreting the findings
• The extent to which review can draw conclusions about the effects of an intervention depends on whether the data and results from the included studies are valid.

• A meta-analysis of invalid studies may produce a misleading result, yielding a narrow confidence interval around the wrong intervention effect estimate.

• The evaluation of the validity of the included studies is therefore an essential component of a review.
We offer critical appraisal skills training, workshops and tools. These help you find and check research for trustworthiness, results & relevance.

Sign up here to find out about upcoming CASP workshops and events......
CASP CHECKLISTS

This set of eight critical appraisal tools are designed to be used when reading research, these include tools for Systematic Reviews, Randomised Controlled Trials, Cohort Studies, Case Control Studies, Economic Evaluations, Diagnostic Studies, Qualitative studies and Clinical Prediction Rule.

These are free to download and can be used by anyone under the Creative Commons License.

CASP Checklists (click to download)

<table>
<thead>
<tr>
<th>Randomised Controlled Trial</th>
<th>Diagnostic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic Review</td>
<td>Cohort</td>
</tr>
<tr>
<td>Qualitative</td>
<td>Economic Evaluation</td>
</tr>
<tr>
<td>Case Control</td>
<td>Clinical Prediction Rule</td>
</tr>
</tbody>
</table>
http://www.strobe-statement.org/

What is STROBE?

STROBE stands for an international, collaborative initiative of epidemiologists, methodologists, statisticians, researchers and journal editors involved in the conduct and dissemination of observational studies, with the common aim of Strengthening the Reporting of Observational studies in Epidemiology.

The STROBE Statement is being endorsed by a growing number of biomedical journals. Click here for full list.

For STROBE-related entries in PubMed click here.

STROBE checklists

Version 4 as published in Oct / Nov 2007!

- STROBE checklist for cohort, case-control, and cross-sectional studies (combined)
  download PDF / Word
- Checklist for cohort studies
  download PDF / Word
- Checklist for case-control studies
  download PDF / Word
- Checklist for cross-sectional studies
  download PDF / Word
- Draft STROBE checklist for conference abstracts
  download PDF

For translations in other languages see Translations page.
Translations of STROBE Statement

  download PDF

- **Spanish** (published in Gaceta Sanitaria):
  download PDF

- **German** (published in Der Internist and Notfall & Rettungsmedizin):
  download PDF

- **Italian** (published in Terapia Evidenza Based):
  download PDF

- **Japanese**:
  download PDF

- **Persian**:
  download PDF

- **Portuguese** (published in Revista de Saúde Pública)
  download PDF

- **Greek PDF**
  download

Translations of STROBE explanatory paper

- **Spanish** (published in Gaceta Sanitaria):
Welcome to the CONSORT Website

CONSORT stands for Consolidated Standards of Reporting Trials and encompasses various initiatives developed by the CONSORT Group to alleviate the problems arising
Welcome to the PRISMA Statement website

PRISMA stands for Preferred Reporting Items for Systematic Reviews and Meta-Analyses. It is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses.

The aim of the PRISMA Statement is to help authors improve the reporting of systematic reviews and meta-analyses. We have focused on randomized trials, but PRISMA can also be used as a basis for reporting systematic reviews of other types of research, particularly evaluations of interventions. PRISMA may also be useful for critical appraisal of published systematic reviews, although it is not a quality assessment instrument to gauge the quality of a systematic review.

The PRISMA Statement consists of a 27-item checklist and a four-phase flow diagram. It is an evolving document that is subject to change periodically as new evidence emerges. In fact, the PRISMA Statement is an update and expansion of the now-out-dated QUOROM Statement. This website contains the current definitive version of the PRISMA Statement.

We invite readers to comment on the PRISMA Statement by contacting us.

The PRISMA Explanation and Elaboration document explains and illustrates the principles underlying the PRISMA Statement. It is strongly recommended that it be used in conjunction with the PRISMA Statement.

PRISMA is part of a broader effort, to improve the reporting of different types of health research, and in turn to improve the quality of research used in decision-making in healthcare.

Please join PRISMA in supporting the All Trials campaign to get all clinical trial results reported.
Objective of the STARD initiative

The objective of the STARD initiative is to improve the accuracy and completeness of reporting of studies of diagnostic accuracy, to allow readers to assess the potential for bias in the study (internal validity) and to evaluate its generalisability (external validity).

The STARD statement consists of a checklist of 25 items and recommends the use of a flow diagram which describe the design of the study and the flow of patients.

News

April 2008
- More than 200 biomedical journals encourage the use of the STARD statement in their instructions for authors.

Last update 22 April 2008
QUALITY ASSESSMENT TOOL FOR QUANTITATIVE STUDIES

QA Tool PDF

QA Dictionary PDF

A Process for Systematically Reviewing the Literature: Providing the Research Evidence for Public Health Nursing Interventions


This EPHP "Quality Assessment Tool for Quantitative Studies" method and tool was developed for use in public health, and can be applied to articles of any public health topic area, including the promotion of family and sexual health and the prevention of chronic disease, injuries and substance misuse. Various types of public health professionals would find this tool relevant to utilize sources of high quality literature to support the decision-making process, especially when designing, implementing and evaluating public health programs and policy.

This knowledge translation and synthesis method requires a group of four to six experts who can facilitate a process that includes generating a research question, searching for literature, appraisal of the literature, data extraction, and the synthesis and dissemination of results. This method requires a review team with at least one member having methodological expertise, and two members with subject expertise.
• Any Question?

• Next → Exercises
Data collection and Data extraction

Arash Jalali
PhD in Biostatistics
Tehran University of Medical Sciences
Data

- Source
- Eligibility
- Methods
- Participants
- Interventions
- Outcomes
- Results
- Miscellaneous
• **Source**
  – Study ID
  – Report ID

• **Eligibility**
  – confirm eligibility for review
  – reason for exclusion
• **Methods**
  
  – Study design
  – Total study duration
  – sequence generation
  – allocation sequence concealment
  – Blinding
  – other concerns about bias
• **Participants**
  – Total number
  – Setting
  – diagnostic criteria
  – age (means or medians with SDs or ranges for the whole study or for each intervention group separately)
  – sex (percentages or counts)
  – country

[socio demographics], [ethnicity], [date of study], ...
• **Interventions**
  
  – Total number of intervention groups

*For each intervention and comparison group of interest:*

- **Specific intervention**
- **Intervention details** (sufficient for replication, if feasible)

*Routes of delivery, doses, timing and length of treatment* may be relevant
• **Outcomes**

  outcomes and time points

*For each outcome of interest:*

- **Outcome definition** *(with diagnostic criteria if relevant)*
- **Unit of measurement** *(if relevant)*
- **For scales:** upper and lower limits, and whether high or low score is good
• **Results**
  
  - number of participants allocated to each intervention group

*For each outcome of interest:*

- **Sample size**
- **Missing participants**
- **Summary data for each intervention group**
  
  (2*2 table for dichotomous data; means and SDs for continuous data)

- [estimate of effect with confidence interval; p-value]
- [subgroup analyses]
• Miscellaneous
  – funding source
  – key conclusions of the study authors
  – miscellaneous comments from the study authors
  – references to other relevant studies
  – correspondence required

...
<table>
<thead>
<tr>
<th>Source</th>
<th>For each outcome of interest:</th>
</tr>
</thead>
</table>
| - Study ID (created by review author);  
- Report ID (created by review author);  
- Review author ID (created by review author);  
- Citation and contact details; | - Outcome definition (with diagnostic criteria if relevant);  
- Unit of measurement (if relevant);  
- For scales: upper and lower limits, and whether high or low score is good; |

<table>
<thead>
<tr>
<th>Eligibility</th>
<th>Results</th>
</tr>
</thead>
</table>
| - Confirm eligibility for review;  
- Reason for exclusion; | - Number of participants allocated to each intervention group; |

<table>
<thead>
<tr>
<th>Methods</th>
<th>For each outcome of interest:</th>
</tr>
</thead>
</table>
| - Study design;  
- Total study duration;  
- Sequence generation*;  
- Allocation sequence concealment*;  
- Blinding*;  
- Other concerns about bias*; | - Sample size;  
- Missing participants*;  
- Summary data for each intervention group (e.g. 2×2 table for dichotomous data; means and SDs for continuous data);  
- [Estimate of effect with confidence interval; P value];  
- [Subgroup analyses]; |

<table>
<thead>
<tr>
<th>Participants</th>
<th>Miscellaneous</th>
</tr>
</thead>
</table>
| - Total number;  
- Setting;  
- Diagnostic criteria;  
- Age;  
- Sex;  
- Country;  
- [Co-morbidity];  
- [Socio-demographics];  
- [Ethnicity];  
- [Date of study]; | - Funding source;  
- Key conclusions of the study authors;  
- Miscellaneous comments from the study authors;  
- References to other relevant studies;  
- Correspondence required;  
- Miscellaneous comments by the review authors. |

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| - Total number of intervention groups;  
**For each intervention and comparison group of interest:**  
- Specific intervention;  
- Intervention details (sufficient for replication, if feasible);  
- [Integrity of intervention]; | - Outcomes and time points (i) collected;  
(ii) reported*; |
• Who Should extract data?
  – Recommended that more than one person extract data from every report to minimize errors and reduce potential biases being introduced
  – Data extractors are from complementary disciplines, i.e. a methodologist and a topic area specialist.
• Extracting data from multiple reports of the same study

• Reliability and reaching consensus
  – Extract data from more than one author -> potential for disagreement
  – Most often is an error by one of the extractors and easily resolved
• Extracting study results and converting to the desired format

\[ n_1 = 25 \]
\[ n_2 = 22 \]
\[ P = 0.008 \]
\[ \text{MD} = 3.8 \]
\[ \text{df} = 25 + 22 - 2 = 45 \]
\[ p(t(45) > x) = 0.008 \Rightarrow x = 2.78 \]
\[ SE = \frac{\text{MD}}{t} = 1.37 \]
Meta-analysis and Publication Bias

Arash Jalali
PhD in Biostatistics
Tehran University of Medical Sciences
What you find from this logo ...
Interventions for replacing missing teeth: antibiotics at dental implant placement to prevent complications

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotics</th>
<th>No antibiotics</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td></td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Abu-Ta'a 2008</td>
<td>0/40</td>
<td>3/40</td>
<td></td>
<td>6.6 %</td>
<td>0.14 [0.01, 2.68]</td>
</tr>
<tr>
<td>Anitua 2009</td>
<td>2/52</td>
<td>2/53</td>
<td></td>
<td>15.4 %</td>
<td>1.02 [0.15, 6.97]</td>
</tr>
<tr>
<td>Esposito 2008a</td>
<td>2/158</td>
<td>8/158</td>
<td></td>
<td>24.2 %</td>
<td>0.25 [0.05, 1.16]</td>
</tr>
<tr>
<td>Esposito 2010</td>
<td>5/252</td>
<td>12/254</td>
<td></td>
<td>53.8 %</td>
<td>0.42 [0.15, 1.17]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>502</strong></td>
<td><strong>505</strong></td>
<td></td>
<td>100.0 %</td>
<td><strong>0.40 [0.19, 0.84]</strong></td>
</tr>
</tbody>
</table>

Total events: 9 (Antibiotics), 25 (No antibiotics)

Heterogeneity: Tau² = 0.0; Chi² = 1.77, df = 3 (P = 0.62); I² = 0.0%

Test for overall effect: Z = 2.41 (P = 0.016)

Outcome: Implant failures
Forest plots could answer ...

1. How many studies are there?
2. How many studies favour treatment?
3. How many studies are statistically significant?
4. Which is the largest study?
5. Which is the smallest study?
6. What is the combined result?
Meta-analysis

• Produce a weighted average effect of all the studies

• Each study is weighted according to some measure of importance

\[ W_i = \frac{1}{V_i} \]

\[
\text{weighted average} = \frac{\text{sum of (estimate} \times \text{weight)}}{\text{sum of weights}} = \frac{\sum Y_i W_i}{\sum W_i}
\]
Meta-analysis

• Individual studies may be far too small to produce precise effects and so MA can improve precision by combining them statistically.

• Some times will just not be feasible
Outcome: HIV Infection
What is heterogeneity?

Variability in effect size estimates which exceeds that expected from sampling error alone.

Stratify the studies into subgroups according to PICO
• Clinical Heterogeneity
  – Populations
  – Interventions
  – Outcomes

• Methodological Heterogeneity
  – Design
  – Quality
Meta-analysis

• Fixed effects
A fixed effect model estimates the average effect assuming that there is a single true underlying effect.

• Random effects
(considers both *between-study* and *within-study* variability)
A random effect model assumes that there is no single underlying value of the effect, but there is a distribution of effects depending on studies’ characteristics.
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>M-H, Fixed, 95% CI</th>
<th>Odds Ratio</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>7.6%</td>
<td>0.25 [0.03, 1.82]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>3</td>
<td>10</td>
<td>6</td>
<td>10</td>
<td>8.0%</td>
<td>0.29 [0.04, 1.82]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>4</td>
<td>15</td>
<td>7</td>
<td>15</td>
<td>9.7%</td>
<td>0.42 [0.09, 1.92]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>3</td>
<td>15</td>
<td>7</td>
<td>15</td>
<td>10.6%</td>
<td>0.29 [0.06, 1.45]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>5</td>
<td>20</td>
<td>9</td>
<td>20</td>
<td>12.8%</td>
<td>0.41 [0.11, 1.56]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>6</td>
<td>20</td>
<td>10</td>
<td>20</td>
<td>13.3%</td>
<td>0.43 [0.12, 1.57]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>7</td>
<td>25</td>
<td>13</td>
<td>25</td>
<td>17.8%</td>
<td>0.36 [0.11, 1.16]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>6</td>
<td>25</td>
<td>14</td>
<td>25</td>
<td>20.2%</td>
<td>0.25 [0.07, 0.83]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>140</strong></td>
<td><strong>140</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.34 [0.20, 0.56]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events 360 710
Heterogeneity: $\chi^2 = 6.95$, df= 7 ($P = 0.43$); $I^2 = 0$
Test for overall effect: $Z = 13.42$ ($P < 0.00001$)
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>20</td>
<td>100</td>
<td>50</td>
<td>100</td>
<td>11.4%</td>
<td>0.25 [0.13, 0.47]</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>50</td>
<td>100</td>
<td>60</td>
<td>100</td>
<td>11.8%</td>
<td>0.67 [0.38, 1.17]</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>70</td>
<td>150</td>
<td>60</td>
<td>150</td>
<td>12.5%</td>
<td>1.31 [0.83, 2.07]</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>50</td>
<td>150</td>
<td>70</td>
<td>150</td>
<td>12.5%</td>
<td>0.57 [0.36, 0.91]</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>90</td>
<td>200</td>
<td>50</td>
<td>200</td>
<td>12.7%</td>
<td>2.45 [1.61, 3.75]</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>100</td>
<td>200</td>
<td>90</td>
<td>200</td>
<td>12.9%</td>
<td>1.22 [0.83, 1.81]</td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>120</td>
<td>250</td>
<td>90</td>
<td>250</td>
<td>13.1%</td>
<td>1.64 [1.15, 2.35]</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>80</td>
<td>250</td>
<td>120</td>
<td>250</td>
<td>13.1%</td>
<td>0.51 [0.35, 0.73]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 1400 1400 100.0% 0.88 [0.55, 1.43]

Total events 580 590

Heterogeneity: Tau² = 0.42; Chi² = 66.29, df = 7 (P < 0.00001); I² = 89%
Test for overall effect: Z = 0.51 (P = 0.61)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>6.0%</td>
<td>0.25 [0.03, 1.82]</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>5</td>
<td>10</td>
<td>6</td>
<td>10</td>
<td>7.5%</td>
<td>0.67 [0.11, 3.92]</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>7</td>
<td>15</td>
<td>6</td>
<td>15</td>
<td>11.2%</td>
<td>1.31 [0.31, 5.58]</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>5</td>
<td>15</td>
<td>7</td>
<td>15</td>
<td>10.8%</td>
<td>0.57 [0.13, 2.50]</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>9</td>
<td>20</td>
<td>5</td>
<td>20</td>
<td>13.1%</td>
<td>2.45 [0.64, 9.39]</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>10</td>
<td>20</td>
<td>9</td>
<td>20</td>
<td>15.2%</td>
<td>1.22 [0.35, 4.24]</td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>12</td>
<td>25</td>
<td>9</td>
<td>25</td>
<td>18.4%</td>
<td>1.64 [0.53, 5.09]</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>8</td>
<td>25</td>
<td>12</td>
<td>25</td>
<td>17.8%</td>
<td>0.51 [0.16, 1.61]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 140 140 100.0% 0.98 [0.60, 1.59]

Total events 58 59

Heterogeneity: Tau² = 0.00; Chi² = 6.63, df = 7 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)
Interventions for replacing missing teeth: antibiotics at dental implant placement to prevent complications

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotics</th>
<th>No antibiotics</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abu-Ta'a 2008</td>
<td>0/40</td>
<td>3/40</td>
<td>n/a</td>
<td>6.6 %</td>
<td>0.14 [ 0.01, 2.68 ]</td>
</tr>
<tr>
<td>Anitua 2009</td>
<td>2/52</td>
<td>2/53</td>
<td>n/a</td>
<td>15.4 %</td>
<td>1.02 [ 0.15, 6.97 ]</td>
</tr>
<tr>
<td>Esposito 2008a</td>
<td>2/158</td>
<td>8/158</td>
<td>n/a</td>
<td>24.2 %</td>
<td>0.25 [ 0.05, 1.16 ]</td>
</tr>
<tr>
<td>Esposito 2010</td>
<td>5/252</td>
<td>12/254</td>
<td>n/a</td>
<td>53.8 %</td>
<td>0.42 [ 0.15, 1.17 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>502</strong></td>
<td><strong>505</strong></td>
<td>n/a</td>
<td>100.0 %</td>
<td>0.40 [ 0.19, 0.84 ]</td>
</tr>
</tbody>
</table>

Total events: 9 (Antibiotics), 25 (No antibiotics)

Heterogeneity: Tau² = 0.0; Chi² = 1.77, df = 3 (P = 0.62); I² = 0.0%

Test for overall effect: Z = 2.41 (P = 0.016)

Outcome: Implant failures
Publication bias

"Positive findings are around twice as likely to be published as negative findings. This is a cancer at the core of evidence-based medicine.”
- Ben Goldacre

The likelihood of finding studies is related to the results of those studies
Publication bias

Sterling study: 97% of papers published in 4 psychology journals showed statistically significant results at alpha level 5%

“Journal of Negative results in Biomedicine”
Funnel plots

• A funnel plot is a scatter plot of treatment effect (Effect Size) against a measure of study size.
Funnel plots

Risk ratio (mortality)

Standard error

Risk ratio (mortality)

0.025 1 40

2

1

0

Standard error

0.25 4
Funnel plots

• A funnel plot is a scatter plot of treatment effect (Effect Size) against a measure of study size.

Fig. 1. Simulated funnel plot. (●) Effect size significantly increased (P < 0.05). (○) Effect size not significant. (——) Expected value of effect size. (— —) Expected 95% confidence region for samples.
Why Funnel?

• Precision in the estimation of the true treatment effect increases as the sample size increases.

• Small studies scatter more widely at the bottom of the graph.

• In the absence of bias the plot should resemble a symmetrical inverted funnel.
Publication Bias
Poor methodological quality

• Smaller studies are, on average, conducted and analyzed with less methodological rigor than larger studies.

• Trials of lower quality also tend to show larger treatment effects
Any question?