Information summary for the *Introduction to Systematic Review and Meta-Analysis of Animal Studies* workshop

Contents

Introduction

Why are Systematic Reviews important?

Systematic reviews (SR) use **transparent and robust methods** to **reduce bias** in identifying, summarizing, presenting, interpreting, and reporting research evidence. SRs can help identify knowledge gaps, resolve inconsistencies, identify strengths and weaknesses to inform future research and provide more reliable evidence than single studies. SRs are routinely performed in the clinical field where they form the cornerstone of evidence-based medicine, while SRs of preclinical data is still not so common, although being equally important for decision-making (e.g. when deciding which treatment to move forward to clinical trials).

To find out more how SRs can be used to benefit future research check the references in slides 35-54 at https://osf.io/8p69m

SR steps:

1. Defining a research question
2. Protocol development
   a. Specify research question and eligibility criteria
   b. Specify search strategy
   c. Specify study details to extract
   d. Specify how study quality will be assessed
   e. Specify how results will be synthesized and presented
   f. Specify methodology and software used for all steps
3. Systematic search strategy
   a. Identify all relevant research
4. Study selection
   a. Screen studies for inclusion
5. Assessing study quality
   a. Assessing the reporting of measures to reduce risk of bias
6. Data extraction from included studies
   a. Study design characteristics
   b. Numerical data from tables or figures
7. Synthesis
   a. Qualitative synthesis
   b. Meta-analysis
8. Reporting

Find out more at:

Gough, D., Oliver, S., & Thomas, J. (Eds.). (2017). *An introduction to systematic reviews*. Sage.

Research question

The most widely used format for defining a research question is the PICO format

P – population or problem

      • What are the characteristics of the population (species, sex, comorbidities, etc.)?

      • What is the condition modelled or disease of interest (e.g., stroke)?

I – intervention or exposure

      • What is the intervention or exposure under consideration for this population?

C – comparison

      • What is the alternative to the intervention (e.g. vehicle, alternative drug, sham surgery)?

O – outcome

      • What are the relevant outcomes (e.g. neurobehavior score, change in clinical status, morbidity, adverse effects, complications)?

Find out about alternative question structures at:

Davies, K. S. (2011). Formulating the evidence based practice question: A review of the frameworks. Evidence Based Library and Information Practice, 10(3), 68-78

Protocol development

A SR protocol describes the rationale, hypothesis, and planned methods of the review. It helps to avoid unplanned duplication and reduce bias by enabling comparison of reported SR methods and outputs with what was planned.

PRISMA and SYRCLE are commonly used guidelines for protocol development of preclinical SR. The appropriate guideline to adhere to will depend on your research question and type of SR you want to perform.

It should be prepared **before** a review is started and used as a guide to carry out the review.

Important!

1. **(Pre)Register** your protocol (eg. on [PROSPERO](#) or [Cohrane](#))
2. Make your protocol **publicly available** (eg. on [OSF](#))

Search strategy development

1. Select databases and other data sources to search (PubMed, Embase, PsycINFO, etc.)

   Database selection will depend on your SR topic and journal coverage; you should search **more than one database** for adequate and efficient coverage!

   Additional sources: preprints (eg. BioXriv), grey literature, reference lists…

2. Select search terms based around the main concepts in your research question (if PICO, focus on P and I)

   Use keywords or synonyms for elements of your research question and database specific index/subject headings (MeSH terms, Emtree)

   Use Boolean operators (*And, Or, Not*; be careful when using *Not*, you might exclude relevant studies!)

3. Compile search strings

Each database uses a different syntax and subject headings, so you will need to write a separate search strategy for each database

To help you translate the syntax between databases check out https://sr-accelerator.com/#/polyglot (**NOTE: does not translate subject headings!**)

We aim to maximize search sensitivity while attempting to maximize precision!

A sensitive search:	A precise search:
+ retrieves most relevant literature	**+** retrieves some relevant literature
+ risk of missing relevant literature is low	**+** retrieves fewer irrelevant results = less time filtering and screening
− retrieves higher proportion of irrelevant literature = more time filtering and screening	**−** risk of missing relevant literature is high

Identifying relevant studies/Screening for inclusion

1. Examine your PICO research question

2. Consider what constraints you want to specify surrounding each of the PICO elements

3. Consider additional restrictions regarding Language, Date, Publication Type, Study Design

4. At least 2 independent screeners should agree if the study is excluded/included. Consider a third screener to arbitrate if an agreement can't be reach
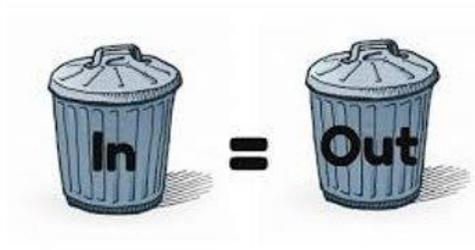
To report your screening decisions use the PRISMA flow diagram

Examples of screening tools: SyRF, EPPI-Reviewer, SysRev, Rayyan

Assessing study quality

In the context of SR, study quality refers to **methodological quality** (how the study was done) and **reporting quality** (how well it was reported).

Understanding the **quality** of the evidence that goes in your SR is **vital** to the **interpretation** of your findings!

What makes a **good** experimental design?

• Hypothesis stated

• Controlled conditions

• Appropriate sample size

• Suitable statistical analysis

• Measures to **reduce the risk of bias**

Bias = systematic error introduced into the experiment that leads to distorted results

After screening/study selection, papers should be assessed for risk of bias by two independent reviewers (best practice to have discrepancies reconciled by a third reviewer)

Type of bias	Description	Reduced by
Selection bias	Systematic difference in baseline characteristics of groups at baseline	Randomisation (Allocation Concealment)
Performance bias	Systematic differences between groups in exposure to factors other than intervention of interest	Allocation Concealment (Blinding personnel)
Detection bias	Systematic differences between groups in how outcomes are determined	Blinded Assessment of Outcome
Attrition bias	Systematic differences between groups in the way drop-outs are handled	Reporting of Drop-outs

Illustrations of different types of bias and how they can impact internal validity can be found here

Selecting a tool for RoB will depend on your research question and type of SR.

RoB tools	Animal intervention	Clinical intervention	Diagnostic study	Prognostic study
SYRCLE	✔			
Cohrane RCTs		✔		
QUADAS-2			✔	
QUIPS				✔

other sources: https://www.equator-network.org/

You can use the results of your risk of bias assessment to:

• Conduct sensitivity analysis (quantitatively using meta-analysis, or qualitatively)

• Exclude studies at high risk of bias from the evidence synthesis. This should be done with caution and pre-specified in your protocol to avoid introducing bias

• Reach an overall conclusion for each outcome as to whether the synthesized result is at high risk of bias

• Use this overall conclusion to inform the overall assessment of the certainty of the evidence, for example using the GRADE approach

Data extraction

What type of data should be extracted for a SR? Depends on your research question, but in general consider:

1. Study design characteristics

    a. All relevant design related data you **pre-defined** in your **protocol**

        i. e.g. PICO information: sex/age/strain of animals, dose/timing/administration of drugs

2. Quantitative outcomes

    a. dichotomous (e.g. mortality)

    b. continuous (e.g. blood pressure)

Before starting data extraction make sure you:

- Plan in advance what data is needed
- **Pilot data extraction form** on several relevant studies
- Provide detailed instructions on how to extract data for your reviewers
- Ensure clear and consistent coding
    - Binary: T/F or Y/N or Reported/Not reported
    - Single choice: A, B, C or D
    - Drop-down lists of options
    - If necessary, free text input option
- Have a defined standardized plan on obtaining missing/additional data
    - Check supplementary materials, contact authors, pre-define response time

Important!

Dual data extraction by two independently working researchers is recommended to prevent errors

Tools for extracting data from graphs: Webplot digitizer, Universal desktop ruler

In-text statistical data: StatCheck

Data synthesis

There are two main ways to synthesize your SR data:

1. Descriptive/qualitative synthesis of main characteristics of reviewed studies

2. Meta-analysis

A **meta-analysis** is the statistical **combination of results** from two or more **separate studies**

Typically, a meta-analysis involves the following steps:

1. Calculate an effect size for each outcome within a study
    a. Mean difference, standardized mean difference, etc. (continuous outcomes)
    b. Odds ratio, risk ratio, etc. (dichotomous outcomes)
2. Combine effect sizes for each outcome
    a. Fixed effect model
    b. Random effects model
3. Investigate heterogeneity (pre-specified variables)
    a. Subgroup analysis
    b. Meta-regression

More information on conducting a meta-analysis can be found at:

Vesterinen HM, Sena ES, Egan KJ, Hirst TC, Churolov L, Currie GL, Antonic A, Howells DW, Macleod MR. Meta-analysis of data from animal studies: a practical guide. J Neurosci Methods. 2014

Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2009). Introduction to Meta-Analysis. John Wiley & Sons, Ltd.

Reporting of SR findings

Transparent reporting of your SR findings enables reproducibility and future updating. Check out PRISMA reporting guidelines, as well as extensions for different types of reviews. To evaluate the certainty of your findings you can use the GRADE approach. Some tools that are usually used for assessing the quality of SRs, like AMSTAR and ROBIS, can also help you in writing up your SR results.