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Risk of Bias in Systematic Reviews with Cost and Cost-Effectiveness Outcomes

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Guidance on cost and cost-effectiveness evidence

Guidances on evaluation or reporting of original cost or cost-effectiveness studies	Guidances on preparing the reviews of evidence	Guidances on evaluating the reviews of evidence
•CHEERS •CHEC •Drummond et al. •Jefferson et al.	•Cochrane •Centre for Reviews and Dissemination at York •PRISMA •Mathes et al.	•AMSTAR •OQAQ •Jefferson et al.

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What are we doing?

- The task force's **goal is to provide recommendations on reporting and evaluating the risk of bias of systematic reviews with cost or cost-effectiveness outcomes** and **various objectives**:

- Variability in outcomes
- Quality of evidence or methods
- Research gaps estimation
- Mixed (clinical & economic reviews)

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Objectives of the workshop

- To inform the ISPOR-membership on the latest developments and recommendations of the TF

- To raise the disputable points in the recommendations of the TF and receive a feedback from the ISPOR-membership

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Outline of the workshop

1. Planning the review and literature search; **Lena Mandrik**
2. Literature selection and validation; **Torbjørn Wisløff**
3. Literature extraction and synthesis; **Hans Severens**
4. Presentation and reporting; **Salah Ghabri**

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Q&A

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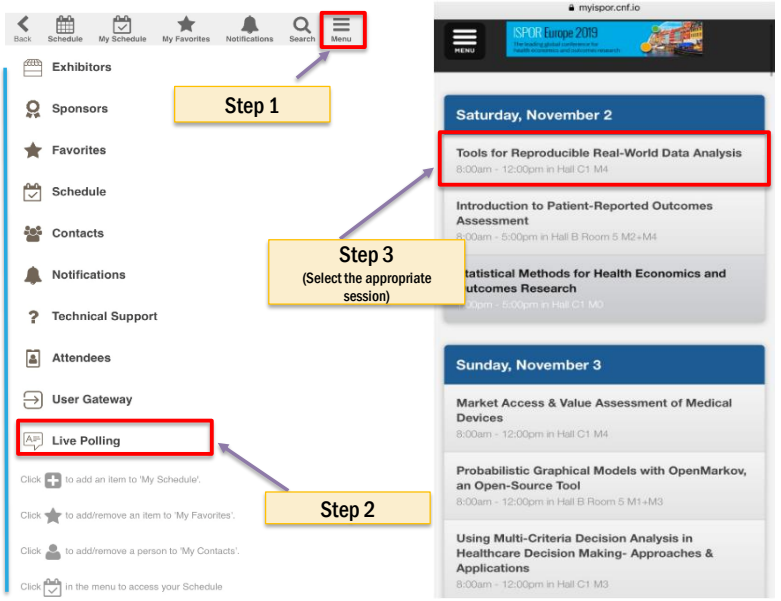

SECTION

1

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Planning the review and literature search

Planning the review (1): the protocol

Includes: (a) pre-established methods (b) reported deviations
Goals:
- Reporting bias
- Transparency

Potential concerns:
- False statements on protocol availablility
- Siginificant unreported deviations
- Difficult to compare the differences

Possible solutions:
- High confidence: publicly available (ex. publication, PROSPERO)
- Moderate confidence: registration and peer-review process (*ex. IRB approval)*

Planning the review (2): the aims and objectives

Potential concerns:

PICO is not applicable
Some components are missing
Obligatory elements depends on the reviews objectives

Possible solutions:

Obligatory elements	Advised elements
❖ **Population** ❖ **Outcome(s)** ❖ **Study design**	❖ Intervention(s) ❖ Comparator(s) ❖ Timeframe ❖ Stakeholder

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Search in systematic reviews (1)

Should be: targeted, sound, complete, and reproducible
Goal: Retrieve all (most) articles relevant to each of the objectives
Transparency

Potential concerns:

Time and resources available
Missed publications
Inconsistencies /low fit to objectives

Potential solutions:

- Involve information specialist or peer-review the search strategy
- Minimise inconsistencies and risk of bias if reusing the searches
- Justify if only 1-2 databases are searched
- Use objective-specific choice of databases and search-terms on either outcome:
  - Reviews with non-Global focus
  - Mixed reviews with clinical outcomes

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Search in systematic reviews (2)

Supplementary searching:

- Bibliography review (snowballing approach)
- Experts' opinion
- Grey literature

Useful resources:

PRESS guideline (McGowan, 2015): peer-review electronic search strategies
Search strategies:
Cochrane section 20 (Box 20.3.d, Box 20.3.e, Box 20.3.f);
Wood at el. (2017), doi: 10.1017/S0266462316000660

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Search in systematic reviews (3): how grey is grey literature?

The main grey literature sources:

- HTA reports (CRD York, BRISA, the WHO, etc)
- Theses/dissertations (EBSCO open Dissertations, ProQuest Dissertations & Theses)

The concerns: Conference abstracts

Pros:

- Missed information
- Publication bias

Cons:

- Insufficient reporting
- Quality/consistency

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Poll: Should conference abstracts be recommended as a source of grey literature for systematic reviews of costs or cost-effectiveness outcomes?

Final remark

- The methodological approach to searching is similar to clinical reviews
- Important differences are in objectives/ search terms and recommendations for grey literature
- The most challenging design is of the reviews reporting both effects and cost

SECTION

2

Literature selection and validation

Selection of evidence (1)

- Includes: Screening of titles, abstracts and full-texts
- Goals:
  - Transparency
  - Include all relevant studies
- Trade-off:
  - Time and resources available
- Potential problems:
  - Including studies that shouldn't be included
  - Excluding studies that should be included
- Possible solutions:
  - Sensitivity analysis including excluded studies

Selection of evidence (2) – possible restrictions

- Publication date
  - Advantage: may increase generalizability if things have changed
- Country / region
  - Limits generalizability
  - Increases internal validity if the scope of the review is local
- Language
  - May bias outcomes

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Validation / assessment (1)

- Evaluate study validity, generalisability and transferability
- Describe methods, assumptions, models and potential biases
- Provide a qualitative description and critique of the evidence base
- Differentiate between piggy-back and model-based economic evaluations

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Validation / assessment (2)

- Useful tools:
  - BMJ checklist (Drummond 1996)
  - CHEC list (Evers 2005)
  - Philips checklist (Philips 2004, 2006)
  - CHEERS (Husereau 2013)
  - ECOBIAS (Adarkwah 2015)
  - Second panel on cost-effectiveness (Sanders 2016)

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Poll: Should all steps of the selection process be duplicated?

SECTION

3

Literature extraction and synthesis

Assessment of methodological quality

- Validity
- Generalizability and transferability

A standard check-list should be chosen and justified for reporting of methodological reviews, cost effectiveness or costing studies.

- British Medical Journal Checklist f (Drummond 1996)
- CHEC list (Evers 2005)
- CHEERs (Husereau 2013)
- Second Panel on Cost-Effectiveness checklist (Sanders, 2016)
- ECOBIAS (Adarkwah et al, 2015)
- Phillips checklist (Philips 2004, 2006).

At least two reviewers should assess the quality of studies independently.

Assessing risk of bias in original evidence

- The study design (partial vs full EE, trial-based (piggyback EE) or model-based).
- Type and quality of the underlying effectiveness data (e.g. trial data, observational data, meta-analysis).
- Non-methodological aspects (authors, year of publication, country/jurisdiction, type of condition, type of intervention, funding, etc.)
- Other methodological aspects of the study (objective, perspective, scoping, comparators, health effects, sources of cost data, inclusion of indirect costs, time horizon, utilities, discount rate, incremental analysis, sensitivity analysis, discussion/recommendations, generalizability)

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Homogeneity / heterogeneity (1)

- Guiding questions (e.g., check boxes) to assess homogeneity:
  - patients comparable
  - interventions comparable
  - study designs/modelling comparable
  - country/jurisdiction
  - Etc
  - Etc

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Synthesis of data

- Possible approaches:
  - (structured) narrative synthesis
  - graphical synthesis (e.g., cost-effectiveness diagram, permutation matrix)
  - quantitative synthesis/meta-analysis.
- There is no best way to synthesize economic evidence.
- The “right” approach depends on the degree of context/setting, clinical, and methodological heterogeneity in the studies:
  - More heterogeneous → narrative synthesis/comparison more appropriate
  - More homogeneous → quantitative methods approprioate that treat numeric estimates from each study as directly comparable

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Synthesis

- Costs:
  - same currency
  - expressed in the same year
  - inflation adjusted
  - report original data (!)
- Separate synthesis in subsections (either narrative or quantitative):
  - modelling and piggyback studies
  - probabilistic and deterministic results
  - sensitivity analysis

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Poll: When is meta-analysis in cost-effectiveness reviews appropriate?

Homogeneity / heterogeneity (2)

- Heterogeneity will imply that pooling such results is not appropriate.
- Only studies considered sufficiently homogeneous regarding contexts, settings, jurisdiction, administrative areas should be synthesized together.

Narrow or broad SR?

- Single/main synthesis is only applicable for narrowly focused SRs.
- SRs with a broad scope, applicable to many jurisdictions:
  - report the results for homogeneous subgroups
  - consciously selected, ideally based on predefined criteria.

SECTION

4

Presentation and reporting

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How Economic outcomes should be presented (1)?

- Economic outcomes should be reported in **summary table(s) → BOX 1**
  - **A minimum of outcomes** should be presented
    - **SRs of CEA**
      - Outcomes of interest (e.g. total costs, life years, quality adjusted life years (QALYs) should be reported for each included study.
    - **SRs of costs**
      - type of costs and costs valuation (volumes and prices separately) should be reported for each included study. Cost and health outcomes should be presented separately for each strategy within each study

How Economic outcomes should be presented (2)?

- **BOX 1: Example of summary table**

1.Countries
2. Population of analysis
3. Time horizon, perspective
4. Adjustment of inflation, Discount rate
5. Interventions compared
6. Method(s) for valuation of economic outcomes
(a) Direct cost(s) (according to the horizon of interest)
(b) Indirect costs (ex. productivity loss)
7. Method(s) for valuation of effectiveness outcomes including source, type of source, estimates, duration
8. Compliance/adherence with treatment
9. Decision analytic modeling or approach to calculation of economic outcomes
10. ICER and health outcomes (e.g. gained life years, number of death avoided, QALY)
11. Uncertainty (e.g. parametric and probabilistic uncertainty)
12. Heterogeneity (e.g. sub-populations analysis)
13. Conflicts of interest and sources of funding
14. Ethical and/or equity consideration
15. Software

How reporting of outcomes should be done ?

- **A compromise** of reporting should be found between both reported outcomes in **summary tables** and their **narrative description** in small paragraphs
  - Page limitations → appendices/supplementary material
- **Extended reporting** is useful for specific studies types:
  - **complex economic decision models**:
    - model type and characteristics
    - model validation
    - most influential parameters affecting uncertainty

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How assessment of potential SR-bias should be reported ?

- The authors of SR should assess the impact of any potential bias related to findings of the conducted review:
  - **conflict of interests**
  - **study funding and**
  - potential factors explaining differences between studies

- The authors of SR should provide an explanation for any heterogeneity observed in the results of the review

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Poll: How publication bias should be assessed in cost and cost-effectiveness reviews?

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Poll: Should authors of cost and cost-effectiveness reviews assess transferability of the included studies to the context of a review?

Objectives of the workshop

- To inform the ISPOR-membership on the latest developments and recommendations of the TF
- To raise the disputable points in the recommendations of the TF and receive a feedback from the ISPOR-membership
  - Abstract as grey literature?
  - Duplicated selection process?
  - Meta-analyses and pooling of data?
  - Assessment of publication bias?
  - Transferability to the context of a review

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ISPOR Task Force

How to JOIN our Task Force Review Group

- Go to the Website
  - Member Groups
  - Task Forces
  - Click on Join a Review Group
  - Expected review March 2020

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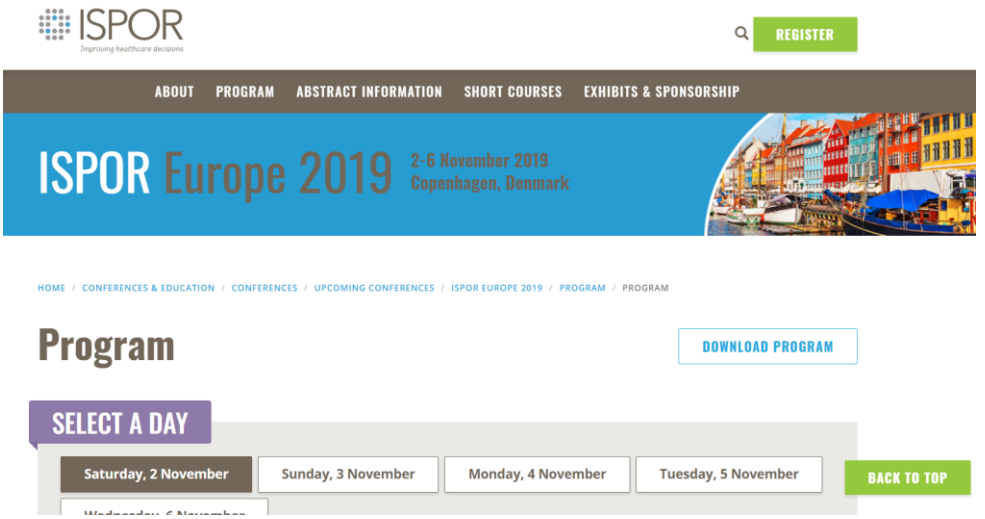
Slides are available on the ISPOR Europe 2019 webpage under program.



Open-ended questions for discussion

Is artificial intelligence tested enough for references screening to be included in the task force report?

Should recommendations on search in social networks be included in the task force report?

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