Including non-randomized studies in systematic reviews

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Evidencia fiable.
Decisiones informadas.
Mejor salud.
Aim of this presentation

To discuss the challenges raised by the inclusion of non-randomized studies in systematic reviews of the effects of healthcare interventions.
Sources used to develop this presentation

- The Cochrane Non-Randomized Studies for Interventions Methods Group


- Special Issue: “Research synthesis methods”, 2013, 4
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Common misconception:

“Cochrane is opposed to including studies other than RCTs in systematic reviews”
1. Cochrane reviews do not always include RCTs

- Diagnosis reviews
- Prognosis reviews
- Qualitative reviews
2. Cochrane: open to including studies other than RCTs

• “NRS can contribute important information and, in principle, should be considered for inclusion in a review”


• Some Cochrane groups have included NRS in their reviews
Cochrane: not opposed to include NRS in the reviews

First Cochrane reviews:
focused on the **potential benefits** of the interventions

First Cochrane reviews tended to include RCTs only
RCT: study design of choice to determine the benefits of healthcare interventions

Emprirical evidence


TRIALS

- Randomized
- Allocation concealment

More likely to provide unbiased information than other study designs
Cochrane reviews of interventions

Balanced information about the intervention effects

Benefits

Harms

Frequent

Rare

Long-term

RCTs

Non-randomized studies

Cochrane Handbook, Box 5.4.a
Cochrane Handbook, chapter 13
NOT OPPOSED to include non-randomized studies in the reviews
## Contents

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Steps of a systematic review

1. Question formulation
2. Plan study eligibility criteria
3. Plan methods
4. Search for studies
5. Apply eligibility criteria
6. Collect data
7. Assess studies risk of bias
8. Analyse and present results
9. Interpret results and draw conclusions
10. Update the review
Eligibility criteria for non-randomized studies (NRS)

1. Justify the inclusion of NRS
   a. Accepted justifications
   b. Poor justifications

2. Define explicitly which NRS will be eligible
a. Accepted justifications to include NRSs

1. **Interventions** that cannot be randomized, or which are extremely unlikely to be randomized.

2. **Outcomes** that cannot be adequately studied in randomized trials, such as:

   - Long term outcomes
   - Rare outcomes

3. **To examine the case for undertaking a randomized trial** by providing an explicit evaluation of the weaknesses of available non-randomized studies.
b. Poor justifications to include NRSs

1. To study the effects of the intervention in patients not recruited to randomized trials.
b. Poor justifications to include NRSs

1. To study effects in patients groups not recruited to randomized trials (such as children, pregnant women, the elderly).

2. To supplement existing randomized trial evidence.

3. When an intervention effect is really large.
Eligibility criteria for NRS

1. Justify the inclusion of NRS

2. Define explicitly which non-randomised studies will be eligible
There are many “study designs labels”, such as:

- Non-randomized controlled trial
- Controlled before-and-after study
- Interrupted-time-series study
- Historically controlled study
- Cohort study
- Case-control study
- Cross-sectional study
- Case series
Study design labels: not explicit & inconsistently used

Quasi-experimental study = Quasi-randomized trial?

An interrupted time series design is an observational design?

What is a prospective cohort study?
Describe which types of non-randomised studies will be included

1. Avoid using study design labels only

2. Describe explicit study design features
Study design features

1. Unit of allocation?
2. Was there a comparison?
3. How were groups created?
4. Which parts of the study were prospective?
5. On which variables was comparability [between groups receiving different interventions] assessed?

Cochrane Handbook chapter 13

Table 13.2a y Table 13.2b
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Searching methods for...

Randomized studies
- Validated methodological filters
- Registers of RCTs
  - Efficient

Non-randomized studies
- Rare methodological filters
- Rare registers of NRSs
  - Efficient
Steps of a systematic review

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Applying selection criteria for non-randomized studies

- No search filters
  - \( \uparrow \) Nr. irrelevant results

- Design description: not clear/not consistent
  - Titles & Abstracts
    - \( \uparrow \) Nr. full texts
  - Full reports
    - \( \downarrow \) reproducibility decisions

\( \uparrow \) Costs
\( \uparrow \) Time
Not consistent definitions for non-randomized designs

Validated tools to classify NRS are needed

- Cochrane Handbook, Chapter 13
- Cochrane EPOC group (http://cort.as/eYHN)
- Hartling et al. Agency for Healthcare Research and Quality (http://cort.as/eYHY)
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Data extraction more complex: additional items to extract

- The **confounding factors** considered.

- The **comparability of groups** on confounding factors.

- Methods used to **control for confounding**.

- Multiple **effect estimates**:
  - Unadjusted estimates
  - Adjusted estimates
Need to customize the data extraction form to each study design
New software to develop systematic reviews

www.covidence.org

Controllled before-and-after design?
### Steps of a systematic review

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a. Protocols for observational studies: unfrequent

- A study protocol is a tool to protect against bias

- The protection offered by a protocol often does not exist for NRSs
b. Worse reporting of non-randomized studies

As systematic reviewer, you depend on the quality of reporting to assess risk of bias

STROBE statement (2007)

The quality of reporting for NRS is likely to be worse, as compared to RCTs

Makes risk of bias assessment more difficult
c. Cochrane tool: The ROBINS-I tool

• “Risk Of Bias In Non-randomized Studies - of Interventions”

• https://sites.google.com/site/riskofbiastool/home

• Based on the Cochrane Risk of Bias tool for randomized trials

• To be launched soon
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A transparent, explicit and rigorous system to classify ...

- The quality of the evidence: Cochrane reviews
- The strength of recommendations: Guidelines
## Summary of findings table

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality of the evidence (GRADE)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
<th>Risk difference with Heparin (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>![GRADE icon] MODERATE due to inconsistency</td>
<td>RR 0.93 (0.85 to 1.02)</td>
<td>Moderate</td>
<td>45 fewer per 1000 (from 97 fewer to 13 more)</td>
</tr>
<tr>
<td>Symptomatic VTE</td>
<td>![GRADE icon] HIGH</td>
<td>RR 0.55 (0.37 to 0.82)</td>
<td>Moderate</td>
<td>13 fewer per 1000 (from 5 fewer to 18 fewer)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>![GRADE icon] MODERATE due to imprecision</td>
<td>RR 1.3 (0.99 to 1.70)</td>
<td>Moderate</td>
<td>2 more per 1000 (from 3 fewer to 13 more)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>![GRADE icon] MODERATE due to imprecision</td>
<td>RR 1.05 (0.75 to 1.46)</td>
<td>Moderate</td>
<td>1 more per 1000 (from 7 fewer to 12 more)</td>
</tr>
<tr>
<td>Health related quality of life</td>
<td>![GRADE icon] LOW* due to risk of bias, imprecision</td>
<td>Not calculable* See*</td>
<td>-</td>
<td>-</td>
</tr>
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*The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio.

**GRADE Working Group grades of evidence**

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

1. Vast majority of studies had allocation concealment, and used blinded outcome and adjudication. We did not downgrade although there was some concern about lack of blinding in some studies; the overall risk of bias was felt to be very low.
2. There is moderate heterogeneity among studies included in the analysis of death at 12 months (I² = 35%). The subgroup analysis for mortality at 12 months was statistically significant and suggested survival benefit in patients with SCLC but not in patients with advanced cancer. Overall we decided to downgrade by one level when considering these issues along with imprecision.
3. CI interval includes effects suggesting benefit as well as no benefit.
4. CI includes possibility of both harms or benefits. * The scores for the 2 scales were similar for the 2 study groups, both at baseline and at follow-up. * High risk of bias and only 135 patients enrolled.
### Quality of the evidence for each systematic review outcome

<table>
<thead>
<tr>
<th>Study design</th>
<th>Initial quality of the evidence</th>
<th>↓ Quality of evidence</th>
<th>↑ Quality of evidence</th>
<th>Final quality of the evidence</th>
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<tr>
<td>RCTS</td>
<td>High</td>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Observational studies</td>
<td>Low</td>
<td></td>
<td></td>
<td>Low</td>
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#### Factors that can affect the quality of evidence:

- **Risk of bias**
  - `-1`: Serious
  - `-2`: Very serious

- **Indirectness**
  - `-1`: Serious
  - `-2`: Very serious

- **Inconsistency**
  - `-1`: Serious
  - `-2`: Very serious

- **Imprecision**
  - `-1`: Serious
  - `-2`: Very serious

- **Publication bias**
  - `-1`: Likely
  - `-2`: Very likely

- **Large effect**
  - `+1`: Large
  - `+2`: Very large

- **Dose response.**
  - `+1`: Present

- **Residual confounding**
  - `+1`

- **Impression**
  - `-1`: Likely
  - `-2`: Very likely

- **Publication bias**
  - `-1`: Likely
  - `-2`: Very likely
## Publication bias: one domain to assess the quality of the evidence

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### Risk of bias
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### Large effect
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- **+2:** Very large

### Imprecision
- **-1:** Serious
- **-2:** Very serious

### Dose response
- **+1:** Present

### Residual confounding
- **+1**

### Publication bias
- **-1:** Likely
- **-2:** Very likely
Publication bias

- Statistically significant
- Favourable findings
- Unpublished studies

Source: Matthias Egger & Jonathan Sterne
All Trials Registered | All Results Reported

Launched in January 2013

http://www.alltrials.net/find-out-more/videos/

Sign the petition

87,948 people
650 organizations
Publication bias: a challenge for non-randomized studies

• It is known that it is relevant for randomized trials

• It may be relevant for non-randomized studies (maybe, even more relevant than for RCTs)

• The likely magnitude and determinants for publication bias in non-randomized studies are not known.

Cochrane Handbook chapter 13
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01 Common misconception
02 Challenges derived from the inclusion of NRSs
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Are you still thinking of including non-randomized studies in your systematic review?
If you have decided to include non-randomized studies in your systematic review

KEEP CALM AND ASK FOR HELP
Thank you very much

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