How well are Cochrane reviews incorporating non-randomised studies of interventions (NRSI)?

Lessons learnt from a scoping review

Emma Axon, Cochrane Methods Support Unit (MSU)

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Authors on the project

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Funding and declarations of interest

This project was not funded.

The author team are all employed by Cochrane.

Scoping review is currently under review by an academic journal.

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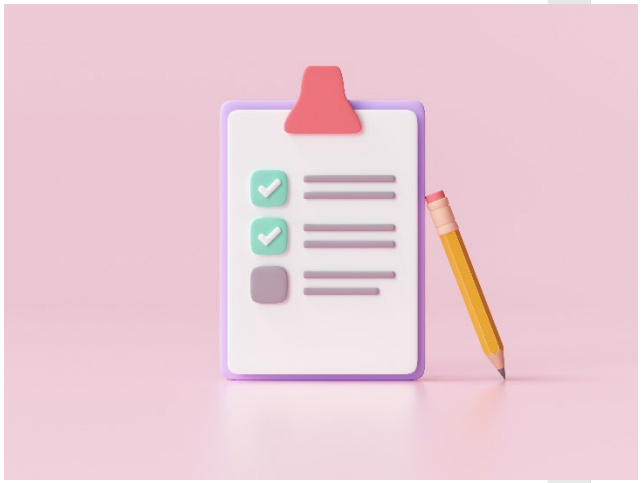

Structure of the session

- Introduction to non-randomised studies.
- Rationale for conducting the project.
- Scoping review methods.
- Scoping review findings.
- Lessons learnt and steps moving forward.
- Questions and feedback from the audience.

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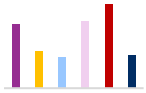
POLL 

Which best describes your role?

1) Researcher/Systematic reviewer
2) Methodologist
3) Statistician
4) Editor
5) Other

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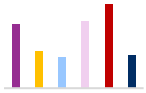

How familiar are you with non-randomised studies of interventions?

1) I know a lot about them and why they can be important in Cochrane reviews.
2) I have some understanding but would like to know more.
3) I'm not very familiar with them.

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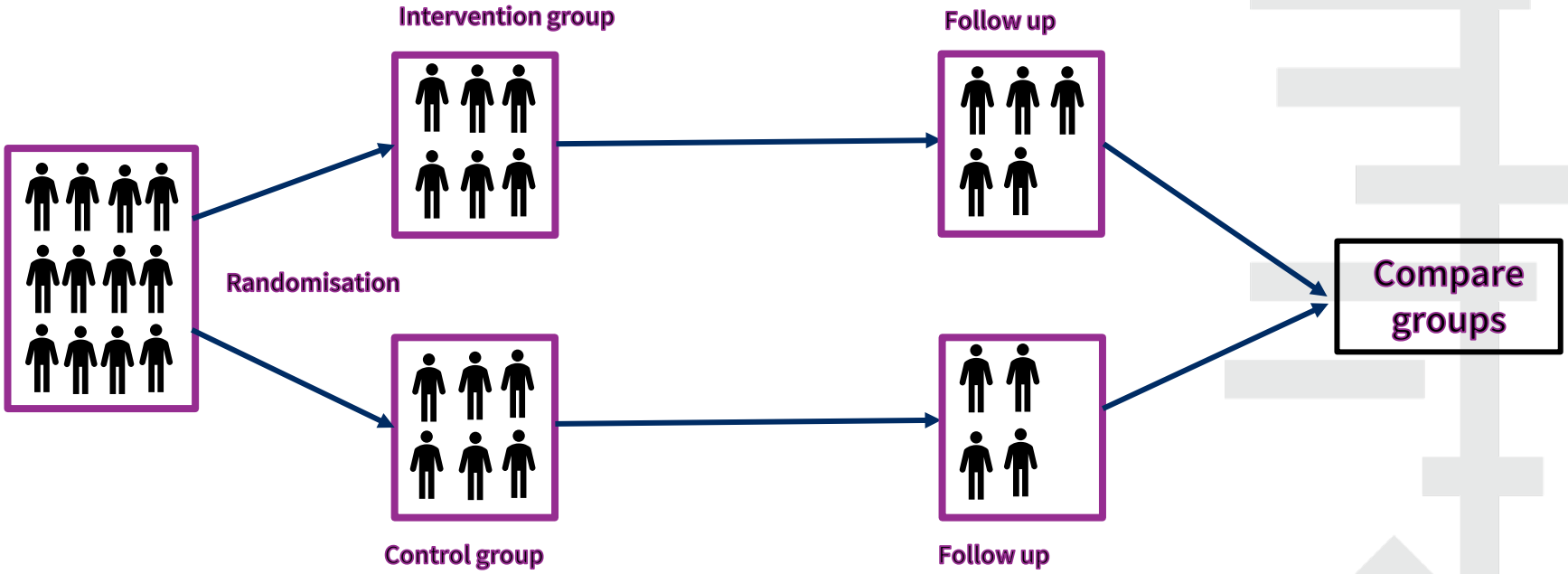
Randomised controlled trials (RCTs)



Randomised controlled trials (RCTs)

- If randomisation is successful, it should avoid influence of known and unknown prognostic factors at baseline.
  - Prognostic factors predict the outcome and may include severity of disease, age, BMI, ethnicity.
  - Imbalance in prognostic factors may lead to bias – 'confounding'.

✓ Therefore, referred to as the 'gold standard'.

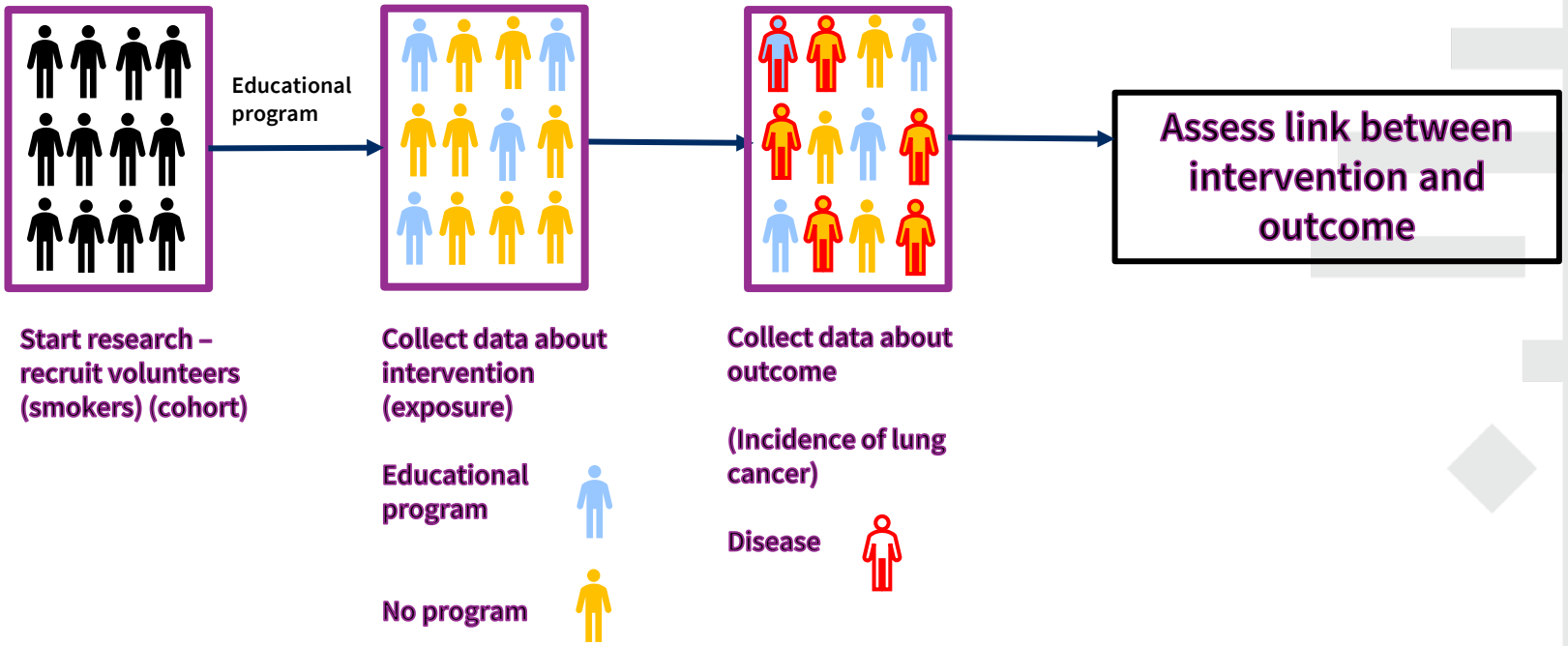
https://training.cochrane.org/handbook/current/chapter-03#a-33-determining-which-study-designs-to-include
https://training.cochrane.org/handbook/current/chapter-08#section-8-3

Non-randomised studies of interventions (NRSI)

- *"…as any quantitative study estimating the effectiveness of an intervention (harm or benefit) that does not use randomization to allocate units (individuals or clusters of individuals) to intervention group".* (Cochrane Handbook, chapter 24)
- Important to providing valuable insights to the real-world performance of interventions, especially in the absence of RCTs.
- Important for long-term or rare outcomes.
- In research areas where it's unethical or unfeasible to randomised participants.

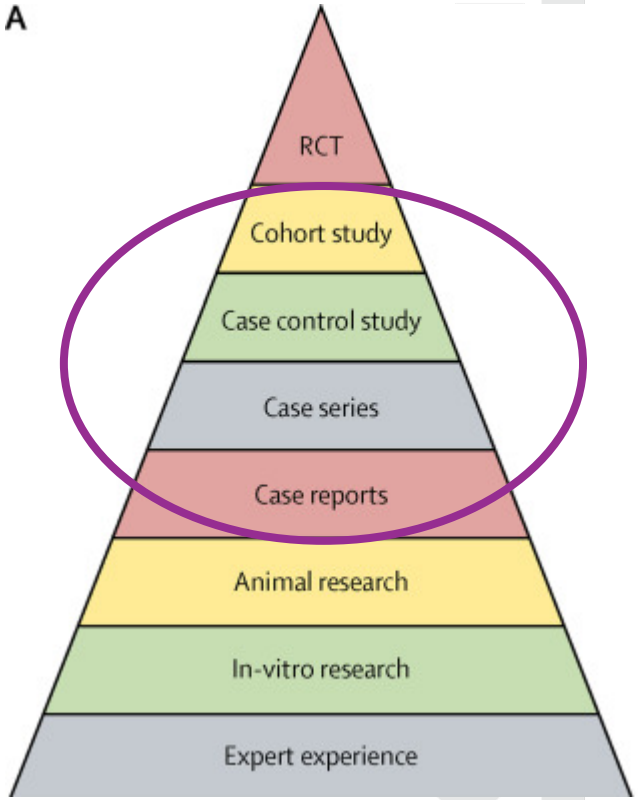
https://training.cochrane.org/handbook/current/chapter-24

Prospective cohort study design (effects of an intervention)



Non-randomised studies of interventions (NRSI)

- Confusion with terminology!
- Study labels generally used:
  - Cohort
  - Case-control
  - Cross-sectional
  - Controlled before-and-after studies
  - Uncontrolled before-and-after studies
  - Interrupted-time-series
  - Quasi-randomised studies
  - Instrumental variable analysis
  - Case series and reports



Djulbegovic, B et al. 2017. The Lancet, 390(10092), 415-23

https://training.cochrane.org/handbook/current/chapter-24

Non-randomised studies of interventions (NRSI)

- Cochrane Handbook recommends using study features rather than study labels for the inclusion criteria and analysis plan.

Box 24.2.a Checklist of study features. Responses to each item should be recorded as: yes, no, or can't tell (Reeves et al 2017). Reproduced with permission of Elsevier

1. Was the intervention/comparator (answer 'yes' to more than one item, if applicable):

   - allocated to (provided for/administered to/chosen by) individuals?
   - allocated to (provided for/administered to/chosen by) clusters of individuals?[a]
   - clustered in the way it was provided (by practitioner or organizational unit)?[b]

2. Were outcome data available (answer 'yes' to only one item):

   - after intervention / comparator only (same individuals)?
   - after intervention/comparator only (not all same individuals)?
   - before (once) AND after intervention/comparator (same individuals)?
   - before (once) AND after intervention/comparator (not all same individuals)?
   - multiple times before AND multiple times after intervention/comparator (same individuals)?
   - multiple times before AND multiple times after intervention/comparator (not all same individuals)?

https://training.cochrane.org/handbook/current/chapter-24

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Why did we decide to conduct a scoping review, looking at how well Cochrane reviews have handled NRSI?

Cochrane's Scientific Strategy 2025 to 2030

Four research priorities:

- Maternal, newborn and child health
- Multiple chronic conditions
- Infectious diseases
- Climate change and sustainability

Four commitments:

- Innovate in methods
- Promote health equity
- Collaborate and involve
- Champion research integrity

https://www.cochrane.org/about-us/scientific-strategy

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Scoping review - Aim

- To conduct a scoping review to see how closely Cochrane review authors are adhering to Cochrane handbook guidance when incorporating non-randomised studies of interventions.

- ✓ This will help identify areas which review authors require further guidance.

Scoping review – Areas of interest

- What percentage of Cochrane reviews during 2019 and 2023 planned to and/or included NRSI?
- What were the characteristics of these reviews? E.g. how many NRSI and RCTs were included, was inclusion of NRSI planned in the protocol?
- Did authors follow the guidance in the Cochrane Handbook, Chapter 24? E.g. Did they justify including NRSI, were potential confounders specified?
- How were NRSI analysed? E.g. in a meta-analysis or a narrative synthesis using SWIM methods.
- How did authors present results from NRSI in the 'Summary of Findings tables'? Was GRADE used?
- Which risk of bias assessments tools were used? E.g. ROBINS-I.

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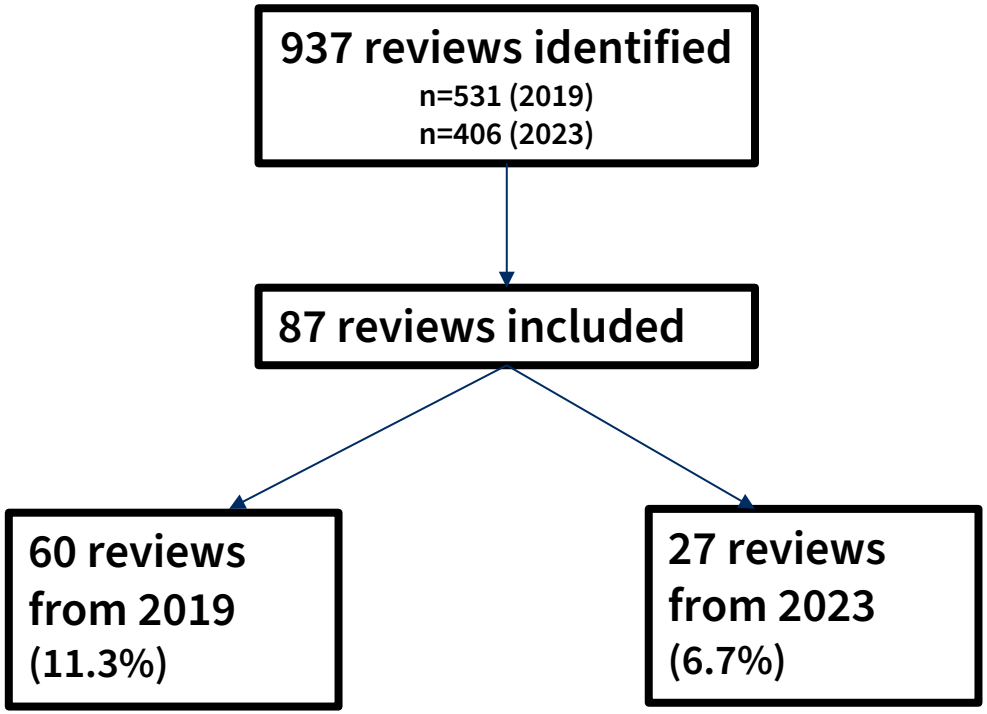
Scoping review - Methods

- Protocol uploaded onto an online repository before search conducted (March 2024).
- Cochrane systematic reviews published in 2019 or 2023.
- Only intervention reviews (e.g. not diagnostic test accuracy, overview of reviews).
- Planned to include NRSI – ‘formally’ or ‘informally’.
- Excluded reviews which only included quasi-RCTs.

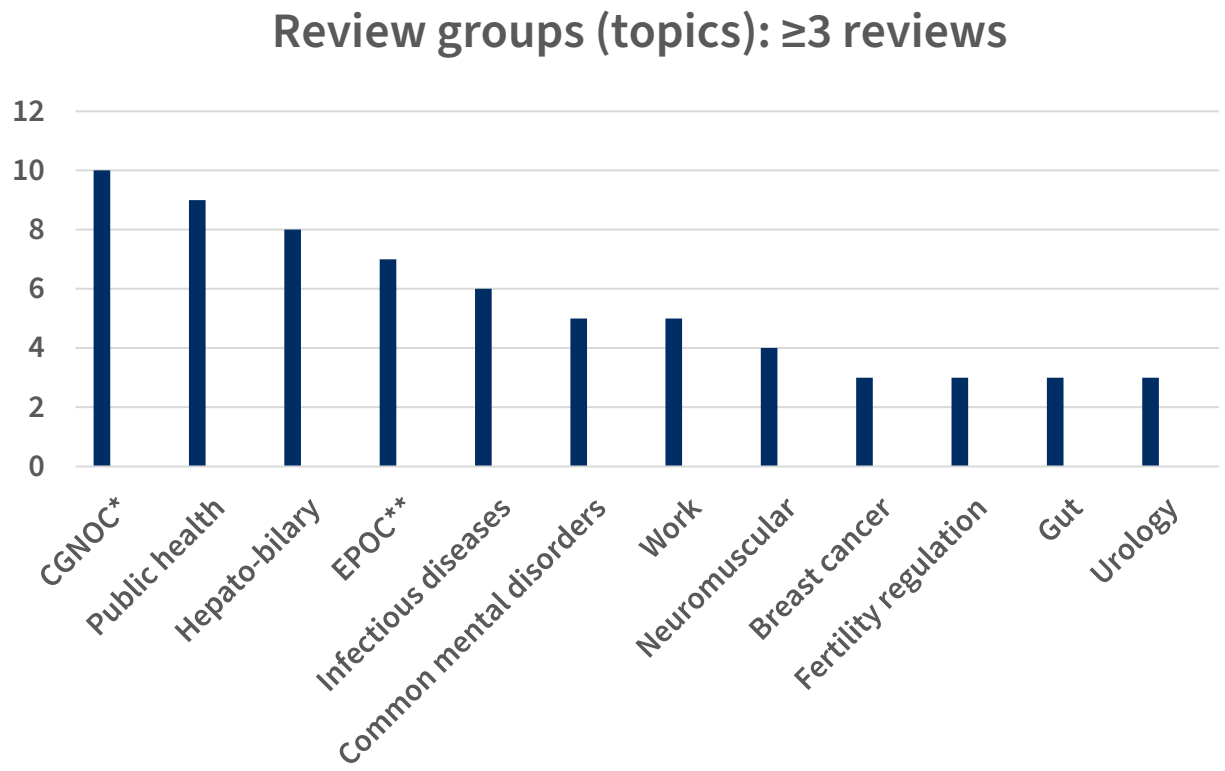
Scoping review - Methods

- Used Rayyan software for screening.
- Screened all reviews in duplicate by two authors.
- Piloted the data extraction form.
- Data extraction of each review conducted by one author.
- Uncertainties discussed as a team.
- Data extractions added to Excel Spreadsheet to produce descriptive statistics.
- Figures created in Rstudio.

Scoping review - Results



Scoping review - Results



*Cochrane Gynaecological, Neuro-oncology and Orphan Cancers
**Cochrane Effective Practice and Organisation of Care

Scoping review - Results

- Across **87 reviews**, **583 RCTs** and **763 NRSIs** were included.

	Mean (per review)	Range
Number of studies (all study designs)	**15**	**0 to 182**
Number of RCTs	**7**	**0 to 41**
Number of NRSI	**9**	**0 to 173**

- **Nine reviews** included zero studies (no RCTs or NRSI, empty reviews).

Scoping review - Results

- **72 reviews** planned to include NRSI for all outcomes.
- **13 reviews** only for adverse events.
- **2 reviews** for other specific outcomes only.

- **82 reviews** specified including NRSI in their protocol.
- **5 reviews** changed their protocol methods to include NRSI.

- **28 reviews** were updates.

Scoping review - Results

Handbook guidance	All reviews (n=87)	2019 (n=60)	2023 (n=27)
Justified including NRSI	36 (41%)	23 (38%)	13 (48%)

Scoping review - Results

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Used study features	36 (41%)	23 (38%)	13 (48%)
Prioritised adjusted effect measures	**25 (29%)**	**17 (28%)**	**8 (30%)**

Scoping review - Results

- **16 reviews** did not formally include NRSI – not included studies.
  - Only in discussion section, appendix, additional table etc.
- In addition, **23 reviews** identified no NRSI.

- Approaches to synthesis in the remaining **48 reviews:**
  - Meta-analysis and narrative summary/synthesis **(n=24)**
  - Narrative summary/synthesis **(n=22)**
  - No meta-analysis or narrative summary/synthesis **(n=2)**

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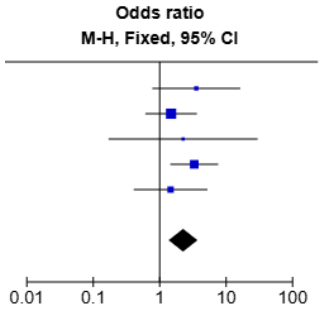

Scoping review - Results

Meta-analysis

- **24 reviews** included at least 1 meta-analysis, including NRSI.
  - **9 reviews** stated using adjusted measures – only **5 reviews** specified the covariates.

- **6 reviews** analysed RCTs and NRSI together.
  - **None** justified this approach.
  - Only **1 review** reported using adjusted variables.

- **6 reviews** analysed different NRSI study designs separately.
- **9 reviews** combined different NRSI study designs together.

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SWiM

Synthesis Without Meta-Analysis

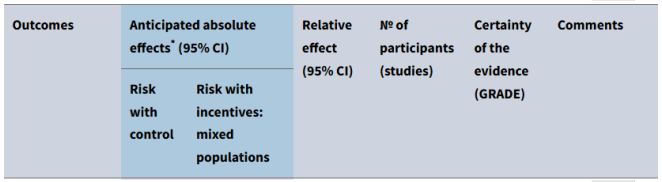
Scoping review - Results

Narrative summaries

- Where meta-analyses couldn't be conducted (includes single study forest plots).
- **46 reviews** included narrative summaries.

- **17 reviews** attempted a narrative synthesis.
  - Included presenting results in tables, harvest plots, direction of effect plots.

- Only **3 reviews** refer to SWIM guidance in their protocol/methods.



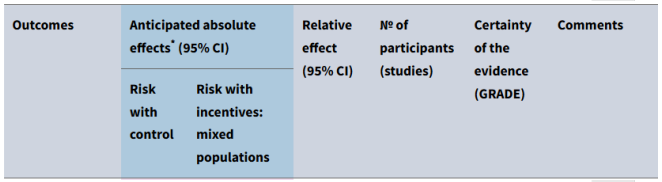
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with incentives: mixed populations				

Scoping review - Results

Summary of Findings (SoF) tables

- **5 reviews** detailed their approach to including different study designs in their protocol/Methods section:
  - RCT and NRSI evidence on separate rows **(n=2)**
  - RCT and NRSI evidence in separate tables **(n=2)**
  - Only include RCT evidence **(n=1)**

- **38 reviews** included NRSI evidence in at least one SoF table.



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Scoping review - Results

Summary of Findings (SoF) tables

- **20 reviews** included RCT and NRSI evidence for the same outcome:
  - Separate rows **(n=11)**
  - Separate SoF tables **(n=5)**
  - Footnotes **(n=2)**
  - Narrative summary at end of table **(n=1)**
  - Comments box **(n=1)**

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Scoping review - Results

Summary of Findings (SoF) tables

- **37/38 reviews** used GRADE to assess certainty of evidence.
- Mainly **very low certainty.**
- Downgraded mostly for study limitations (risk of bias).
- **2 reviews** upgraded evidence (large effect, dose response gradient).

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Scoping review - Results

RoB tools*	All reviews (n=87)	2019 (n=60)	2023 (n=27)
ROBINS-I	25 (29%)	12 (20%)	13 (48%)
EPOC	20 (23%)	14 (23%)	6 (22%)
None	17 (20%)	11 (18%)	6 (22%)
RoB 1/adaptation	13 (15%)	9 (15%)	4 (15%)
EPOC ITS adaption	10 (11%)	6 (10%)	4 (15%)
Newcastle-Ottawa	9 (10%)	9 (15%)	0
Other tools**	10 (11%)	10 (17%)	0

*Some reviews used more than one tool.

**Other tools included 'Downs and Black checklist' (3), Authors' own tool (1), Checklists for observational studies according to Evidence-Based Medicine Criteria (1), EPHPP (1), GRADE 'risk of bias' framework (1), Hayden 2013 study (1), Modified GATE tool (1)

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Conclusions and lessons learnt

- Reduction in reviews published in 2023 compared to 2019, and a **reduction in reviews including NRSI evidence.**
  - Closure of many UK Cochrane review groups.
  - High focus on COVID-19 pandemic reviews.
- **Adherence to Cochrane Handbook guidance was low.**
  - Not justifying inclusion of NRSI.
  - Too much focus on study design labels instead of study features.
  - Not prioritising adjusted measures and stating which variables were adjusted for.
  - Not listing potential confounders.

Conclusions and lessons learnt

Meta-analysis

- Not clear if adjusted effect measures were used.
- No justification for combining different study designs.

Narrative summaries

- SWIM guidelines not mentioned in most reviews published in 2023.
- More common to summarise data, instead of conducting a narrative synthesis.
- Limited by low number of studies (single study forest plots were common).

Conclusions and lessons learnt

SoF tables

- Most reviews didn't specify how they would deal with different study designs.
- Different approaches to handle outcomes which had both RCT and NRSI evidence.
- GRADE was used – mostly very low certainty (risk of bias).

Risk of bias assessments

- ROBINS-I only used in 48% in 2023 (20% in 2019).

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Next steps

- More specific guidance on how to incorporate NRSI evidence into Cochrane intervention reviews.
- Better signposting to currently available guidance.
- Development of guidance in different formats e.g. tutorial articles and webinars.
- Promotion of upcoming guidance, such as new GRADE guidance on incorporating RCT and NRSI into the same SoF table.

Resources

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Research Methods & Reporting

Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline

BMJ 2020 ; 368 doi: https://doi.org/10.1136/bmj.l6890 (Published 16 January 2020)
Cite this as: *BMJ* 2020;368:l6890

ROBINS-I tool

(Risk Of Bias In Non-randomized Studies - of Interventions)

Welcome to the website for the ROBINS-I tool (Risk Of Bias In Non-randomized Studies - of Interventions)

NEW 22nd November 2024: We are pleased to announce a revised version, ROBINS-I V2

Cochrane Training

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Chapter 24: Including non-randomized studies on intervention effects

Search Handbook

variants on randomized trials

Barnaby C Reeves, Jonathan J Deeks, Julian PT Higgins, Beverley Shea, Peter Tugwell, George A Wells; on behalf of the Cochrane Non-Randomized Studies of Interventions Methods Group

This Issue | Views 7,609 | Citations 224 | Altmetric 21

Guide to Statistics and Methods | Reporting Guidelines

April 7, 2021

MOOSE Reporting Guidelines for Meta-analyses of Observational Studies

Benjamin S. Brooke, MD, PhD[1]; Todd A. Schwartz, DrPH, MS[2,3]; Timothy M. Pawlik, MD, MPH, PhD[4,5]

» Author Affiliations

JAMA Surg. 2021;156(8):787-788. doi:10.1001/jamasurg.2021.0522

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Chapter 12: Synthesizing and presenting findings using other methods

Joanne E McKenzie, Sue E Brennan

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Thank you for listening.

Any questions?