Cochrane Methods
NRS for Interventions

University of BRISTOL

How Cochrane's decision to include non-randomized studies has led to important methods research

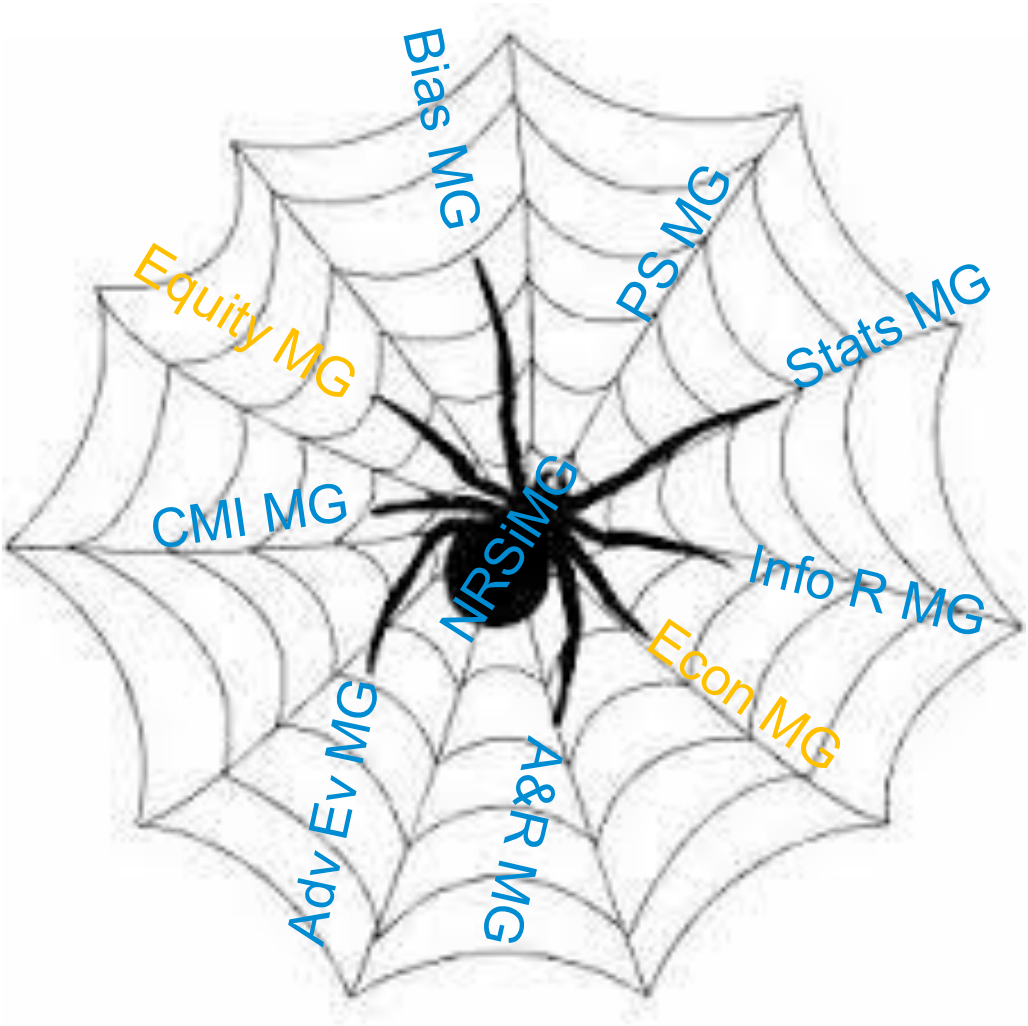
Barney Reeves

Trusted evidence.
Informed decisions.
Better health.

Cochrane Methods
NRS for Interventions

University of BRISTOL

Methods research setting



Cochrane Methods
NRS for Interventions

University of BRISTOL

Cochrane's position about NRSi

- Cochrane has always recognised that NRSi can contribute important information [Oxman et al.,1994]
- "We (Cochrane) gather and summarize the best evidence from research to help you make informed choices about treatment." [www.cochrane.org/about-us]
- NRSiMG recommendation: Review authors should formally consider whether NRSi are necessary to answer the review question. [Reeves et al., J Res Methods Synth, 2013]
- Recommendation not based on "methods research", but:
  - many important questions are not addressed by RCTs
  - e.g. in 2012, specific harms outcomes were reported in only 38% of new Cochrane reviews [Saini et al. BMJ 2014]

Cochrane Methods
NRS for Interventions

University of BRISTOL

What's different when including NRSi?

- ~~Title~~
- Protocol
- Design of searches / searching
- 'Triage' abstracts for eligibility
- 'Triage' full papers for eligibility
- Data extraction, including risk of bias (RoB) assessment
- Data synthesis
- Interpretation

Cochrane Methods
NRS for Interventions

University of BRISTOL

Protocol

- Review question
  - What would a RCT of the review question look like ("target trial")? [Sterne et al. www.riskofbias.info]
  - What is the nature of the target comparison? [Sterne et al. www.riskofbias.info]
  - Confounding domains [Sterne et al. www.riskofbias.info]
- Criteria for study eligibility
  - Specify study design features cf. labels [Handbook, Ch.13]
- Plan for synthesis [Handbook, Ch.13]
  - Meta-analyse or not? Forest plots without pooled estimates
  - Adjusted vs unadjusted effect estimates
  - Multiple adjusted effect estimates

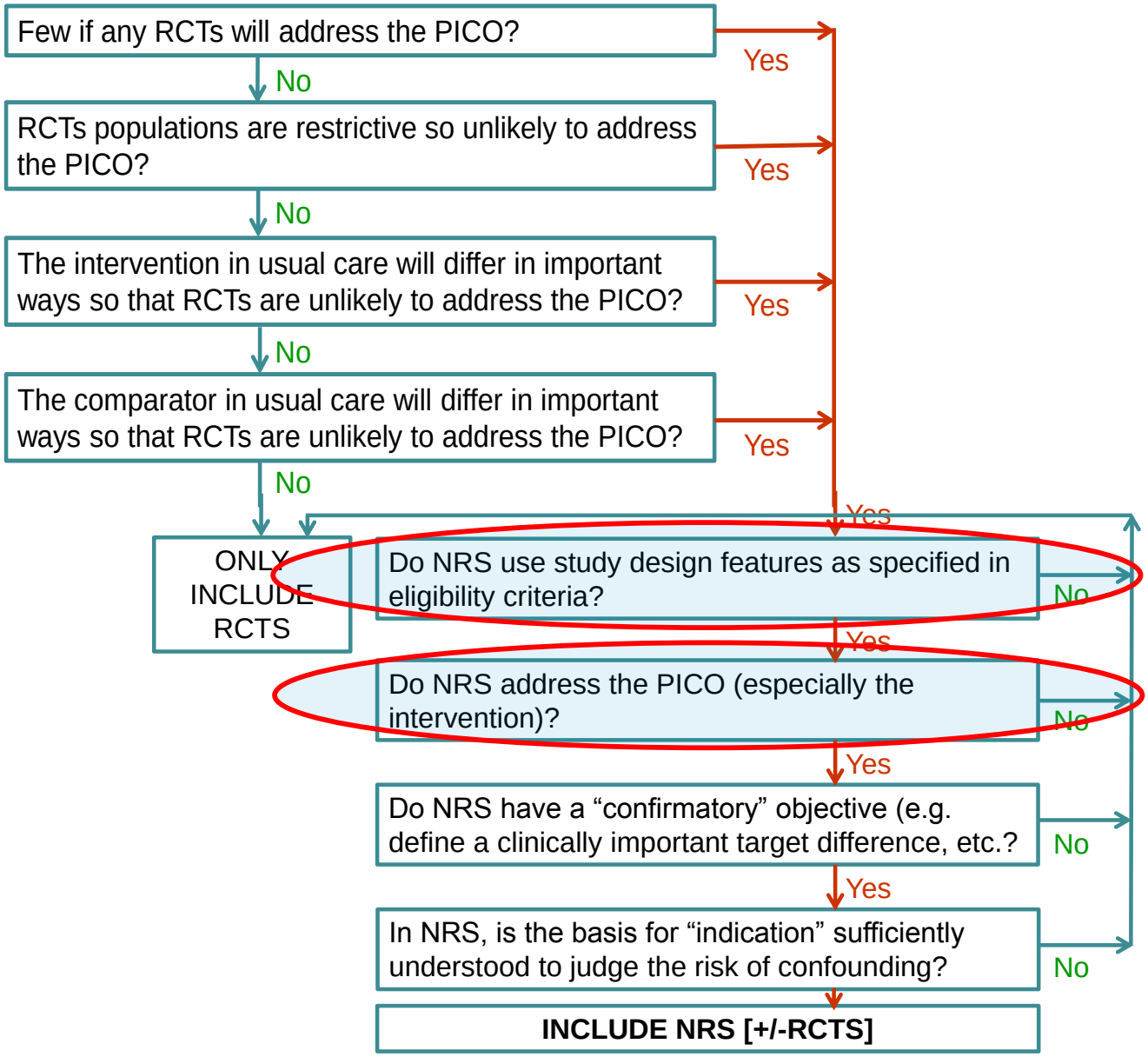
Study design features, not labels

[Higgins et al. J Res Synthesis Meth, 2013]

Table 1. Checklist of study design features for studies formed by classifying individuals by intervention and comparator.

	Yes	No	Can't tell	N/A
1. *Was there a relevant comparison:*				
Between two or more groups of participants receiving different interventions?	❐	❐	❐	❐
Within the same group of participants over time?	❐	❐	❐	❐
2. *Were groups formed by:*				
Randomization?	❐	❐	❐	❐
Quasi-randomization?	❐	❐	❐	❐
Other action of researchers?	❐	❐	❐	❐
Time differences?	❐	❐	❐	❐
Location differences?	❐	❐	❐	❐
Healthcare decision makers?	❐	❐	❐	❐
Participant preferences?	❐	❐	❐	❐
On the basis of outcome?	❐	❐	❐	❐
Some other process? (specify) _____				
3. *Were the key steps of the study described below carried out after the study was designed:*				
Identification of participants?	❐	❐	❐	❐
Assessment before intervention?	❐	❐	❐	❐
Actions/choices leading to an individual becoming a member of a group?	❐	❐	❐	❐
Assessment of outcomes?	❐	❐	❐	❐
4. *On which variables was comparability between groups assessed:*				
Potential confounders?	❐	❐	❐	❐
Assessment of outcome variables before intervention?	❐	❐	❐	❐

When to include NRSi



Cochrane Methods
NRS for Interventions

University of BRISTOL

Searching for and 'triaging' studies

- Searching:
  - Avoid design terms [Handbook, Ch.13]
  - Less comprehensive search?
  - Harms: search specific adverse effect databases; use "adverse effect" subheadings; search for a specific harm outcome [Golder et al. J Clin Epi, 2008, 2013]
- 'Triaging' abstracts
  - Difficult to exclude abstracts based on abstract
- Final selection from full papers
  - Apply study design checklist [Handbook, Ch.13]
  - Exclude "critical" risk of bias? [Sterne et al. www.riskofbias.info]

Cochrane Methods
NRS for Interventions

University of BRISTOL

Data extraction

- Assess risk of bias (ACROBAT-NRSi) [Sterne et al. www.riskofbias.info]
  - Study level information: target trial same as for review question? nature of comparison? specific effect to be appraised?
  - Outcome level information: signalling questions, domain-level RoB, outcome-level RoB

Bias due to confounding	1.1 Is confounding of the effect of intervention unlikely in this study? **If Y or PY to 1.1**, the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered 1.2. **If N or PN to 1.1**: Were participants analysed according to their initial intervention group throughout follow up? **If Y or PY to 1.2**, answer questions 1.4 to 1.6, which relate to baseline confounding 1.3. **If N or PN to 1.2**: Were intervention discontinuations or switches unlikely to be related to factors that are prognostic for the outcome? **If Y or PY to 1.3**, answer questions 1.4 to 1.6, which relate to baseline confounding **If N or PN to 1.1 and 1.2 and 1.3**, answer quest 1.4. Did the authors use an appropriate analysis me 1.5. **If Y or PY to 1.4**: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study? 1.6. Did the authors avoid adjusting for post-interve 1.7. Did the authors use an appropriate analysis me nding? 1.8. **If Y or PY to 1.7**: Were confounding domains **Risk of bias judgement** *(Optional) Predicted direction of bias*
Bias in selection of participants into the study	2.1. Was selection into the study unrelated to inter 2.2. Do start of follow-up and start of intervention 2.3. **If N or PN to 2.1 or 2.2**: Were adjustment techniques used that are likely to correct for the presence of selection biases? **Risk of bias judgement** *(Optional) Predicted direction of bias*
Bias in measurement of interventions	3.1 Is intervention status well defined? 3.2 Was information on intervention status recorded at the time of intervention? 3.3 Was information on intervention status unaffect **Risk of bias judgement** *(Optional) Predicted direction of bias*
Bias due to departures from intended interventions	4.1. Were the critical co-interventions balanced across intervention groups? 4.2. Were numbers of switches to other interventic 4.3. Was implementation failure minor? 4.4. **If N or PN to 4,1, 4.2 or 4.3**: Were adjustment techniques used that are likely to correct for these concerns? **Risk of bias judgement** *(Optional) Predicted direction of bias*
Bias due to missing data	5.1 Are outcome data reasonably complete? 5.2 Was intervention status reasonably complete for those in whom it was sought? 5.3 Are data reasonably complete for other variables in the analysis? 5.4 **If N or PN to 5.1, 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? 5.5 **If N or PN to 5.1, 5.2 or 5.3**: Were appropriate statistical methods used to account for missing data? **Risk of bias judgement** *(Optional) Predicted direction of bias*
Bias in measurement of outcomes	6.1 Was the outcome measure objective? 6.2 Were outcome assessors unaware of the intervention received by study participants? 6.3 Were the methods of outcome assessment comparable across intervention groups? 6.4 Were any systematic errors in measurement of the outcome unrelated to intervention received? **Risk of bias judgement** *(Optional) Predicted direction of bias*
Bias in selection of the reported result	Is the reported effect estimate unlikely to be selected, on the basis of the results, from... 7.1 ...among multiple outcome measurements within the outcome domain? 7.2 ...among multiple analyses of the intervention-outcome relationship? 7.3 ...among different subgroups? **Risk of bias judgement** *(Optional) Predicted direction of bias*
Overall risk of bias	**Risk of bias judgement** *(Optional)L Predicted direction of bias*

1. Seven domains

2. Signalling questions

3. Free text descriptions

4. Risk of bias judgements

(5. Predict direction of bias)

6. Overall risk of bias judgement

Sterne et al. www.riskofbias.info

Domain	Related terms
Bias due to confounding	Selection bias *as it is often used in relation to clinical trials* (and currently in widespre use within The Cochrane Collaborati Allocation bias; Case-mix bias.
Bias in selection of participants into the study	Selection bi *d in relation to cl* ception bias; Lead-tim time bias
Bias in classification of interventions	Mis ication bias; Information bias; Recall bias; Measurement bias; Observer bias
Bias due to departures from intended interventions	Performance bias; Time-varying confo ng
Bias due to missing data	Attrition bias; Selecti *used in relation* es
Bias in measurement of outcomes	Dete nformation bias, M Observer bias
Bias in selection of the reported result	Ou porting bias, Analysis reporting bias

Pre/at-intervention features, for which considerations of bias in NRSI are mainly distinct from those in RCTs

Post-intervention features, for which considerations of bias in NRSI are similar to those in RCTs

Cochrane Methods
NRS for Interventions

University of BRISTOL

Agenda for the future

Current initiatives include:

- Adapting the algorithm for deciding when to include NRSi so that it can inform GRADE
- Extending study feature checklist to cover types of studies used by health systems, social care and policy researchers
- Validating ACROBAT-NRSi (in collaboration with the Bias and Statistics MG). [Higgins et al.]

Looking further ahead:

- Explore how treatment effects change with searches of varying comprehensiveness.
- Research the risk of confounding and selection of participants in NRSi in different circumstances.