



Cochrane Learning live webinar: November 11<sup>th</sup> 2020  
RoB2: Overall risk of bias

# RoB 2: Overall risk of bias and incorporating RoB assessments into reviews

Jelena Savović  
Population Health Sciences  
Bristol Medical School

With special thanks to Julian Higgins, Jonathan Sterne, Matthew Page, Roy Elbers, Barney Reeves, Asbjørn Hróbjartsson, Isabelle Boutron, Luke McGuinness, Vincent Cheng and all RoB 2 collaborators

**Trusted evidence.**  
**Informed decisions.**  
**Better health.**



# Session outline

- Brief overview of RoB 2
- Reaching the overall RoB 2 judgement for the result
- Options for incorporating RoB 2 into synthesis
  - Primary analysis restricted to studies at low risk of bias
  - Present multiple (stratified) analyses and explore the impact of RoB
  - Present all studies and provide a narrative discussion
- Questions

For each outcome (each key synthesis in the review)

For each study

**Risk of bias assessment for a specific result**

1. Specify result being assessed

2. Specify effect of interest

3. List sources of information used to inform assessment

4. Answer signalling questions

5. Judge risk of bias for each domain

6. Judge overall risk of bias for the result

For the synthesis

Integrate judgement(s) into results and conclusions

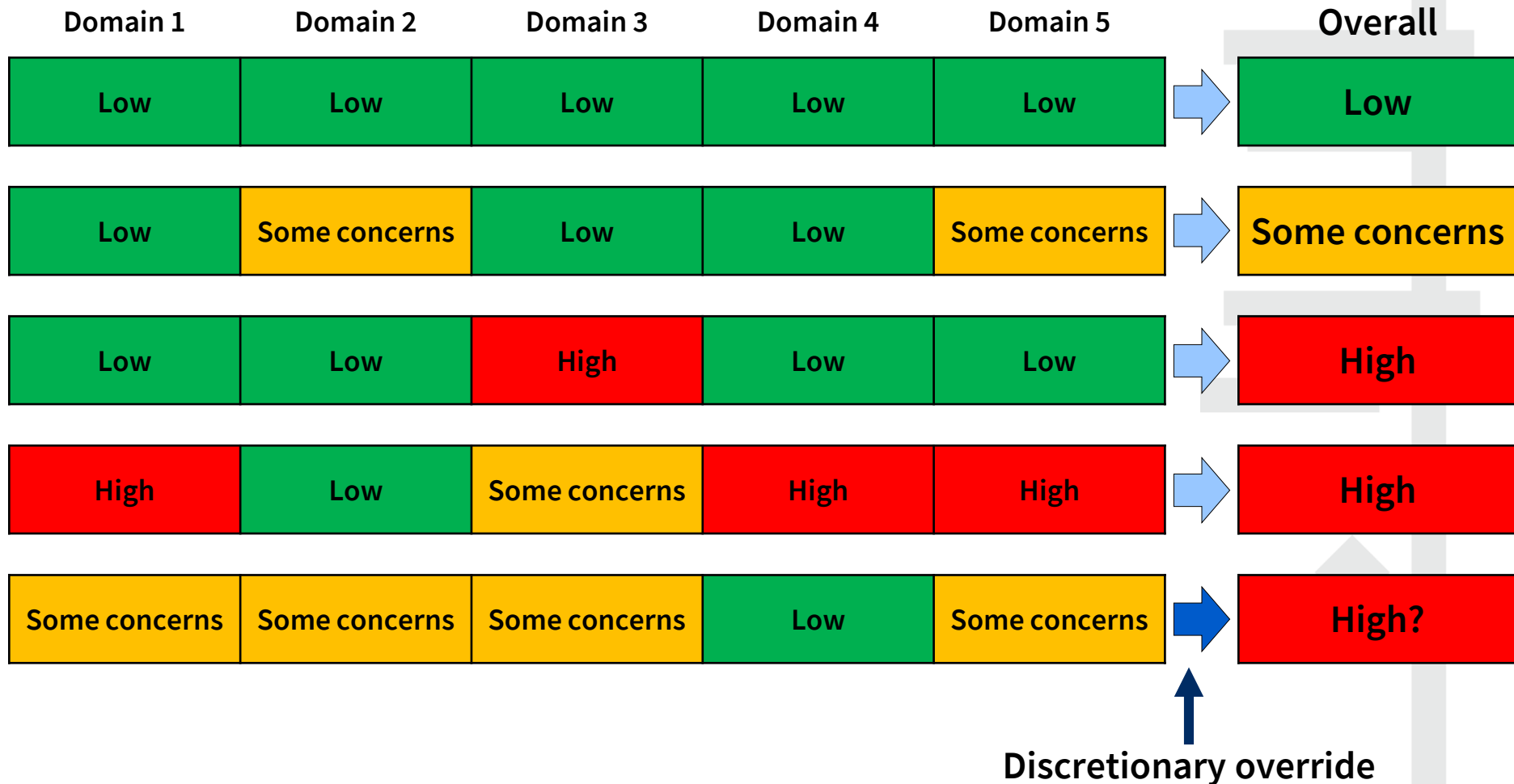
**Risk of bias for a parallel group trial with interest in the effect of assignment to intervention**

Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y/PY/PN/N/NI
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y/PY/PN/N/NI
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Y/PY/PN/N/NI
	<b>Risk of bias judgement</b>	Low/High/Some concerns
	Optional: What is the predicted direction of bias arising from the randomization process?	
Bias due to deviations from intended interventions	2.1. Were participants aware of their assigned intervention during the trial?	Y/PY/PN/N/NI
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y/PY/PN/N/NI
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA/Y/PY/PN/N/NI
	2.4 If Y/PY/NI to 2.3: Were these deviations likely to have affected the outcome?	NA/Y/PY/PN/N/NI
	2.5. If Y/PY to 2.4: Were these deviations from intended intervention balanced between groups?	NA/Y/PY/PN/N/NI
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y/PY/PN/N/NI
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA/Y/PY/PN/N/NI
	<b>Risk of bias judgement</b>	Low/High/Some concerns
	Optional: What is the predicted direction of bias due to deviations from intended interventions?	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y/PY/PN/N/NI
	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA/Y/PY/PN/N
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA/Y/PY/PN/N/NI
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA/Y/PY/PN/N/NI
	<b>Risk of bias judgement</b>	Low/High/Some concerns
	Optional: What is the predicted direction of bias due to missing outcome data?	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Y/PY/PN/N/NI
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Y/PY/PN/N/NI
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Y/PY/PN/N/NI
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA/Y/PY/PN/N/NI
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA/Y/PY/PN/N/NI
	<b>Risk of bias judgement</b>	Low/High/Some concerns
	Optional: What is the predicted direction of bias in measurement of the outcome?	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y/PY/PN/N/NI
	Is the numerical result being assessed likely to have been selected, <u>on the basis of</u> the results, from...	
	5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Y/PY/PN/N/NI
	5.3 ... multiple eligible analyses of the data?	Y/PY/PN/N/NI
	<b>Risk of bias judgement</b>	Low/High/Some concerns
	Optional: What is the predicted direction bias due to selection of the reported results?	
Overall bias	<b>Risk of bias judgement</b>	Low/High/Some concerns
	Optional: What is the overall predicted direction of bias for this outcome?	

# Overall risk of bias judgement

Low risk of bias	The study is judged to be at low risk of bias for all domains for this result.
Some concerns	The study is judged to be at some concerns in at least one domain for this result.
High risk of bias	The study is judged to be at high risk of bias in at least one domain for this result. OR The study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

# Suggested overall risk of bias judgement



# RoB 2 Excel tool includes a suggested overall judgement

RoB 2 assessment for individual randomized, parallel group trials

Assessment ID  Assessor  20/11/10

Study ID  Ref. or label

Experimental  Comparator

Specify which outcome  Specify the numerical result

Is the review team's aim for this result to assess...?  Weight for analysis

If the aim is to assess the effect of adhering to intervention...(select one at least)

occurrence of non-protocol interventions

failures in implementing the intervention that could have affected the outcome

non-adherence to their assigned intervention by trial participants

Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)

Journal article(s)

Trial protocol

Statistical analysis plan (SAP)

Non-commercial trial registry record (e.g. ClinicalTrials.gov record)

Company-owned trial registry record (e.g. GSK Clinical Study Register record)

"Grey literature" (e.g. unpublished thesis)

Conference abstract(s) about the trial

Regulatory document (e.g. Clinical Study Report, Drug Approval Package)

Research ethics application

Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Overall bias

**Overall bias**

Randomisation process  Deviations from the intended interventions  Missing outcomes  Measurement of the outcome  Selection of reported results

**Risk of bias judgement**

Algorithm result  Assessor's judgement

Optional: What is the overall predicted direction of bias arising for this outcome?

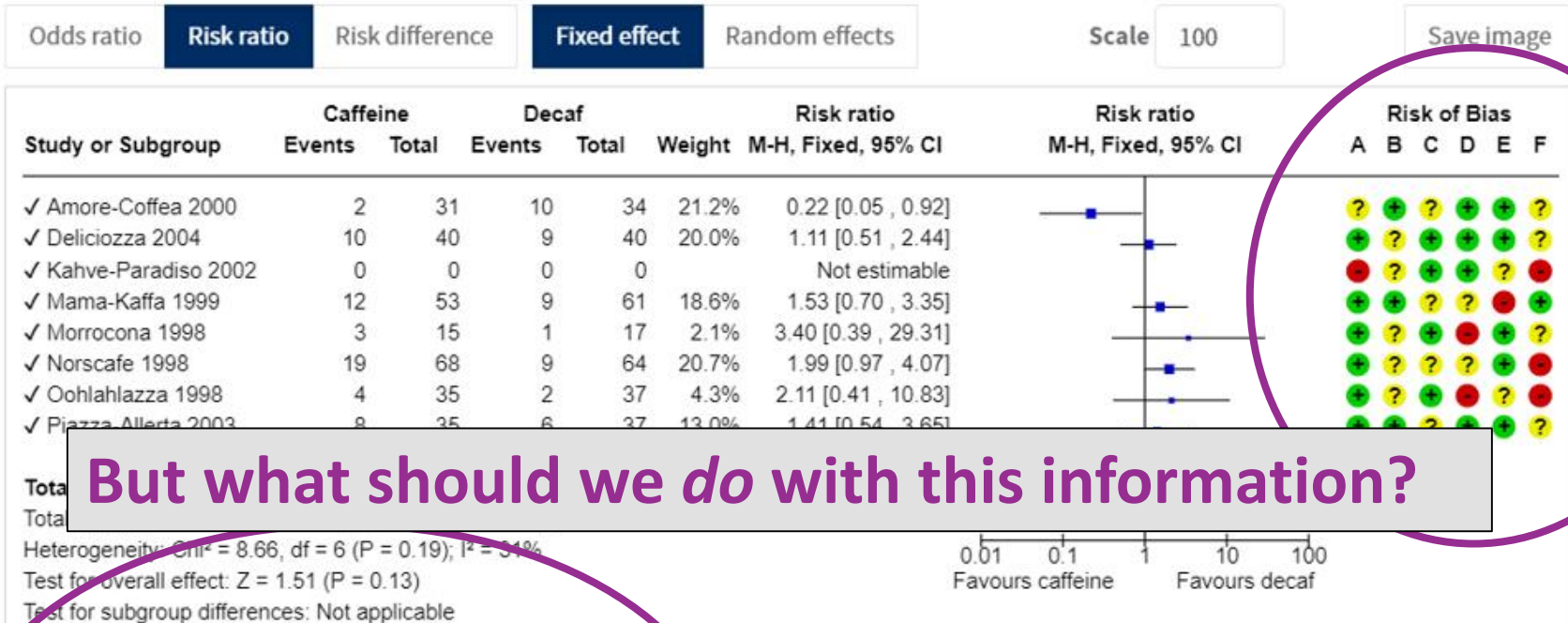
Open label trial and SAE are subjective leading to some concerns that ascertainment of SAE may have been influenced by knowledge of the intervention received, but it is difficult to tell how likely this is .

Risk of bias for analysis 1.4 Submaximal cardiorespiratory fitness (gas exchange threshold) [Open in table viewer](#)

Study	Bias					Overall
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	
Moalla 2006	⚠	✓	✓	⚠	⚠	⚠
Westhoff-Bleck 2013	⚠	✓	⚠	⚠	⚠	⚠
Duppen 2015	✓	✓	✓	⚠	⚠	⚠
Avila 2016	✓	✓	✓	⚠	⚠	⚠
Novakovic 2018	✓	✓	✓	⚠	⚠	⚠
Novakovic 2018	✓	✓	✓	⚠	⚠	⚠



## Investigate sensitivity - 1.1 Headache



**But what should we do with this information?**

### Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions: Headache
- (C) Bias due to missing outcome data: Headache
- (D) Bias in measurement of the outcome: Headache
- (E) Bias in selection of the reported result: Headache
- (F) Overall bias: Headache

<https://documentation.cochrane.org/revman-kb/assessing-risk-of-bias/how-to-use-risk-of-bias-2-0-rob-2-0-tool-in-revman-web>

# Incorporating bias assessments in analyses

## Cochrane Handbook, Chapter 7:

***“It is not appropriate to present analyses and interpretations while ignoring flaws identified during the assessment of risk of bias”***



# Incorporating bias assessments in analyses: Suggested approaches

## Cochrane Handbook, Chapter 7

### **Suggested approaches:**

- 1) Primary analysis restricted to studies at low risk of bias (or low + some concerns)
- 2) Present multiple (stratified) analyses / Explore the impact of RoB
- 3) Present all studies and provide a narrative discussion

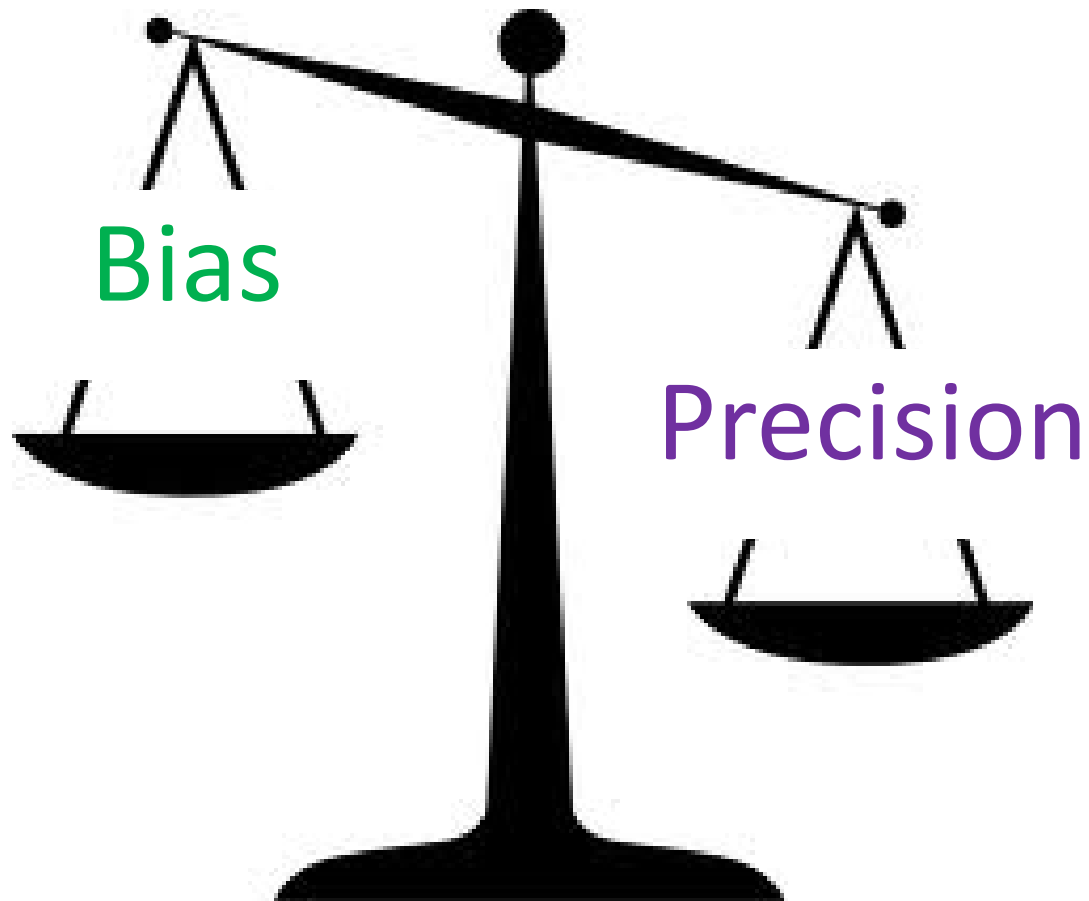
# Incorporating bias assessments in analyses (1)

- 1) **Restrict primary synthesis to studies at low risk of bias / low risk & some concerns**
  - based on overall risk of bias judgment for the result
  - relatively simple with RoB 2 due to overall RoB judgment
  - sensitivity analysis including all studies is encouraged

# Incorporating bias assessments in analyses (1)

- 1) **Restrict primary synthesis to studies at low risk of bias / low risk & some concerns**
  - based on overall risk of bias judgment for the result
  - relatively simple with RoB 2 due to overall RoB judgment
  - could also explore specific domains, if deemed useful
  - sensitivity analysis including all studies is encouraged

***What are the potential problems with this approach?***



**Bias is a key potential source of heterogeneity – we can use the same tools that are used to explore heterogeneity:**

- *Subgroup analysis*
- Formal test for a difference between subgroups
- *Meta-regression (calculate difference or ratio of subgroup estimates and CI)*

# Incorporating bias assessments in analyses (2)

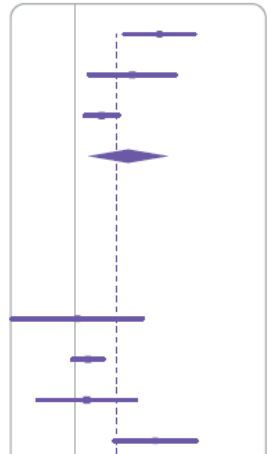
## 2) Provide multiple stratified analyses (subgroup analysis):

- Forest plot stratified by overall risk of bias
- Multiple estimates:
  - the ‘overall’ estimate (all studies)
  - Subgroup estimate for lower risk of bias studies
  - Subgroup estimate for higher risk of bias studies



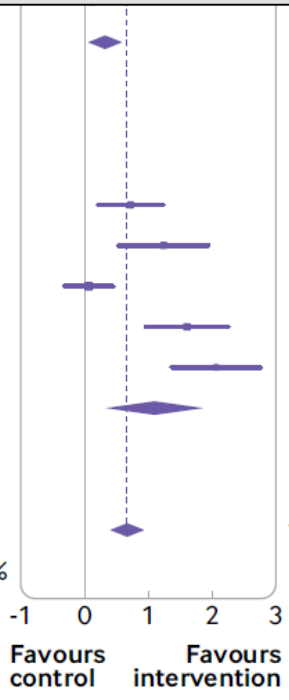


Subgroup or study	Standardised mean difference (95 CI)	Weight (%)	Standardised mean difference (95 CI)	R	D	Mi	Me	S	O
<b>Low risk of bias</b>									
Šerifović 2007		6.7	1.33 (0.79 to 1.87)	+	?	?	+	+	+
Loreen 2012		5.9	0.91 (0.25 to 1.57)	+	+	+	?	+	+
Jamala 2016		8.8	0.43 (0.18 to 0.68)	+	+	+	?	+	+
Subtotal		21.4	0.85 (0.25 to 1.45)						
Test for heterogeneity: $\tau^2=0.22$ ; $\chi^2=9.60$ , $df=2$ , $P=0.008$ ; $I^2=79\%$									
Test for overall effect: $Z=2.79$ , $P=0.005$									
<b>Some concerns</b>									
Ruslana 2004		3.9	0.05 (-0.96 to 1.06)	?	+	+	?	?	?
Zelmerlöv 2015a		8.8	0.21 (-0.03 to 0.45)	?	+	+	?	+	?
Zelmerlöv 2015b		5.2	0.19 (-0.57 to 0.95)	?	+	+	?	?	?
Wurst 2014		6.1	1.26 (0.63 to 1.89)	+	+	+	+	?	?



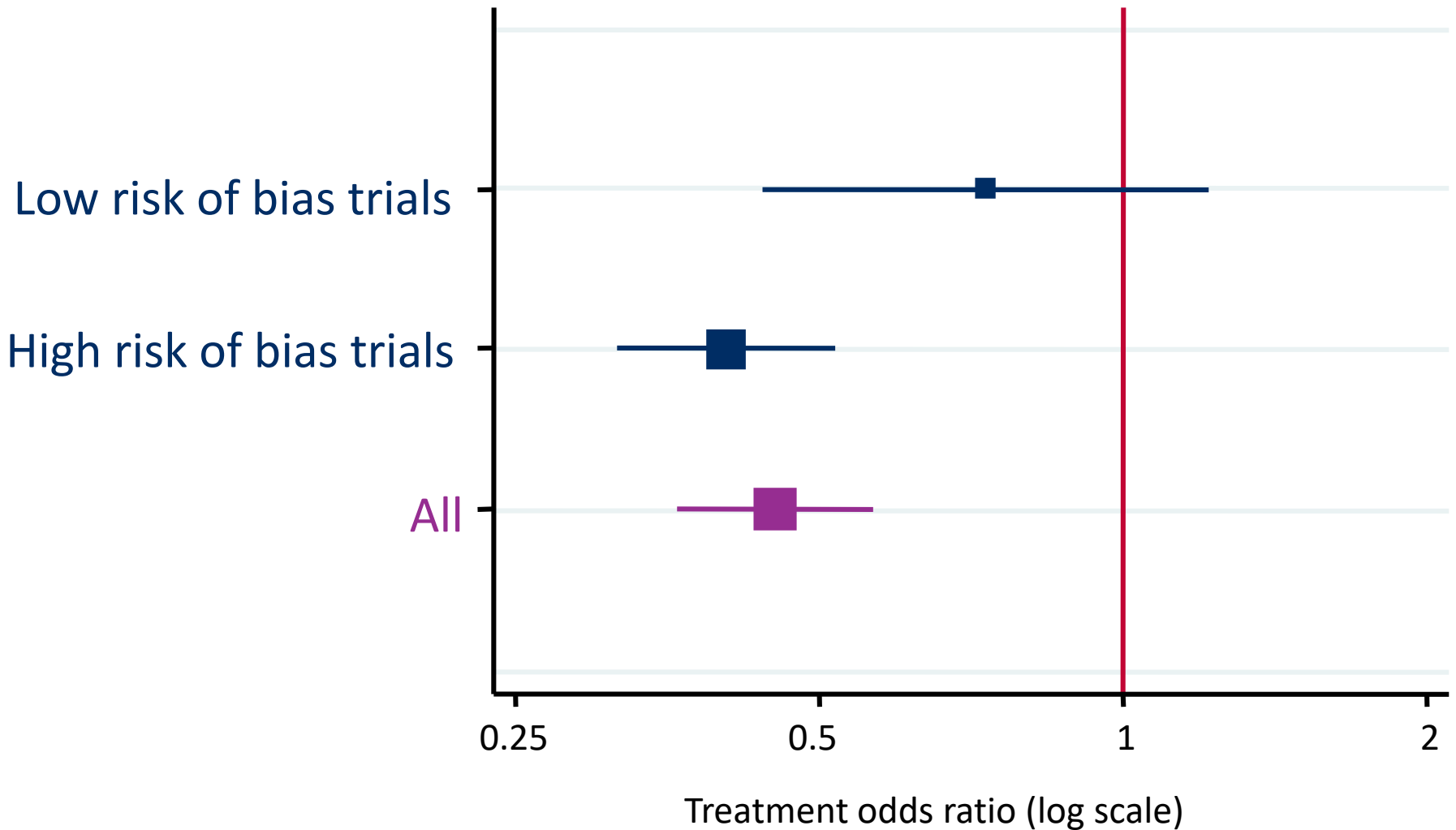
*What are the potential problems with this approach?*

Subtotal		46.0	0.33 (0.08 to 0.59)						
Test for heterogeneity: $\tau^2=0.05$ ; $\chi^2=13.59$ , $df=6$ , $P=0.03$ ; $I^2=56\%$									
Test for overall effect: $Z=2.59$ , $P=0.01$									
<b>High risk of bias</b>									
Rybak 2009		7.1	0.72 (0.23 to 1.21)	-	?	?	?	?	-
Netta 2018		5.7	1.24 (0.56 to 1.92)	-	+	+	+	?	-
Lena 2010		8.0	0.07 (-0.30 to 0.44)	+	+	-	+	-	-
Salvador 2017		6.1	1.60 (0.97 to 2.23)	?	+	-	?	?	-
Sobral 2017		5.7	2.06 (1.38 to 2.74)	?	+	-	?	?	-
Subtotal		32.7	1.11 (0.37 to 1.84)						
Test for heterogeneity: $\tau^2=0.61$ ; $\chi^2=36.05$ , $df=4$ , $P<0.001$ ; $I^2=89\%$									
Test for overall effect: $Z=2.96$ , $P=0.003$									
<b>Total (95% CI)</b>									
Test for heterogeneity: $\tau^2=0.18$ ; $\chi^2=71.47$ , $df=14$ , $P<0.001$ ; $I^2=80\%$									
Test for overall effect: $Z=5.14$ , $P<0.001$									
Test for subgroup differences: $\chi^2=5.55$ , $df=2$ , $P=0.06$ ; $I^2=64\%$									



Favours control Favours intervention

# Example 1. Clozapine versus neuroleptic medication for schizophrenia



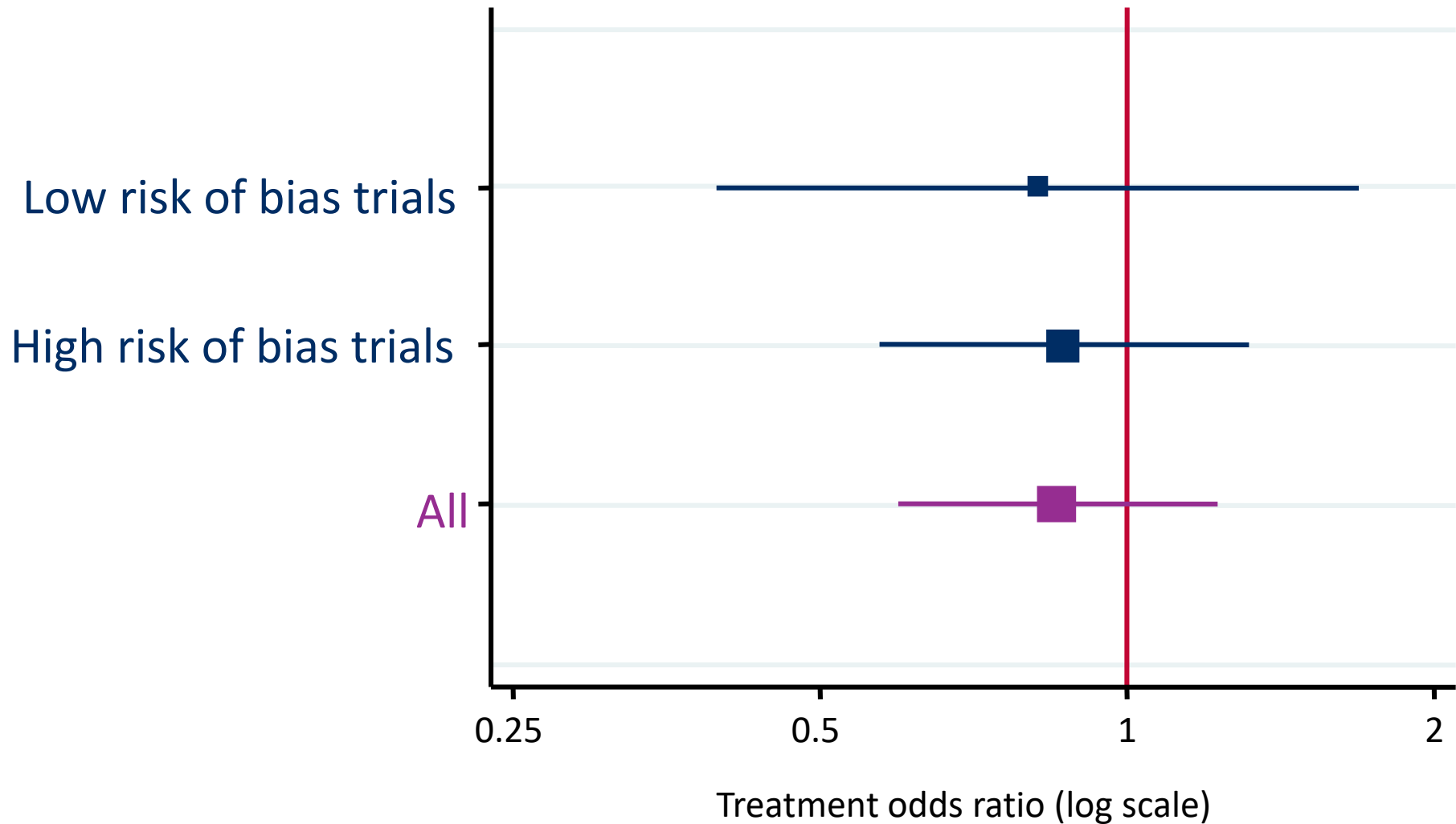
## Poll 1

**Should your main estimate (the one for SoF) be:**

- A. Based on low risk of bias trials only
- B. Based on high risk of bias trials only
- C. Based on all trials



# Example 2. Ovulation suppression compared to Danazol for endometriosis

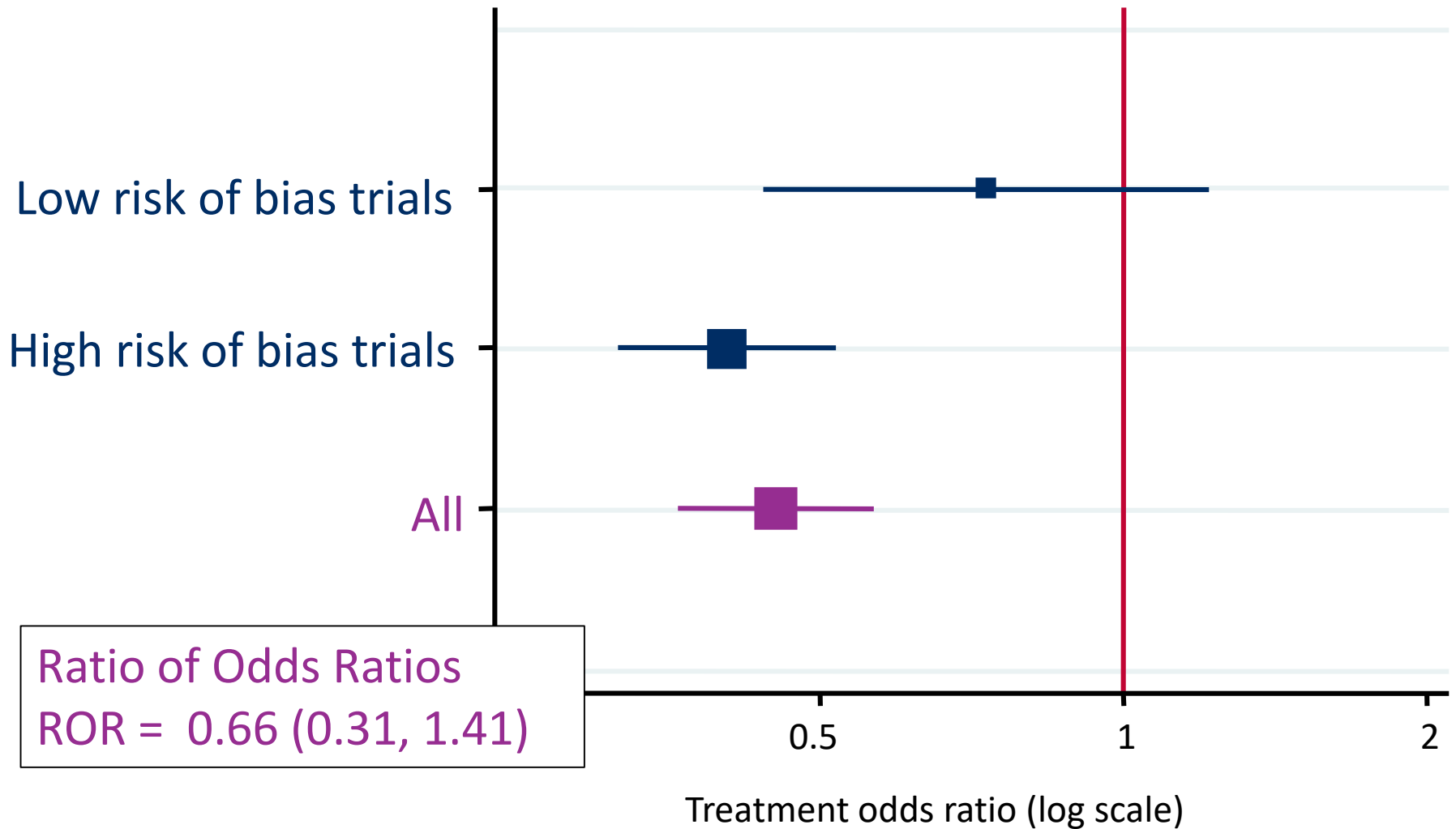


**Should your main estimate (the one for SoF) be:**

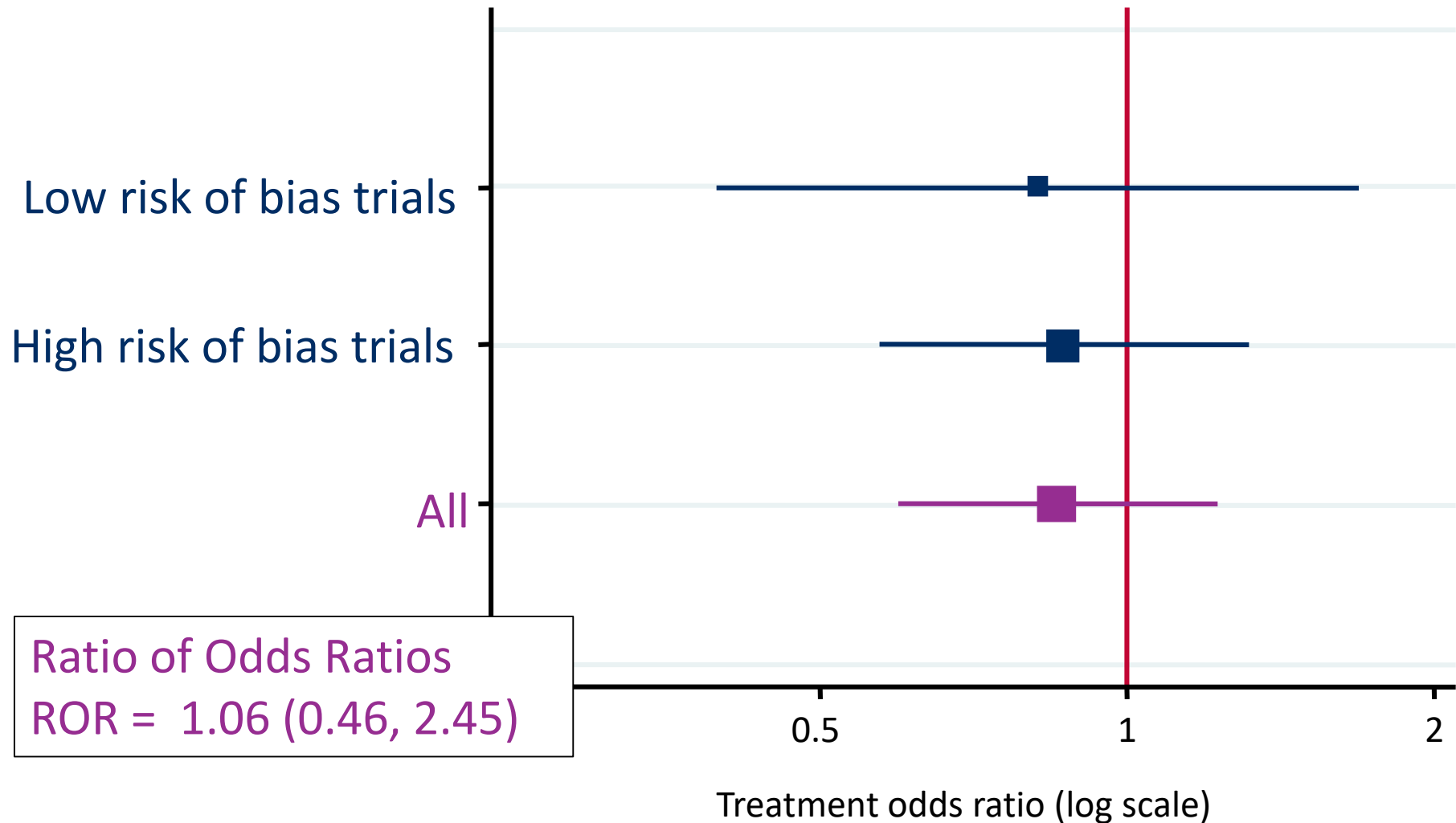
- A. Based on low risk of bias trials only
- B. Based on high risk of bias trials only
- C. Based on all trials



# Example 1. Clozapine versus neuroleptic medication for schizophrenia



# Example 2. Ovulation suppression compared to Danazol for endometriosis



# Incorporating bias assessments in analyses (2)

## *Caution with test for differences and meta-regression:*

- Low power
  - Individual review may not have enough studies in each ROB category to identify meaningful differences
  - Lack of a statistically significant difference between studies at high and low risk of bias does not mean absence of bias
- A significant difference between subgroups is not necessarily due to bias (there may be other sources of heterogeneity)



# Incorporating bias assessments in analyses (2)

## *Other potential problems with approach 2:*

- Three estimates per outcome: which one is the main result?
- May be confusing for readers
- Decision-makers want a single estimate of effect
- Summary of findings tables require single result per outcome

## *What are the main advantages?*

- Transparency

# How to choose the right approach for you?

**Restricting to lower risk of bias results**

**vs**

**Presenting all subgroups and overall estimates**

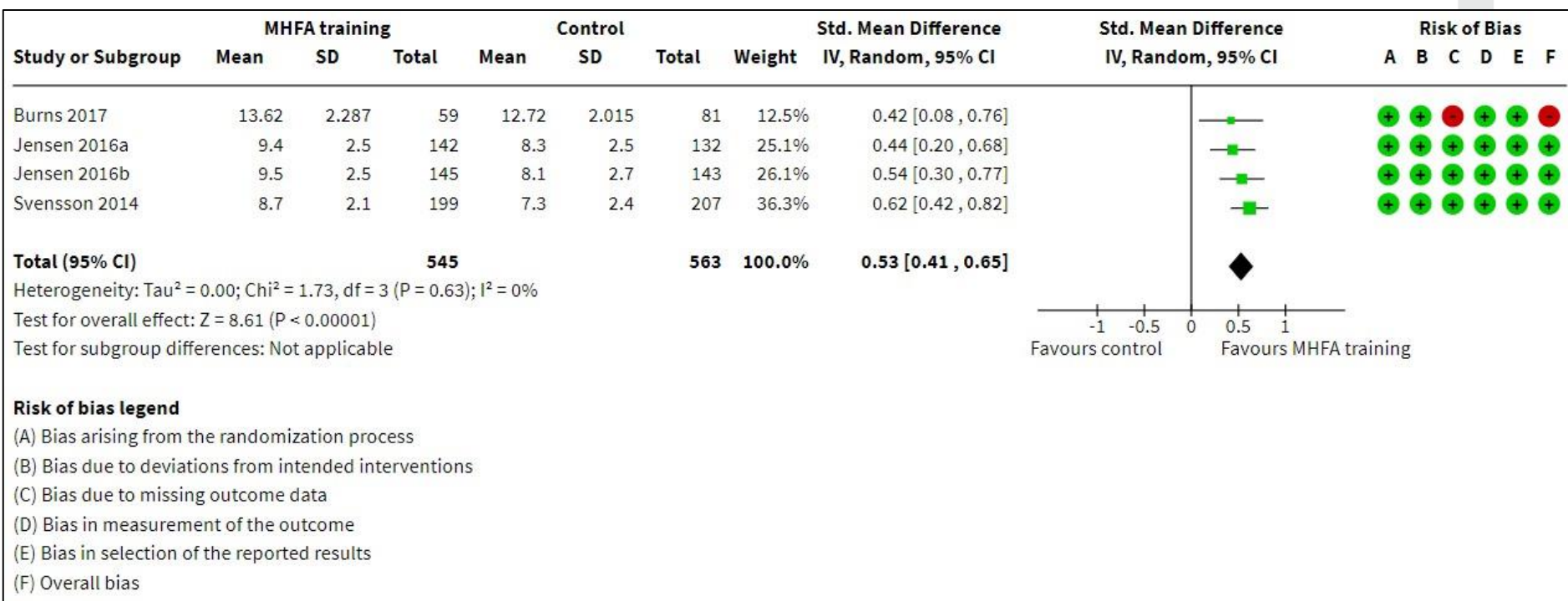
*How to decide between these two main strategies ?*

This decision should be made based on the balance between the potential for bias and the loss of precision resulting from exclusion of high risk of bias studies.

# Incorporating bias assessments in analyses (3)

## 3) Include all studies in the meta-analysis and provide a narrative discussion of bias

- Provide detailed description of RoB by individual domains
- Display and describe summary of RoB across studies
- Display all RoB judgements on forest plots



# Incorporating bias assessments in analyses (3)

## 3) Include all studies in the meta-analysis / synthesis and provide a narrative discussion of bias

- The simplest approach?
- Probably most common across literature

### *What are the potential problems with approach 3?*

- Descriptions of RoB in Results/Discussion
- They get lost in Abstract / SoF / Conclusions (= potentially biased estimate gets used)
- Does not down-weight studies at high risk of bias → overall estimate is too precise (as well as potentially biased)

# Incorporating bias assessments in analyses (3)

## *When is it acceptable to use strategy 3?*

- When all studies are at the same risk of bias
- **Discouraged** when studies have different risk of bias
- Ensure summary RoB assessment incorporated into explicit measures of the certainty of evidence (GRADE)





# Summary of methods for dealing with bias

## Primary analysis

- all 'at Low risk of bias overall'?
- stratified analyses?

## Does RoB 2 explain heterogeneity?

- subgroup analyses
- meta-regression

## Secondary analysis

- sensitivity analyses?

## Certainty of the evidence

- RoB 2 will feed directly into GRADE

## Which method will you use in your next review?

- a) Restrict to lower risk of bias results
- b) Subgroups by risk of bias +/- meta-regression
- c) Include all studies and describe RoB in text
- d) Something else



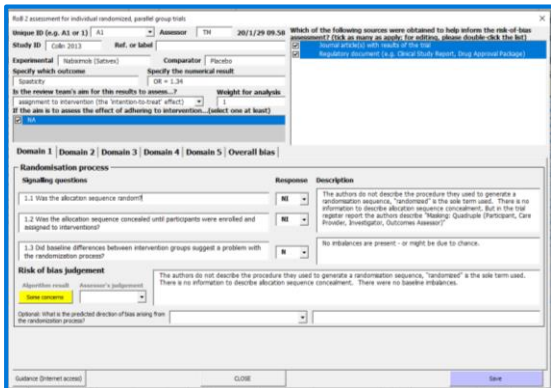
# Resources available





# Implementation options

## Excel tool



RoB2 assessment for individual randomized, parallel group trials

Study ID: [ ] Assessor: [ ] Date: 2017/29 09:58

Which of the following sources were obtained to help inform the risk of bias assessment? *Click as many as apply for editing, please double-check the list!*

Expected: [ ] Interventions (Surveys) [ ] Comparator: [ ] Pictorial [ ]

Specify which outcome: [ ] OR = 1.24

Is the review team's aim for the results to assess...? [ ] Weight for analysis: [ ]

assignment to intervention (the 'intention-to-treat' effect)? [ ]

of the aim is to assess the effect of adjuvant to intervention. (select one at least)

Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Overall bias

**Randomisation process**

Signalling question	Response	Description
1.1 Was the allocation sequence random?	NI	The authors do not describe the procedure they used to generate a randomisation sequence, 'randomised' is the site term used. There is no information to describe allocation concealment. See in the text register report the authors describe 'blinded' 'Quadrant (Participant, Case Provider, Investigator, Outcome Assessor)'
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	No imbalances are present - or might be due to chance.
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	NI	No imbalances are present - or might be due to chance.

**Risk of bias judgement**

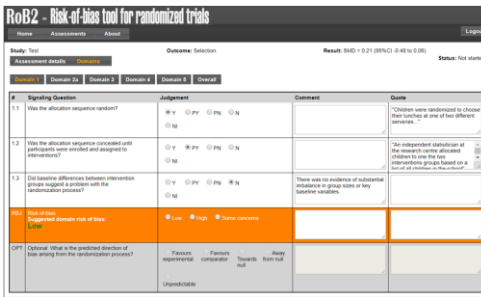
Algorithm result: [ ] Assessor's judgement: [ ]

The authors do not describe the procedure they used to generate a randomisation sequence, 'randomised' is the site term used. There is no information to describe allocation concealment. There were no baseline imbalances.

Options: What is the predicted direction of bias arising from the randomisation process? [ ]

Substance (Internet access) [ ] CLOSE [ ] Save [ ]

## Online platform (coming soon)



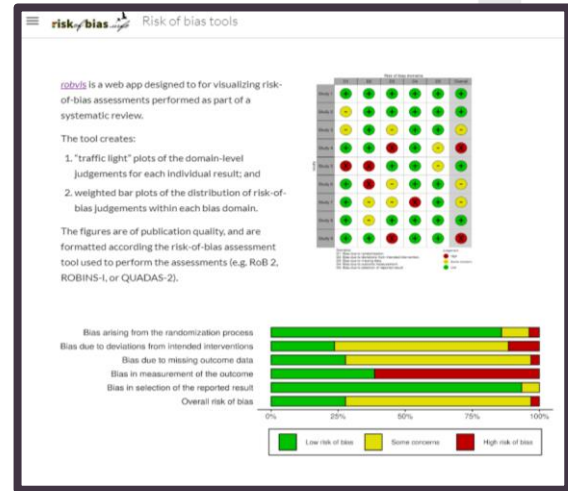
RoB2 - Risk-of-bias tool for randomized trials

Assessment details: [ ] Outcome Selection: [ ] Result: [ ] (95% CI: [ ] to [ ]) Status: Not started

Signalling Question	Judgement	Comments	Done
1.1 Was the allocation sequence random?	NI		<input type="checkbox"/>
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI		<input type="checkbox"/>
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	NI		<input type="checkbox"/>
Overall risk of bias	Low		<input type="checkbox"/>
Optional: What is the predicted direction of bias arising from the randomisation process?	None		<input type="checkbox"/>

- RevMan 5 
- RevMan Web 

## robvis



The recommended way to do RoB 2 assessments at the moment

## Covidence (in development)



Covidence Risk of Bias

ORIGINAL ARTICLE

**A Randomized Controlled Open Comparative Trial of Varenicline vs Nicotine Patch in Adult Smokers**

—Efficacy, Safety and Withdrawal Symptoms (The VN-SEESAW Study)—

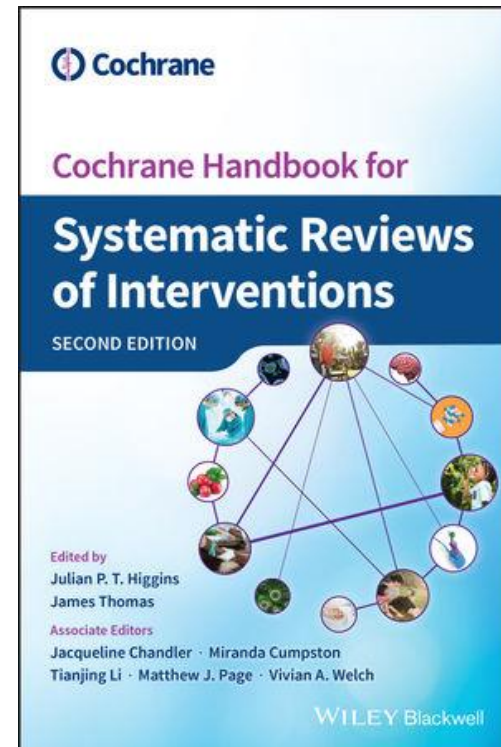
Helen Traubner, PhD, Kate Stock, MB, Kaitlyn Fahn, MSc

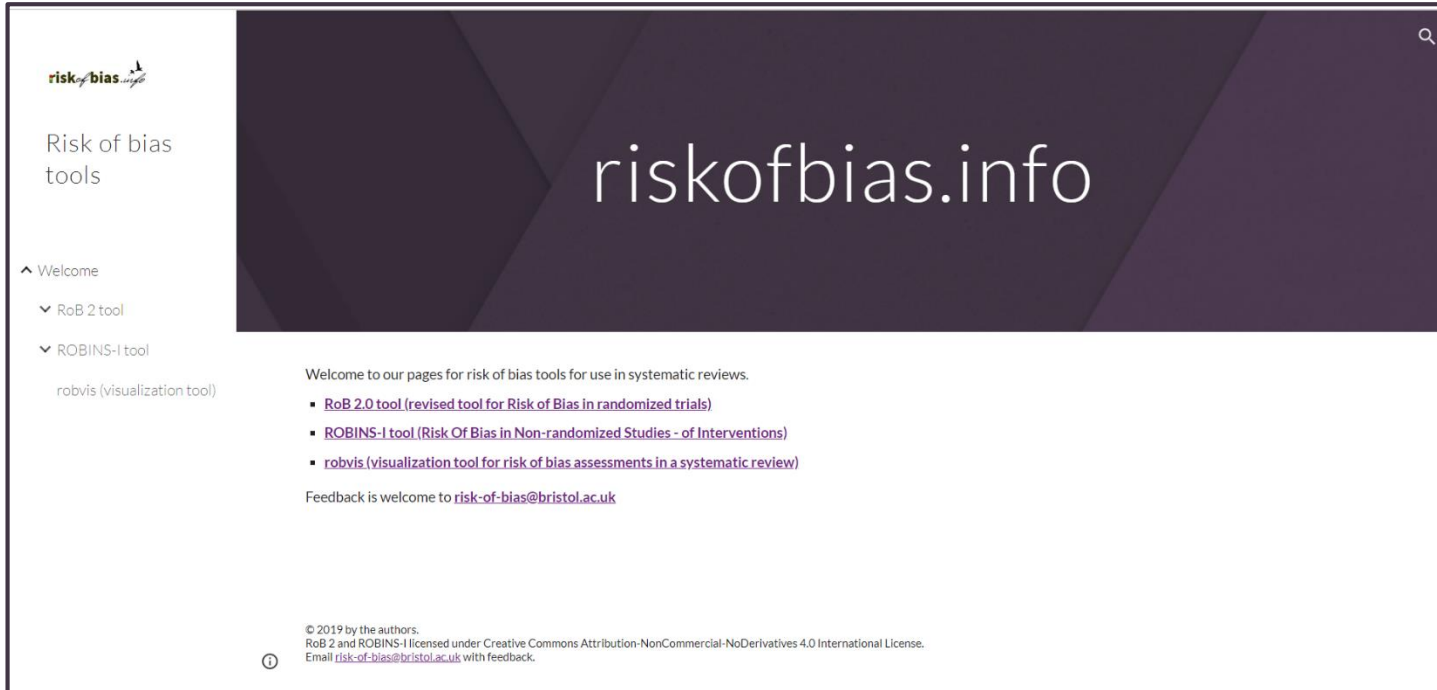
Background: This trial was registered for publication on the public register of clinical trials, but the trial was not published in a peer-reviewed journal. The general public may be interested in the results of this trial, and the authors should be encouraged to publish the results of this trial in a peer-reviewed journal.

Conclusions: The authors do not describe the procedure they used to generate a randomisation sequence, 'randomised' is the site term used. There is no information to describe allocation concealment. There were no baseline imbalances.

# Cochrane Handbook (v 6)

- **Chapter 7** explains risk of bias issues in general
- **Chapter 8** provides a brief overview of the RoB 2 tool
- **MECIR** items summarize *Handbook* guidance





The screenshot shows the homepage of riskofbias.info. The header features the 'risk of bias.info' logo and the text 'Risk of bias tools'. A navigation menu on the left includes 'Welcome', 'RoB 2 tool', and 'ROBINS-I tool' (with a sub-item 'robvis (visualization tool)'). The main content area has a dark purple background with the text 'riskofbias.info' and a search icon. Below this, a welcome message is followed by a bulleted list of tools: 'RoB 2.0 tool (revised tool for Risk of Bias in randomized trials)', 'ROBINS-I tool (Risk Of Bias in Non-randomized Studies - of Interventions)', and 'robvis (visualization tool for risk of bias assessments in a systematic review)'. A feedback email address is provided. At the bottom, there is a copyright notice for 2019 and a Creative Commons license.

**risk of bias.info**

Risk of bias tools

^ Welcome

▼ RoB 2 tool

▼ ROBINS-I tool

robvis (visualization tool)

Welcome to our pages for risk of bias tools for use in systematic reviews.

- [RoB 2.0 tool \(revised tool for Risk of Bias in randomized trials\)](#)
- [ROBINS-I tool \(Risk Of Bias in Non-randomized Studies - of Interventions\)](#)
- [robvis \(visualization tool for risk of bias assessments in a systematic review\)](#)

Feedback is welcome to [risk-of-bias@bristol.ac.uk](mailto:risk-of-bias@bristol.ac.uk)

© 2019 by the authors.  
RoB 2 and ROBINS-I licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.  
Email [risk-of-bias@bristol.ac.uk](mailto:risk-of-bias@bristol.ac.uk) with feedback.

## Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne  
on behalf of the RoB2 Development Group

22 August 2019

Dedicated to Professor Douglas G Altman, whose contributions were of fundamental importance to  
development of risk of bias assessment in systematic reviews



This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License](https://creativecommons.org/licenses/by-nc-nd/4.0/).

### Contents

1	Introduction .....	2
1.1	Signalling questions .....	3
1.2	Risk-of-bias judgements .....	3
1.3	Specifying the nature of the effect of interest .....	5
2	Issues in implementation of RoB 2 .....	6
2.1	Multiple assessments .....	6
2.2	The data collection process .....	7
2.3	Presentation of risk-of-bias assessments .....	7
2.4	Rapid assessments .....	7
3	Detailed guidance: preliminary considerations .....	8
4	Detailed guidance: bias arising from the randomization process .....	10
4.1	Background .....	10
4.2	Empirical evidence of bias arising from the randomization process .....	11
4.3	Using this domain of the tool .....	12
4.4	Signalling questions and criteria for judging risk of bias .....	16
5	Detailed guidance: bias due to deviations from intended interventions .....	21
5.1	Background .....	21
5.2	Empirical evidence of bias due to deviations from intended interventions .....	26
5.3	Using this domain of the tool .....	26

# Questions

Trusted evidence.  
Informed decisions.  
Better health.

