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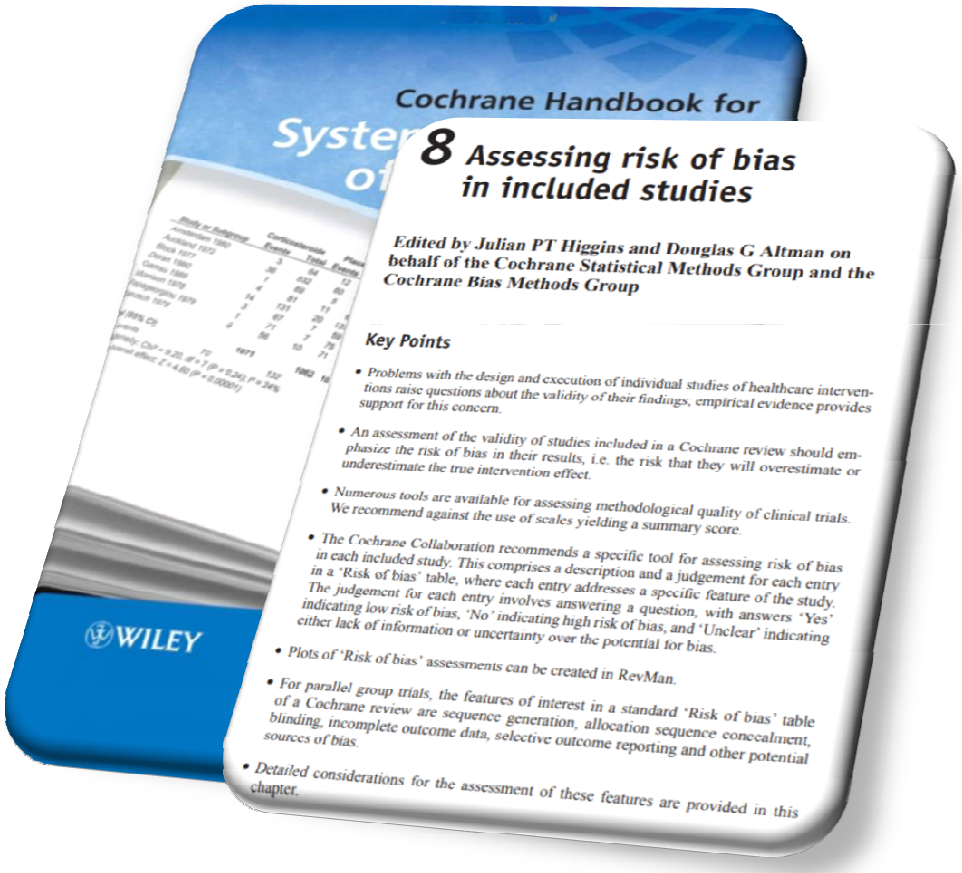
Taichung Veterans General Hospital



RoB 2.0

SIMPLY
CLEARLY
EASILY
DETAILEDLY

Presenter: Shih-Ming Huang

Development process

Revision of the RoB tool started in May 2015

1st Development meeting held in Bristol in August 2015

1st 'working draft' of the tool completed January 2016

Piloting phase Feb – March 2016

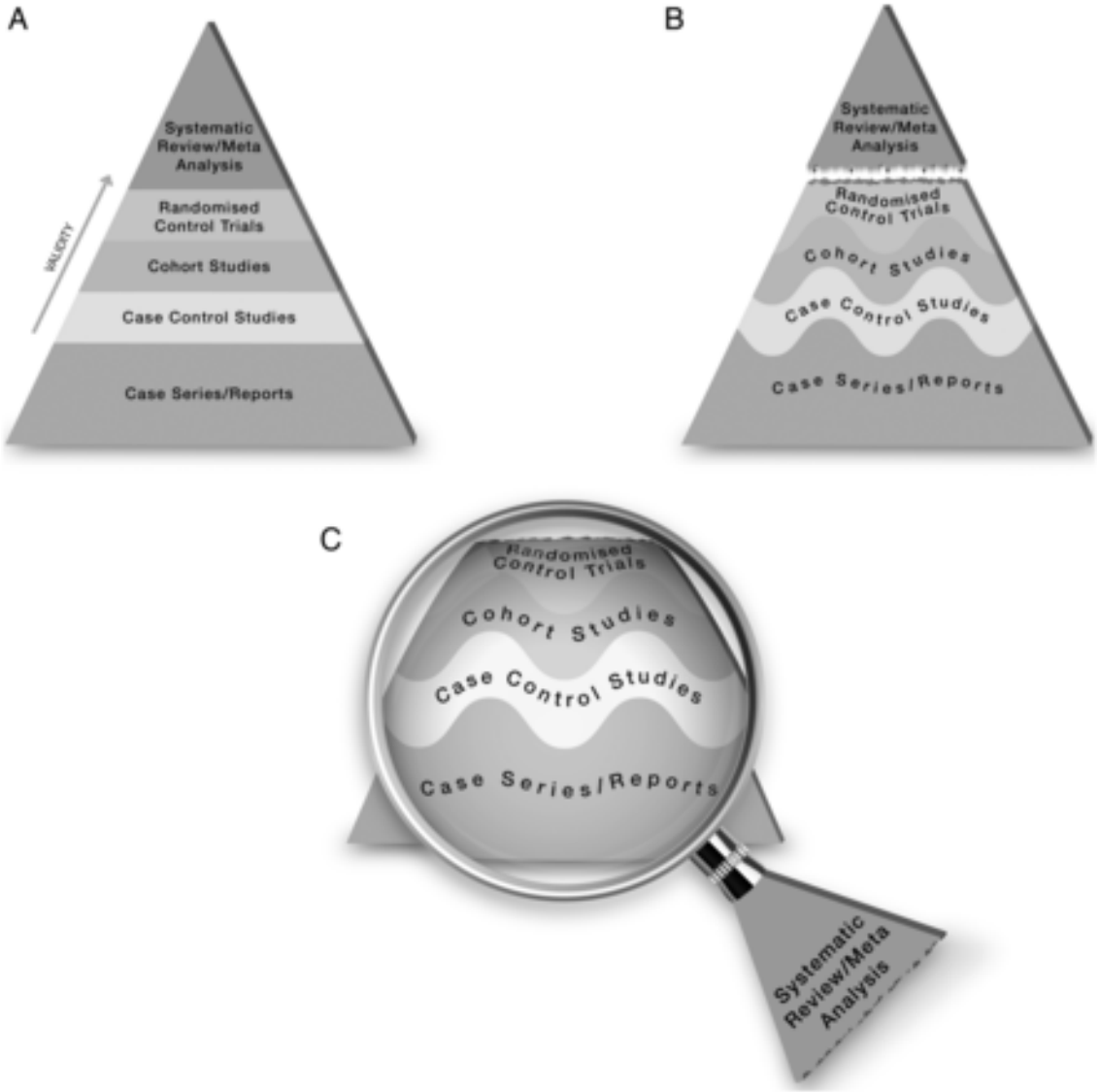
Revised 'working draft'

2nd Development meeting held in Bristol on 21-22 April 2016

Development of further guidance and piloting

Released for Seoul Colloquium

New evidence-based medicine pyramid



BMJ Evidence-Based Medicine 2016;**21:**125-127

Table 1 Characteristics of QATs and key study quality domains addressed

QAT domain	EPHPPT	CASP	NOS	Liverpool	GATE	ROB
Applicability	RCT, non-randomised trial, cohort, case-control, cross-sectional	RCT, cohort, case-control, diagnostic tests, economic evaluations, qualitative research, systematic reviews	Cohort, case-control	RCT, non-randomised trial, cohort, case-control, cross-sectional	RCT, non-randomised trial, cohort, case-control, cross-sectional	RCT, non-randomised trial, cohort, case-control, cross-sectional
Classification	Checklist	Checklist	Scale	Scale	Checklist	Checklist
Summary score	Qualitative	No	Quantitative	Quantitative	Qualitative	No
Number of components (questions)	8 (22) (only six components included in summary score)	3 (10–12 depending on study design)	9 (9)	8–9 (8–9 depending on study design)	5 (25)	9 (9)
Methods for selecting study population	Yes	Yes	Yes	Yes	Yes	Partial (only for RCTs)
Methods for measuring exposure and outcome variables	Yes	Partial RCT: outcome only cohort: both case-control: exposure only	Yes	Yes	Partial (outcome only)	Partial (outcome only)
Design-specific sources of bias (excluding confounding)	Partial (only for RCTs, non-randomised trials)	Yes	Yes	Yes	Yes (only for RCTs, non-randomised trials)	Partial (only for RCTs, non-randomised trials)
Methods to control confounding	Yes	Yes	Yes	Yes	Yes	Yes
Statistical methods (excluding control of confounding)	Partial (not included in summary score)	Partial (no decision made about quality)	No	No	Yes	No
Conflict of interest	No	No	No	No	No	No
Major strengths and weaknesses (in addition to features above)	Use is possible without advanced epidemiological training 'One size fits all' tool does not do justice to strengths and weaknesses of different study designs	Use is possible without advanced epidemiological training Low inter-rater reliability* due to combination of main questions and subquestions Too few answer categories for several questions	High inter-rater reliability* due to very specific answer categories Too few answer categories for several questions	Broad applicability of four companion tools, each geared towards specific study design features Adaptation of considerations on exposure and outcome measurement to systematic review question	Broad applicability of two companion tools, each geared towards specific study design features High inter-rater reliability* due to very specific questions Combination of indepth assessment of specific limitations with a two-component summary assessment	Compatibility with the most-widely used tool for systematic reviews of RCTs 'One size fits all' tool does not do justice to strengths and weaknesses of different study designs Use requires advanced epidemiological training

J Epidemiol Community Health 2013;67:98–104.

Methodological assessment tools

評讀工具	評讀項目
Cochrane risk of bias tool (RoB 2.0)	RCT
CASP (Critical Appraisal Skills Programme)	SR, RCT, Cohort, Case Control, Diagnostics, Economics, Qualitative Researches
CAT (Critical Appraisal Tools) from Oxford CEBM	SR, RCT, diagnostics, Prognostic
A Measurement Tool to Assess Systematic Reviews (AMSTAR)	SR
Appraisal of Guidelines for Research and Evaluation (AGREE)	Guideline development and the quality of reporting

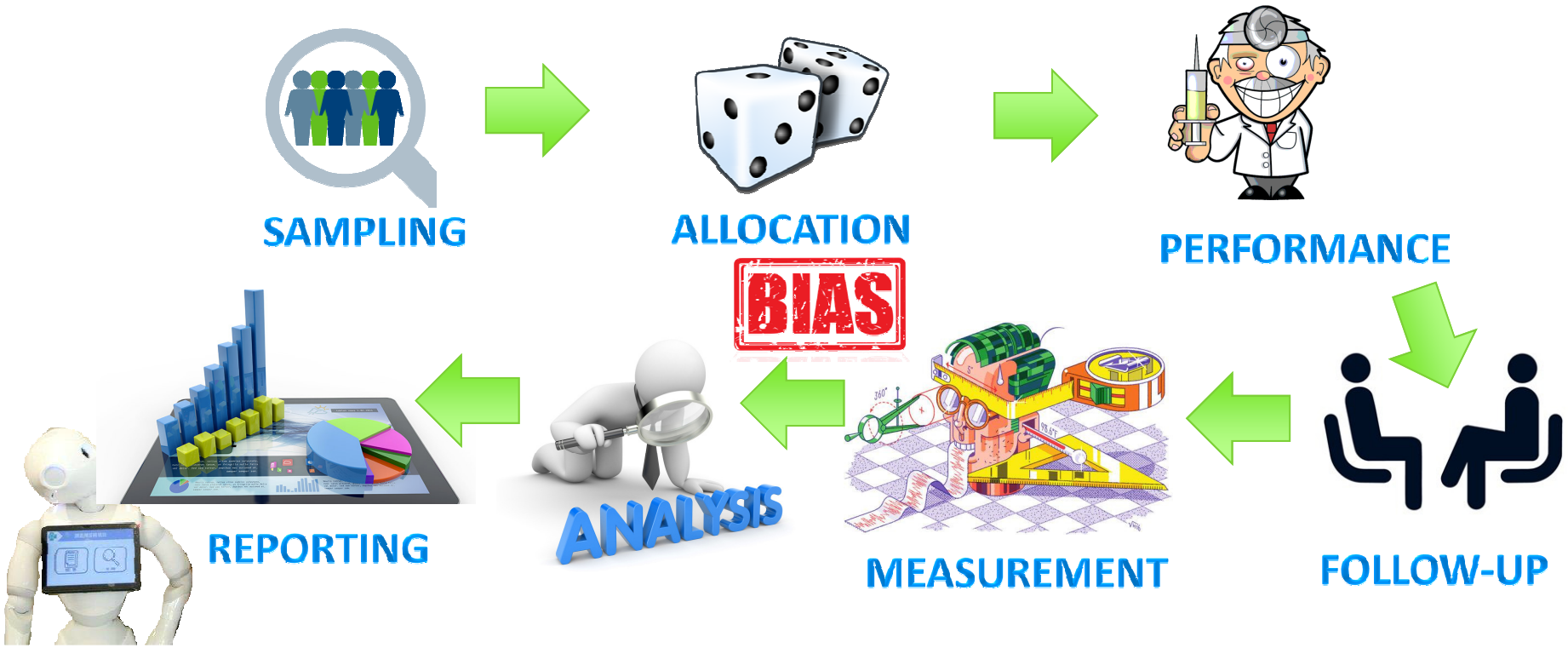
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were randomised in blocks of six to one of the two treatment groups using sequentially numbered, sealed opaque envelopes." Comment: sequence generation not reported.
Allocation concealment (selection bias)	Low risk	Quote: "Subjects were randomised in blocks of six to one of the two treatment groups using sequentially numbered, sealed, opaque envelopes." Comment: allocation process adequate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Because the study was not blinded, secondary absorbent dressing and peri ulcer treatments used were at the discretion of the investigator." Comment: stated as not being blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Because the study was not blinded, secondary absorbent dressing and peri ulcer treatments used were at the discretion of the investigator." Comment: stated as not being blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: numbers withdrawing and reasons reported by group (Group 1: 14/60 (23%); Group 2: 5/58 (9%)) but a higher proportion of participants withdrew from Group 2 and analysis not undertaken as ITT.
Selective reporting (reporting bias)	Unclear risk	Comment: although all trial outcomes described in the published report are in the supplied RCT protocol, it was unclear from the published report what the primary outcomes were (maceration in the protocol). A secondary outcome of 'ability to adapt' in the protocol (translated from Danish) is not identifiable in the published report.

Six sources of bias (with optional 'Other')

https://training.cochrane.org/resource/rob-20-webinar

More and more popular

- Cochrane RoB tool is very widely used (Jorgensen 2016)
  - 100 out of 100 Cochrane reviews from 2014 (100%)
  - 31 out of 81 non-Cochrane review (38%)
- >2700 citations from non-Cochrane sources
- The scientific debate on risk of bias has continued

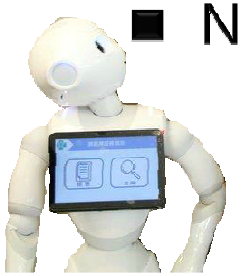


Some issues raised with existing tool

- Used **simplistically**
- Used **inconsistently (domains added or removed)**
- Modest **agreement rates**
- Only 5-10% of trials in Cochrane reviews are scored as Low risk of bias

OVERUSE OF "UNCLEAR RISK"?

- RoB judgements are **difficult for some domains, particularly** incomplete outcome data and selective reporting
- Not well suited to **cross-over trials or cluster-randomized trials**
- Not well set up to assess **overall risk of bias**



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Cochrane Training

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RoB 2.0: A revised tool to assess risk of bias in randomized trials [webinar]

This webinar, presented by Dr Matthew Page, explains the development and application of the revised tool for assessing risk of bias in randomized trials (RoB 2.0).

The RoB 2.0 tool for assessing risk of bias in randomized trials builds on the established Cochrane risk-of-bias tool first released through the Cochrane Handbook for Systematic Reviews of Interventions in 2008 and updated in 2011. The development team have reacted to feedback and evaluations of the original tool and made several amendments and improvements.

This webinar, which was part of the Cochrane Learning Live series, is presented by Dr Matthew Page, a postdoctoral research fellow based at the University of Bristol, UK. Matthew has expertise in systematic review methodology and bias in biomedical and public health research.

The webinar is presented in four parts:

1. Reminder of the Cochrane RoB tool for RCTs
2. The new RoB tool: development and key innovations
3. A walk-through the new RoB tool: Part I
4. A walk-through the new RoB tool: Part II

https://training.cochrane.org/resource/rob-20-webinar

riskofbias.info

Risk of bias tools

- Welcome
  - RoB 2 tool
    - Current version of RoB 2
    - Archive: RoB 2.0 (2016)
    - Archive: RoB 2.0 cluster-randomized trials (2016)
    - Archive: RoB 2.0 cross-over trials (2016)
  - ROBINS-I tool

RoB 2 tool

A revised Cochrane risk of bias tool for randomized trials

A revised tool to assess risk of bias in randomized trials (RoB 2)

Welcome to the website for the RoB 2 tool.

The latest version **(October 2018)** is suitable for individually-randomized, parallel-group trials.

We are also maintaining an archive of the previous version, which had variants for three different trial designs (see below).

Citing the tool

As an interim measure, the revised tool may be cited as: Higgins JPT, Sterne JAC, Savović J, Page MJ, Hróbjartsson A, Boutron I, Reeves B, Eldridge S. A revised tool for assessing risk of bias in randomized trials In: Chandler J, McKenzie J, Boutron I, Welch V (editors). Cochrane Methods. *Cochrane Database of Systematic Reviews* 2016, Issue 10 (Suppl 1). dx.doi.org/10.1002/14651858.CD201601.

MRC Hubs for Trials Methodology Research

This work was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/1- N61). Infrastructure support was provided by the Medical Research Council ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomized controlled Trials In Invasive procedures – MR/K025643/1).

Risk of bias tools

- Welcome
  - RoB 2 tool
    - Current version of RoB 2
    - Archive: RoB 2.0 (2016)
    - Archive: RoB 2.0 cluster-randomized trials (2016)
    - Archive: RoB 2.0 cross-over trials (2016)
  - ROBINS-I tool

Archived: individually-randomized, parallel group trials

Available:

- Background information and detailed guidance for using the RoB 2.0 tool.
- The tool itself
- Blank template for completing the tool
  - Implement RoB 2.0 when interest is in the effect of assignment to intervention
  - Implement RoB 2.0 when interest is in the effect of starting and adhering to intervention
- Excel implementation of the tool (cross-over trials) (contains macros)

View videos: RoB 2.0 tool Part 1, RoB 2.0 tool Part 2, RoB 2.0 tool Part 3, RoB 2.0 tool Part 4.

Archived: Cluster randomized trials (parallel groups)

Available:

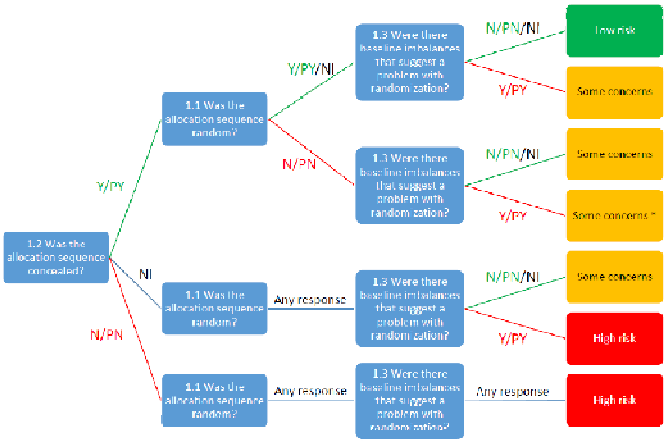
- Background information and detailed guidance for using the RoB 2.0 tool for cluster-randomized trials
- The tool (cluster-randomized trials) itself
- Blank template for completing the tool, which is currently available in one version
  - Implement RoB 2.0 for cluster-randomized trials when interest is in the effect of assignment to intervention

Archived: Cross-over trials (individually randomized)

Available:

- Background information and detailed guidance for using the RoB 2.0 tool for cross-over trials
- The tool (cross-over trials) itself

Key innovations



- **Result-focussed** assessments
- Fixed (inclusive) bias domains, **not modifiable**
- "**Signalling questions**" to facilitate risk of bias judgements
- New **response options** for risk of bias, without 'Unclear' option
- Formal **overall** risk of bias judgement

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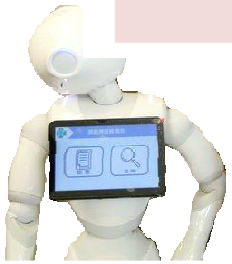
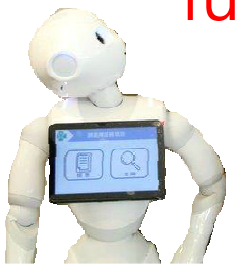
RoB 1.0	RoB 2.0
Random sequence generation (*selection bias*)	Bias arising from the randomization process
Allocation concealment (*selection bias*)	
Blinding of participants and personnel (*performance bias*)	Bias due to deviations from intended interventions
Incomplete outcome data (*attrition bias*)	Bias due to missing outcome data
Blinding of outcome assessment (*detection bias*)	Bias in measurement of the outcome
Selective reporting (*reporting bias*)	Bias in selection of the reported result
Other bias	N/A
N/A	Overall bias



https://training.cochrane.org/resource/rob-20-webinar

Other bias: funding?

- Cochrane Handbook: Funding and conflict of interest should not be addressed as a risk of bias domain.
- The Handbook provides no clear approach as to how funding and conflicts of interests should be addressed.
- **32% of Cochrane reviews published in 2014 incorporated funding into the "other bias"** function.



Jørgensen et al. Syst Rev. 2016 May 10;5:80.

Signaling questions and judgments

- Signalling questions are introduced to make the tool easier (and more transparent)
  - 'Yes', 'Probably yes', 'Probably no', 'No', 'No information'
- Risk of bias judgements follow from answers to signalling questions (can be over-ridden)
  - **'Low risk of bias', 'Some concerns', 'High risk of bias'**

- A change in the interpretation of the judgements, so that a 'High risk of bias' judgement in one domain puts the whole study at high risk of bias
- Overall risk of bias judgement can then be completed automatically (can be over-ridden)

https://training.cochrane.org/resource/rob-20-webinar

Overall risk of bias judgment

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.

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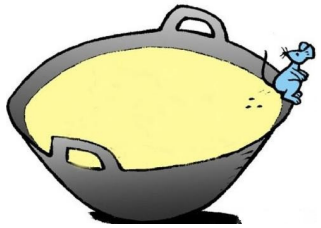
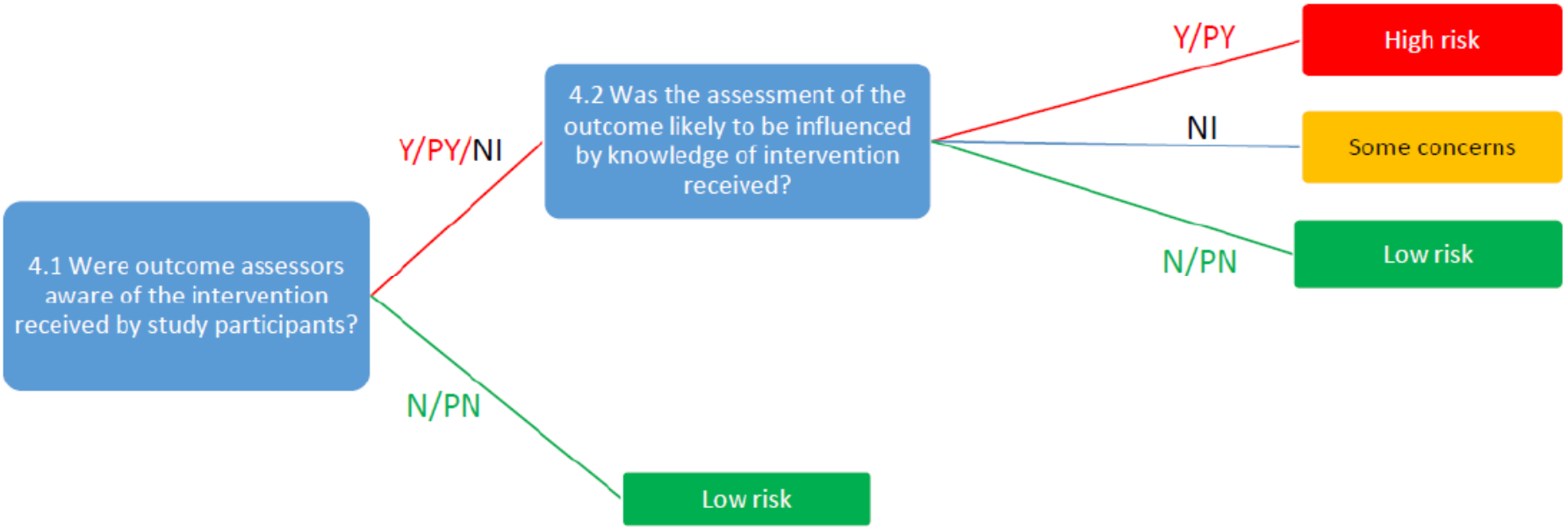


Examples of algorithm



Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y / PY / PN / N / NI	[Description]
	1.2 Was the allocation sequence concealed until participants were recruited and assigned to interventions?	Y / PY / PN / N / NI	[Description]
	1.3 Were there baseline imbalances that suggest a problem with the randomization process?	Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias arising from the randomization process?		[Rationale]
Bias due to deviations from intended interventions	2.1. Were participants aware of their assigned intervention during the trial?	Y / PY / PN / N / NI	[Description]
	2.2. Were carers and trial personnel aware of participants' assigned intervention during the trial?	Y / PY / PN / N / NI	[Description]
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention beyond what would be expected in usual practice?	NA / Y / PY / PN / N / NI	[Description]
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?	NA / Y / PY / PN / N / NI	[Description]
	2.5 Were any participants analysed in a group different from the one to which they were assigned?	Y / PY / PN / N / NI	[Description]
	2.6 If Y/PY/NI to 2.5: Was there potential for a substantial impact (on the estimated effect of intervention) of analysing participants in the wrong group?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias due to deviations from intended interventions?		[Rationale]
Bias due to missing outcome data	3.1 Were outcome data available for all, or nearly all, participants randomized?	Y / PY / PN / N / NI	[Description]
	3.2 If N/PN/NI to 3.1: Are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?	NA / Y / PY / PN / N / NI	[Description]
	3.3 If N/PN/NI to 3.1: Is there evidence that results were robust to the presence of missing outcome data?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias due to missing outcome data?		[Rationale]
Bias in measurement of the outcome	4.1 Were outcome assessors aware of the intervention received by study participants?	Y / PY / PN / N / NI	[Description]
	4.2 If Y/PY/NI to 4.1: Was the assessment of the outcome likely to be influenced by knowledge of intervention received?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias due to measurement of the outcome?		[Rationale]
Bias in selection of the reported result	Are the reported outcome data likely to have been selected, on the basis of the results, from...		
	5.1. ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Y / PY / PN / N / NI	[Description]
	5.2 ... multiple analyses of the data?	Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias due to selection of the reported result?		[Rationale]
Overall bias	**Risk of bias judgement**	Low / High / Some concerns	[Support]
	Optional: What is the overall predicted direction of bias for this outcome?		[Rationale]

The RoB 2.0 tool (individually randomized, parallel group trials)

Study design

- ☑ Randomized parallel group trial
- ☐ Cluster-randomized trial
- ☐ Randomized cross-over or other matched design

Specify which outcome is being assessed for risk of bias

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Is your aim for this study…?

- ☐ to assess the effect of *assignment to interventio*
- ☐ to assess the effect of *starting and adhering to i*

Which of the following sources have you <u>obtained</u> to help inform your risk of bias judgements (tick as many as apply)?

- ☐ Journal article(s) with results of the trial
- ☐ 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
- ☐ Grant database summary (e.g. NIH RePORTER, Research Councils UK Gateway to Research)
- ☐ Personal communication with trialist
- ☐ Personal communication with the sponsor

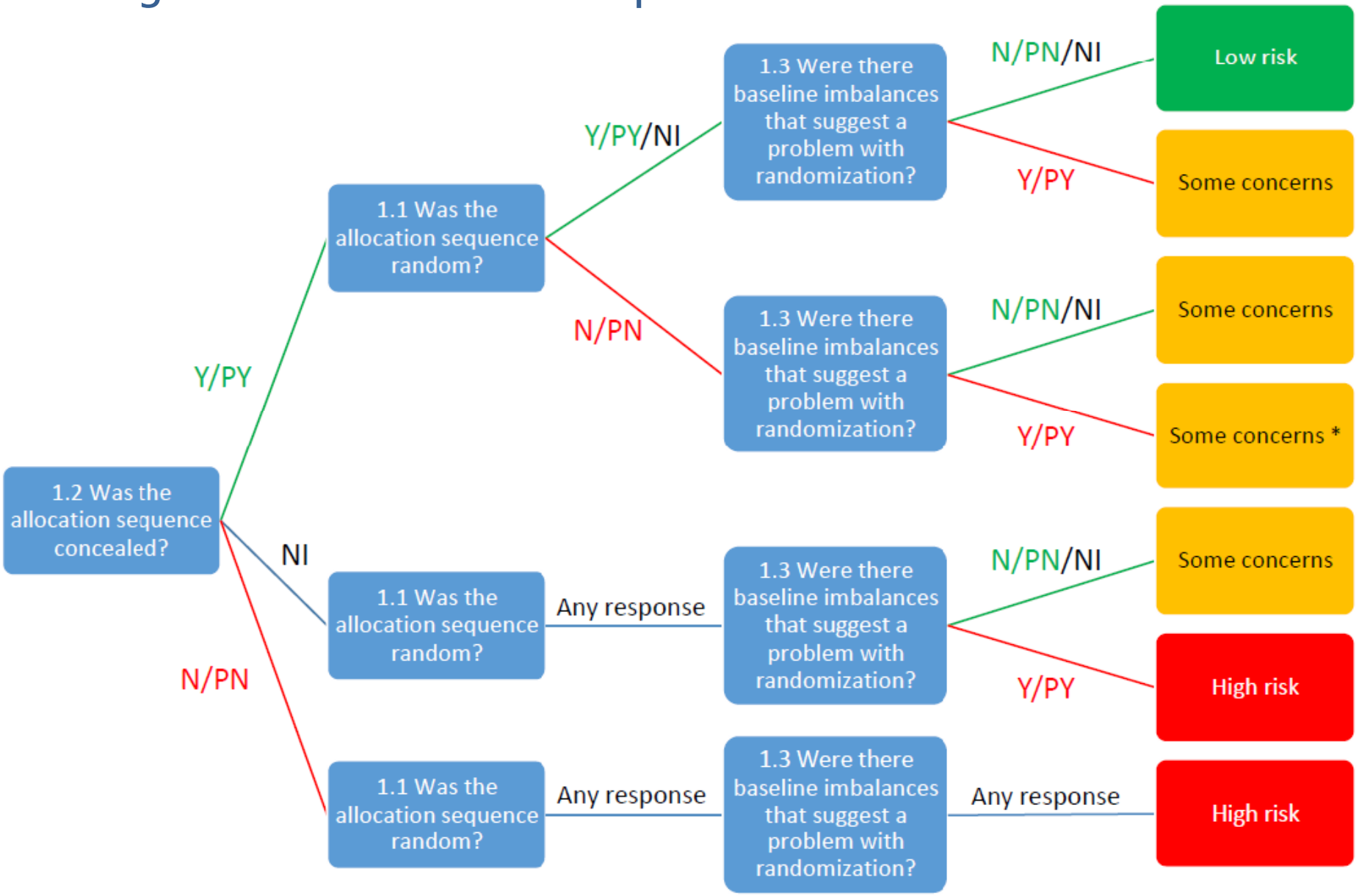
The RoB 2.0 tool

- ☑ Bias arising from the randomization process
- ☐ Bias due to deviations from intended interventions
- ☐ Bias due to missing outcome data
- ☐ Bias in measurement of the outcome
- ☐ Bias in selection of the reported result

Bias arising from the randomization process

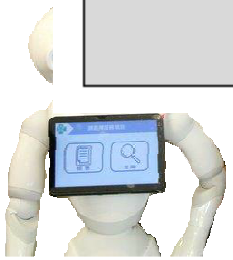
1.1 Was the allocation sequence random? 1.2 Was the allocation sequence concealed until participants were recruited and assigned to interventions?	**Randomization methods**
1.3 Were there baseline imbalances that suggest a problem with the randomization process?	**Additional evidence of problems**

Suggested algorithm for reaching risk of bias judgments for bias arising from the randomization process



Box 4. The RoB 2 tool (part 2): Risk of bias arising from the randomization process

Signalling questions	Elaboration	Response options
1.1 Was the allocation sequence random?	Answer 'Yes' if a random component was used in the sequence generation process. Examples include computer-generated random numbers; reference to a random number table; coin tossing; shuffling cards or envelopes; throwing dice; or drawing lots. Minimization is generally implemented with a random element (at least when the scores are equal), so an allocation sequence that is generated using minimization should generally be considered to be random. Answer 'No' if no random element was used in generating the allocation sequence or the sequence is predictable. Examples include alternation; methods based on dates (of birth or admission); patient record numbers; allocation decisions made by clinicians or participants; allocation based on the availability of the intervention; or any other systematic or haphazard method. Answer 'No information' if the only information about randomization methods is a statement that the study is randomized. In some situations a judgement may be made to answer 'Probably no' or 'Probably yes'. For example, if the study was large, conducted by an independent trials unit or carried out for regulatory purposes, it may be reasonable to assume that the sequence was random. Alternatively, if other (contemporary) trials by the same investigator team have clearly used non-random sequences, it might be reasonable to assume that the current study was done using similar methods.	Y / PY / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Answer 'Yes' if the trial used any form of remote or centrally administered method to allocate interventions to participants , where the process of allocation is controlled by an external unit or organization, independent of the enrolment personnel (e.g. independent central pharmacy, telephone or internet-based randomization service providers). Answer 'Yes' if envelopes or drug containers were used appropriately. Envelopes should be sequentially numbered, sealed with a tamper-proof seal and opaque. Drug containers should be sequentially numbered and of identical appearance. This level of detail is rarely provided in reports, and a judgement may be required to justify an answer of 'Probably yes' or 'Probably no'. Answer 'No' if there is reason to suspect that the enrolling investigator or the participant had knowledge of the forthcoming allocation.	Y / PY / PN / N / NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	*Note that differences that are compatible with chance do not lead to a risk of bias.* Answer 'No' if no imbalances are apparent or if any observed imbalances are compatible with chance Answer 'Yes' if there are imbalances that indicate problems with the randomization process, including: (1) substantial differences between intervention group sizes, compared with the intended allocation ratio; or (2) a substantial excess in statistically significant differences in baseline characteristics between intervention groups, beyond that expected by chance; or (3) imbalance in one or more key prognostic factors, or baseline measures of outcome variables, that is very unlikely to be due to chance and for which the between-group difference is big enough to result in bias in the intervention effect estimate.	Y / PY / PN / N / NI



4 Detailed guidance: bias arising from the randomization process

4.1 Background

If successfully accomplished
(factors that predict the outc
assignment. This means tha
intervention. If prognostic f
estimated effect of intervent
intervention group assignr
intervention effect estimate
influenced by prognostic fac

To randomize participants i
on some chance (random) p
taken to prevent participant
hs confirmed. This process i

Knowledge of the next assig
enrolment of participants o
intervention deemed to be
bias. Other participants ma
delaying their entry into
manipulation of the assigne
sequence concealment is a v

Some review authors confus
Allocation concealment see
participants from knowing
implemented, regardless of
after assignment (16, 17), an
comparing surgical with nor
of the intervention and blin

4.3.1.1 *Assessing sequence generation when insufficient information is provided about the methods used*

A simple statement such as "we randomly allocated" or "using a randomized design" is often insufficient to be confident that the allocation sequence was genuinely randomized. Indeed, it is common for authors to use the term "randomized" even when it is not justified: many trials with declared systematic allocation have been described by the authors as "randomized". In some situations, a reasonable judgement may be made about whether a random sequence was used. For example, if the study was large, conducted by an independent trials unit or carried out for regulatory purposes, it may be reasonable to assume that the sequence was random and to answer 'Probably yes' to the signalling question. Alternatively, if other (contemporary) trials by the same investigator team have clearly used non-random sequences, it might be reasonable to assume that the current study was done using similar methods, and answer 'Probably no' to the signalling question. If users of the tool are not able (or insufficiently confident) to make such judgements, an answer of 'No information' should be provided.

Trial authors may describe their approach to sequence generation incompletely, without confirming that there was a random component. For example, authors may state that blocked allocation was used without describing the process of selecting the order of allocation within the blocks. In such instances, an answer of 'No information' should generally be provided.

4.3.2 *Assessing concealment of allocation sequence*

Among the methods used to conceal allocation, central randomization by a third party is the most desirable. Methods using envelopes are more susceptible to manipulation than other approaches (15, 21). If investigators use envelopes, they should develop and monitor the allocation process to preserve concealment. In addition to use of sequentially numbered, opaque, sealed envelopes, they should ensure that the envelopes are opened sequentially, and only after the envelope has been irreversibly assigned to the participant. When blocking is used, it be may be possible to predict the last intervention assignments within each block. This will be a problem when the person recruiting participants knows the start and end of each block and the allocations are revealed after assignment. The problem is likely to be more serious if block sizes are small and of equal sizes. In such situations, an answer of 'No' or 'Probably no' should be provided for the signalling question concerning whether allocations were concealed.

The RoB 2.0 tool

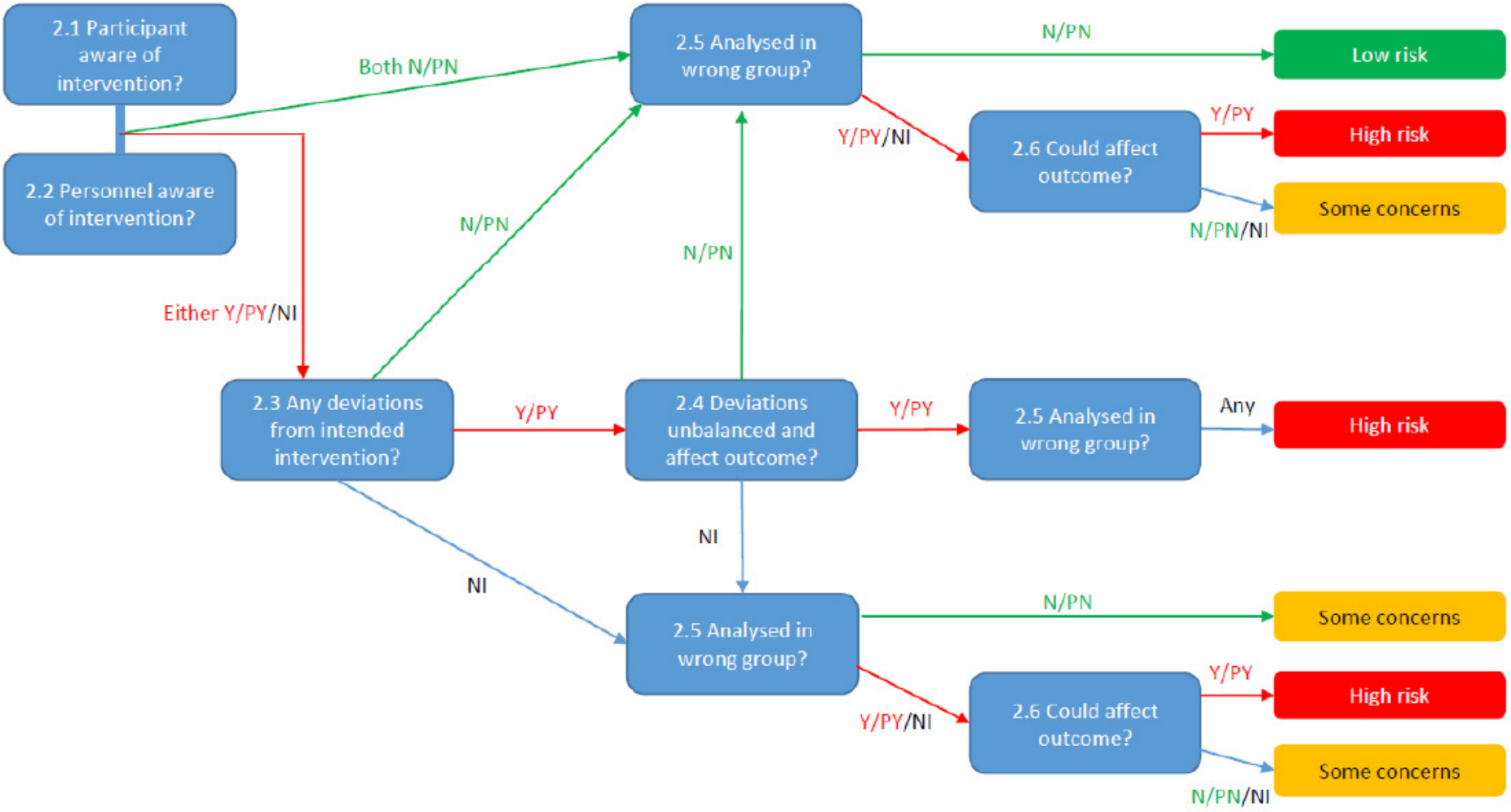
- ☐ Bias arising from the randomization process
- ☑ Bias due to deviations from intended interventions
- ☐ Bias due to missing outcome data
- ☐ Bias in measurement of the outcome
- ☐ Bias in selection of the reported result

Bias due to deviations from intended interventions

Effect of assignment to intervention

2.1. Were participants aware of their assigned intervention during the trial? 2.2. Were carers and trial personnel aware of participants' assigned intervention during the trial?	**Blinding**
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention beyond what would be expected in usual practice? 2.4. If Y/PY to 2.3: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?	**Deviations reflect usual practice?**
2.5 Were any participants analysed in a group different from the one to which they were assigned? 2.6 If Y/PY/NI to 2.5: Was there potential for a substantial impact (on the estimated effect of intervention) of analysing participants in the wrong group?	**First principle of ITT**

Suggested algorithm for reaching risk of bias judgments for bias due to deviations from intended interventions (*effect of assignment to intervention*).



Bias due to deviations from intended interventions

Effect of starting and adhering to intervention

2.1. Were participants aware of their assigned intervention during the trial? 2.2. Were carers and trial personnel aware of participants' assigned intervention during the trial?	**Blinding**
2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups? 2.4. Was the intervention implemented successfully? 2.5. Did study participants adhere to the assigned intervention regimen?	**Specific deviations**
2.6. If N/PN/NI to 2.3, 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	**Overcome by analysis?**

The RoB 2.0 tool

- ☐ Bias arising from the randomization process
- ☐ Bias due to deviations from intended interventions
- ☑ Bias due to missing outcome data
- ☐ Bias in measurement of the outcome
- ☐ Bias in selection of the reported result

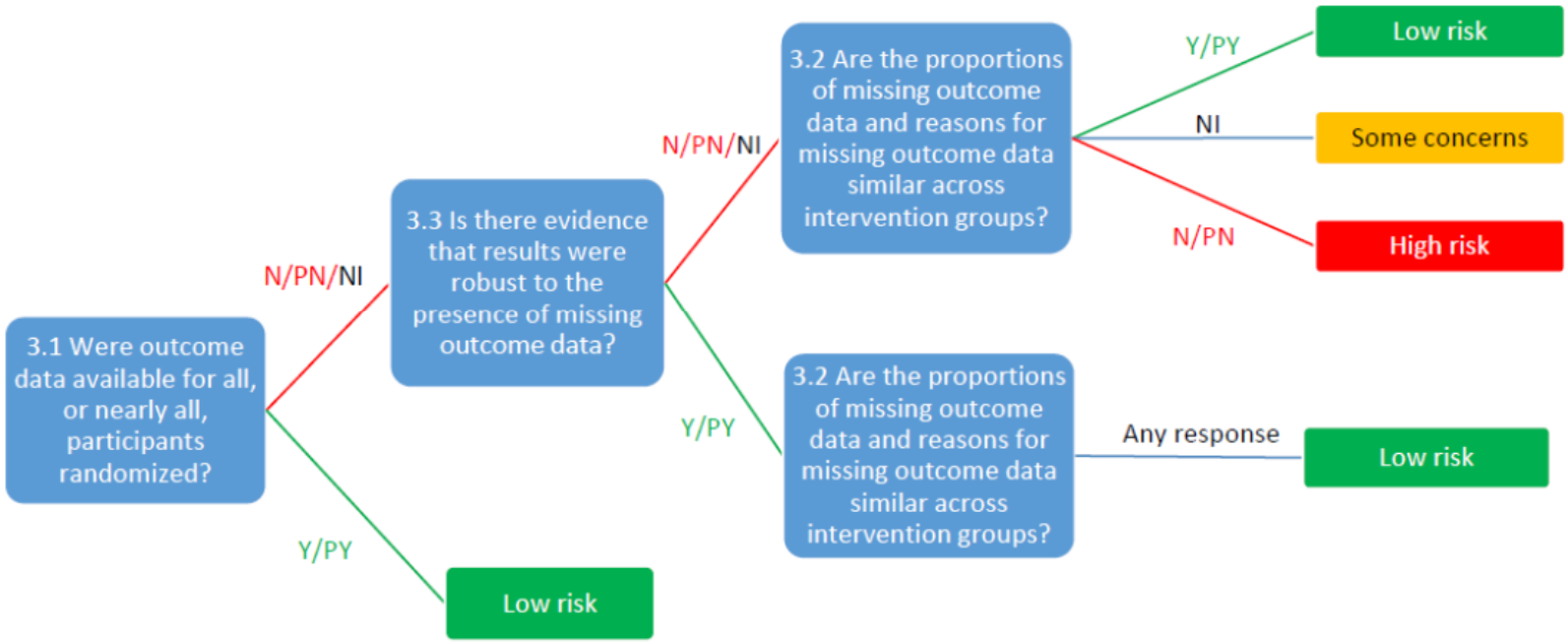
Bias due to missing outcome data

- When complete outcome data for all participants is not available for your review
  - attrition - loss to follow up, withdrawals, other missing data
  - exclusions – some available data not included in report
- Considerations
  - how much data is missing from each group? (include numbers in your description)
  - why is it missing?
  - how were the data analysed?

Bias due to missing outcome data

3.1. Were outcome data available for all, or nearly all, participants randomized?	**Any missing data?**
3.2. If N/PN/NI to 3.1: Are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?	**Amount and reasons?**
3.3. If N/PN/NI to 3.1: Is there evidence that results were robust to the presence of missing outcome data?	**Results robust?**

Bias due to missing outcome data



The RoB 2.0 tool

- ☐ Bias arising from the randomization process
- ☐ Bias due to deviations from intended interventions
- ☐ Bias due to missing outcome data
- ☑ Bias in measurement of the outcome
- ☐ Bias in selection of the reported result

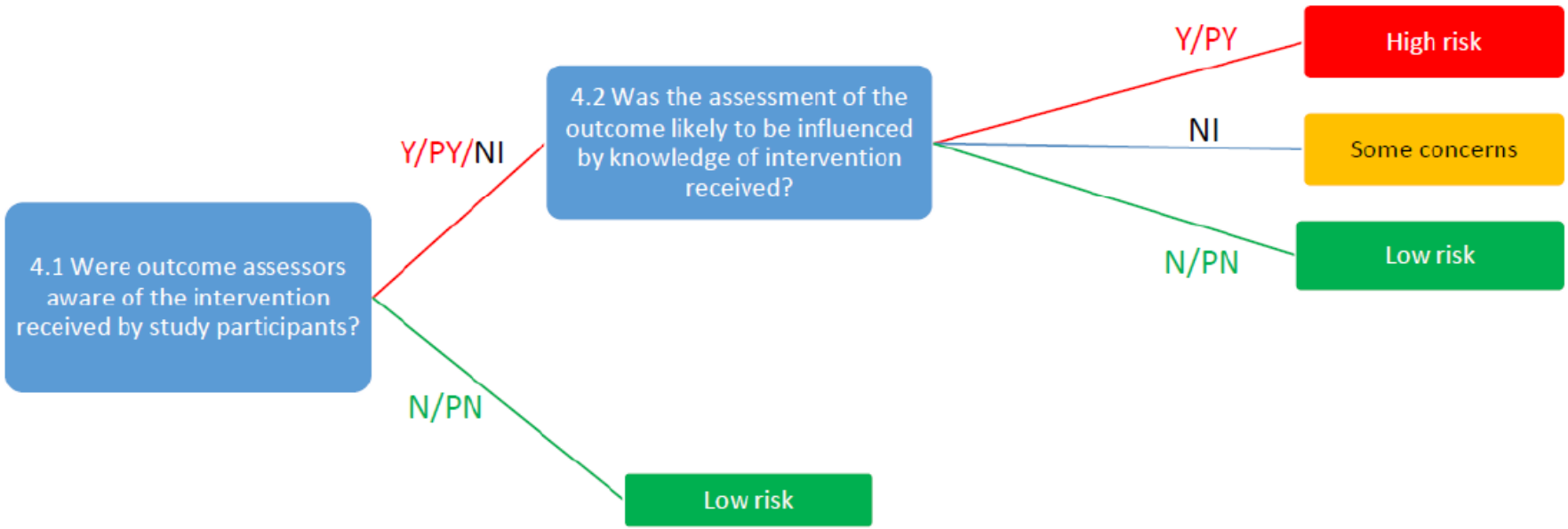
Bias in measurement of the outcome

- Systematic differences between groups in how outcomes are assessed
- Some outcomes are more prone to bias than others
  - Patient-reported outcome (e.g. pain, quality of life)
  - Observer-reported involving judgement (e.g. clinical examination)
  - Observer-reported not involving judgement (e.g. all-cause mortality)

Bias in measurement of the outcome

4.1. Were outcome assessors aware of the intervention received by study participants?	**Blinding?**
4.2. If Y/PY/NI to 4.1: Was the assessment of the outcome likely to be influenced by knowledge of intervention received?	**Assessment influenced?**

Suggested algorithm for reaching risk of bias judgments for bias in measurement of the outcome.



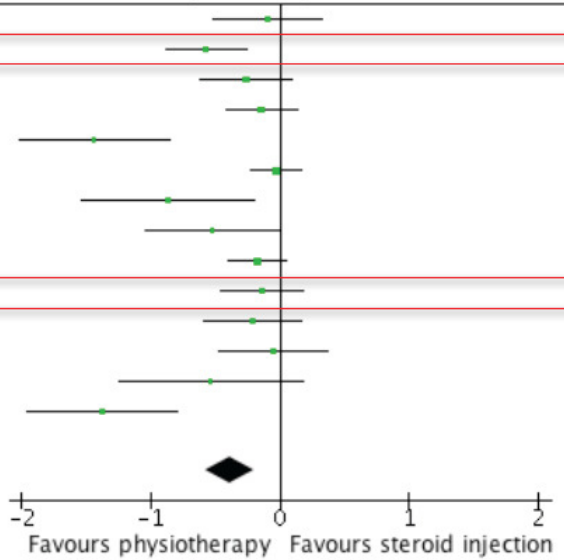
The RoB 2.0 tool

- ☐ Bias arising from the randomization process
- ☐ Bias due to deviations from intended interventions
- ☐ Bias due to missing outcome data
- ☐ Bias in measurement of the outcome
- ☑ Bias in selection of the reported result

Study or Subgroup	Physiotherapy Mean	SD	Total	Steroid injection Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Djordjevic 2012	10.8	20.3	42	12.8	21	46	7.1%	-0.10 [-0.51, 0.32]	+ ? + + + + +
Engebretsen 2009	5.6	3.4	80	7.8	4.3	78	8.3%	-0.57 [-0.88, -0.25]	+ + - - + - -
Ginn 2005	33	45	60	44	40	65	7.9%	-0.26 [-0.61, 0.09]	? ? - - + ? +
Giombini 2006	2.5	2.7	100	2.9	3	97	8.8%	-0.14 [-0.42, 0.14]	+ ? - - + + +
Haahr 2005	2.3	1.5	30	4.7	1.8	28	5.4%	-1.43 [-2.02, -0.85]	+ + - - + ? +
Kaya 2014	12.4	23	200	13.2	33	200	9.8%	-0.03 [-0.22, 0.17]	+ ? - - + ? +
Kromer 2013	0.5	1.8	18	2	1.6	20	4.6%	-0.87 [-1.53, -0.20]	+ + - - + + +
Littlewood 2014	34	20	30	44	18	30	6.0%	-0.52 [-1.03, -0.00]	+ + - - + + +
Ludewig 2003	1	2.1	150	1.4	2.5	148	9.4%	-0.17 [-0.40, 0.05]	+ ? - - + ? +
Martins 2012	11	33	75	15	24	76	8.3%	-0.14 [-0.46, 0.18]	? ? ? ? + - +
Moosmayer 2014	1.8	2.3	55	2.3	2.4	55	7.6%	-0.21 [-0.59, 0.16]	+ + - - + ? +
Rhon 2014	1.6	1.93	42	1.7	2.02	46	7.1%	-0.05 [-0.47, 0.37]	+ + - - + + +
Struyf 2013	18	23	16	30	21	16	4.3%	-0.53 [-1.24, 0.18]	+ + ? ? + + +
Teys 2008	1.8	1.5	30	4.1	1.8	28	5.4%	-1.37 [-1.95, -0.80]	+ ? + + + ? +
Total (95% CI)			**928**			**933**	**100.0%**	**-0.38 [-0.57, -0.19]**	

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 47.04$, df = 13 ($P < 0.00001$); $I^2 = 72\%$

Test for overall effect: $Z = 3.97$ ($P < 0.0001$)



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias): Self-reported outcomes

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

Bias in selection of the reported result

Trial result is biased because it has been selected on the basis of the results from multiple:

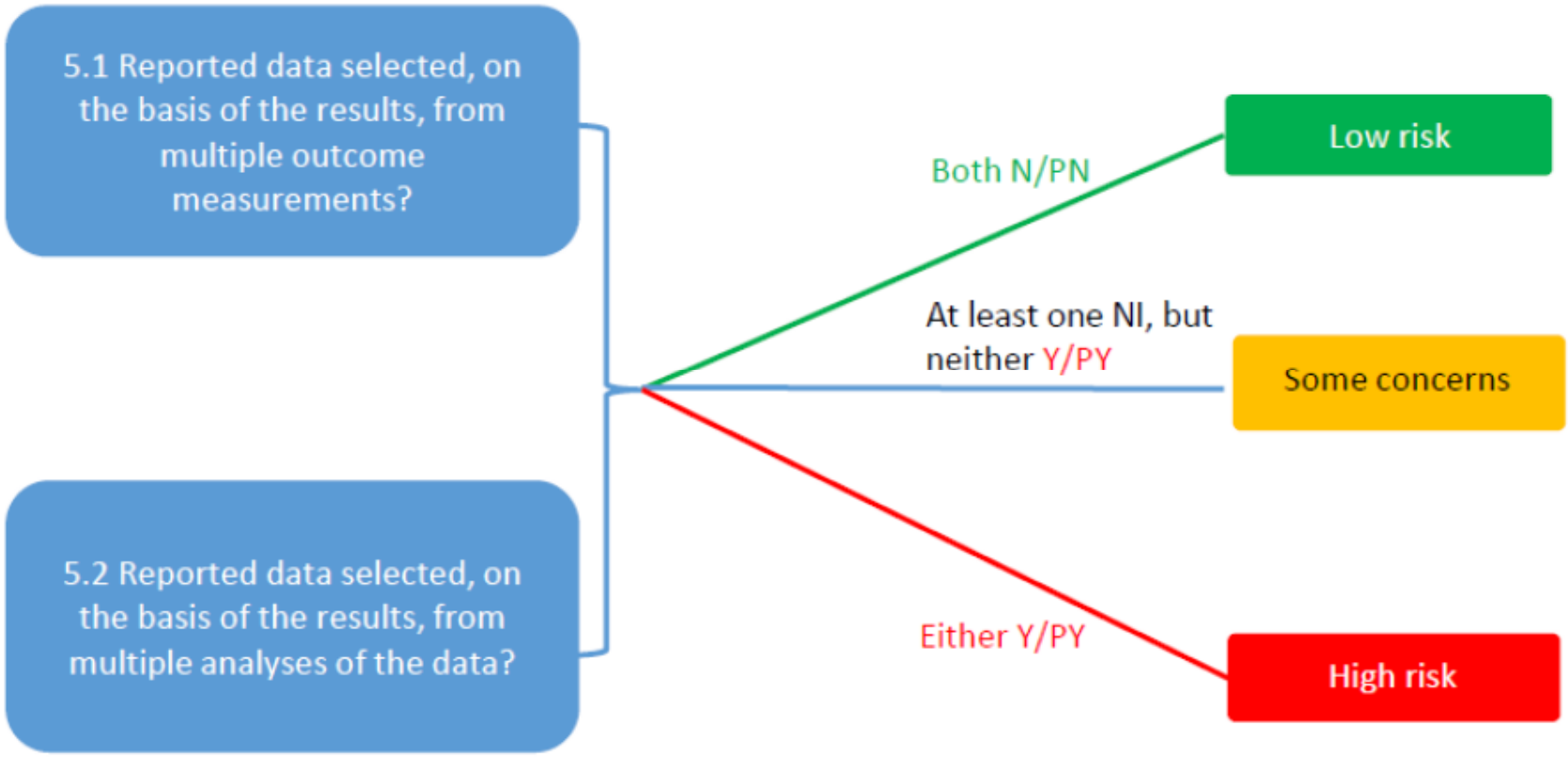
- Outcome measurements
  - Scales
  - Definitions of/criteria for an event
  - Time points
- Analyses
  - Unadjusted vs adjusted models
  - Different sets of covariates in adjusted models
  - Final values vs change from baseline vs analysis of covariance
  - Continuous scale converted to categorical data with different cut-points

Bias in selection of the reported result

Are the reported outcome data likely to have been selected, on the basis of the results, from...

5.1. ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	**Selective outcome reporting**
5.2 ... multiple analyses of the data?	**Selective analysis reporting**

Bias in selection of the reported result



Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y / PY / PN / N / NI	[Description]
	1.2 Was the allocation sequence concealed until participants were recruited and assigned to interventions?	Y / PY / PN / N / NI	[Description]
	1.3 Were there baseline imbalances that suggest a problem with the randomization process?	Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias arising from the randomization process?		[Rationale]
Bias due to deviations from intended interventions	2.1. Were participants aware of their assigned intervention during the trial?	Y / PY / PN / N / NI	[Description]
	2.2. Were carers and trial personnel aware of participants' assigned intervention during the trial?	Y / PY / PN / N / NI	[Description]
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention beyond what would be expected in usual practice?	NA / Y / PY / PN / N / NI	[Description]
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?	NA / Y / PY / PN / N / NI	[Description]
	2.5 Were any participants analysed in a group different from the one to which they were assigned?	Y / PY / PN / N / NI	[Description]
	2.6 If Y/PY/NI to 2.5: Was there potential for a substantial impact (on the estimated effect of intervention) of analysing participants in the wrong group?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias due to deviations from intended interventions?		[Rationale]
Bias due to missing outcome data	3.1 Were outcome data available for all, or nearly all, participants randomized?	Y / PY / PN / N / NI	[Description]
	3.2 If N/PN/NI to 3.1: Are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?	NA / Y / PY / PN / N / NI	[Description]
	3.3 If N/PN/NI to 3.1: Is there evidence that results were robust to the presence of missing outcome data?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias due to missing outcome data?		[Rationale]
Bias in measurement of the outcome	4.1 Were outcome assessors aware of the intervention received by study participants?	Y / PY / PN / N / NI	[Description]
	4.2 If Y/PY/NI to 4.1: Was the assessment of the outcome likely to be influenced by knowledge of intervention received?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias due to measurement of the outcome?		[Rationale]
Bias in selection of the reported result	Are the reported outcome data likely to have been selected, on the basis of the results, from...		
	5.1. ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Y / PY / PN / N / NI	[Description]
	5.2 ... multiple analyses of the data?	Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias due to selection of the reported result?		[Rationale]
Overall bias	**Risk of bias judgement**	Low / High / Some concerns	[Support]
	Optional: What is the overall predicted direction of bias for this outcome?		[Rationale]

Useful implement

RoB 2.0 Assessment Form | Summary | Populate Printing

ion

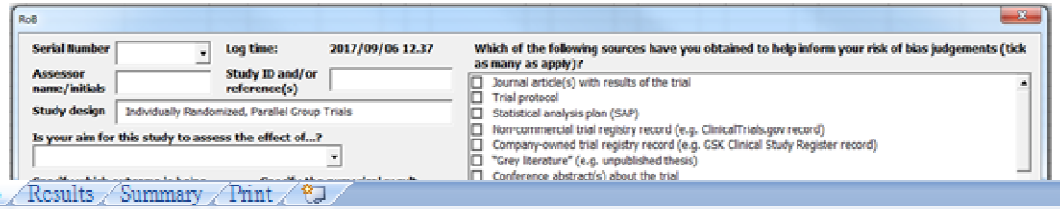
eractive form built for Risk of Bias 2.0 (RoB 2.0) assessment. This Excel form is built using Visual Basic for Application (VBA) under Microsoft Excel environment.

System and software Requirement

Microsoft Excel 2016 in Windows or Macintosh operating systems.
The compatibility of older versions of Microsoft Excel has not tested yet.

Start an RoB 2.0 Assessment Form

1. Please enable Macros while opening this form.
2. Click the 'Rob 2.0 Assessment Form' button in this page.
3. This will initial the Rob 2.0 Assessment Form as below. The form will look slightly different in Macintosh operating systems but it does not affect the function.



RoB 2.0 Individual randomized, parallel group trials

Serial Number test **Log time:** 2018/07/03 05.37

Assessor name/initials Samuel **Study ID and/or reference(s)** TVGH2018

Study design Individually Randomized, Parallel Group Trials

Is your aim for this study to assess the effect of...?

assignment to intervention

Specify which outcome is being assessed for risk of bias

Pain

Specify the numerical result being assessed.

Which of the following sources have you obtained to help inform your risk of bias judgements (tick as many as apply)?

- [x] Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
- [x] Company-owned trial registry record (e.g. GSK Clinical Study Register record)
- [x] "Grey literature" (e.g. unpublished thesis)
- [x] Conference abstract(s) about the trial
- [x] Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- [x] Research ethics application
- [x] Grant database summary (e.g. NIH RePORTER, Research Councils UK Gateway to Research)
- [x] Personal communication with trialist
- [x] Personal communication with the sponsor

Randomisation | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of reported results | Overall bias

Randomisation

1.1 Was the allocation sequence random?	PY
1.2 Was the allocation sequence concealed until participants were recruited *and assigned to interventions?*	PY
1.3 Were there baseline imbalances that suggest a problem with the randomization process?	PN

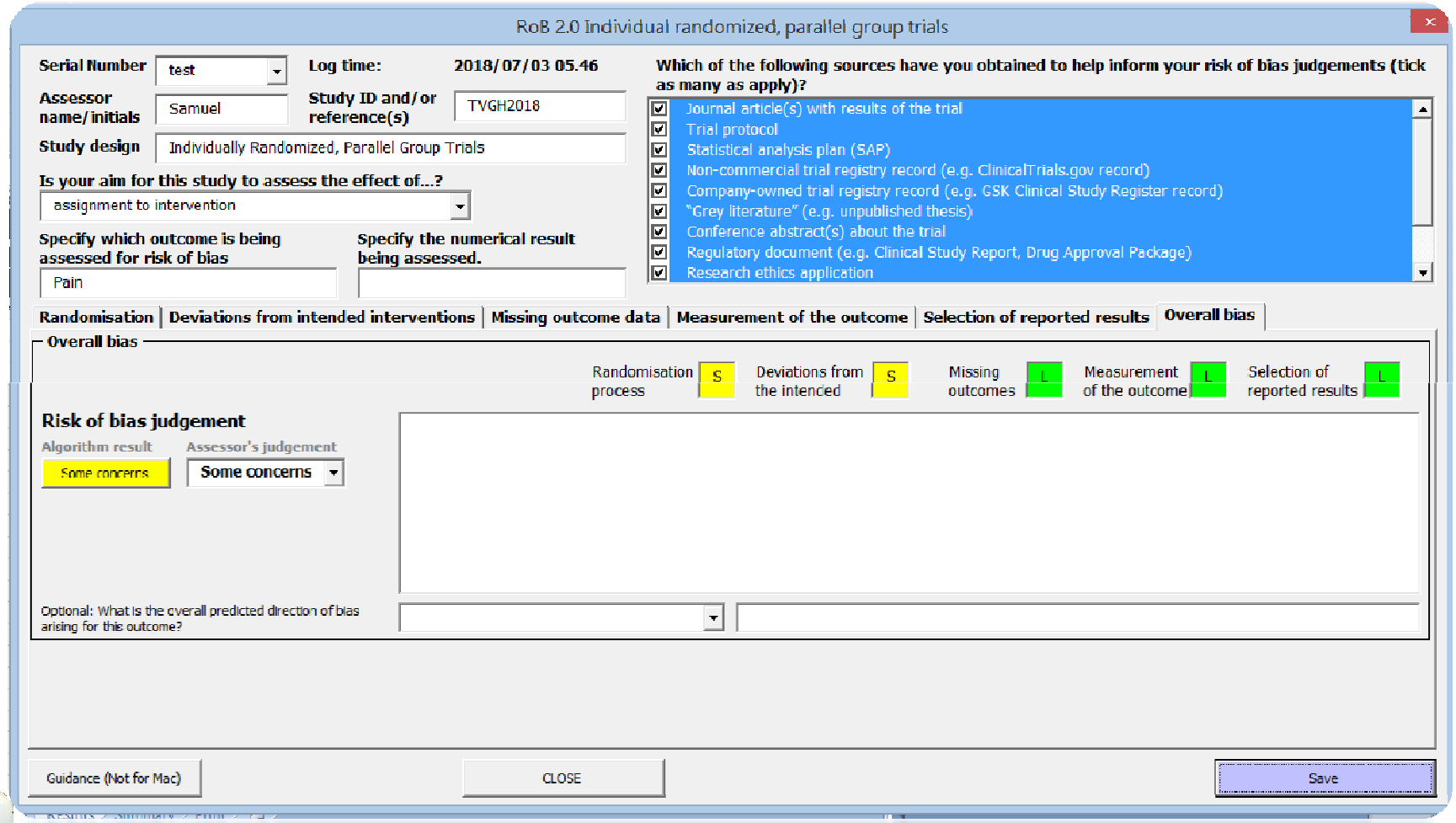
RIsk of bias judgement

Algorithm result: Low

Assessor's judgement: Some concerns

Optional: What is the predicted direction of bias arising from the randomization process?

Guidance (Not for Mac) CLOSE Save

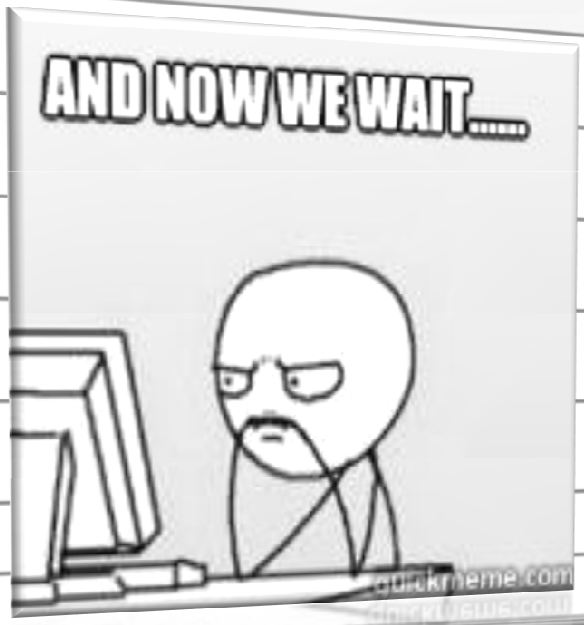


	Serial Numbe	Reviewer	Study ID	Outcome	Result	Randomization process	Deviations from intended interventions	Mising outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
2	test	Daisy	TVGH2018	Pain	SMD blabla	Some concerns	Some concerns	Low	Low	Low	Some concerns
3	test2	Samuel	TVGH2018	Pain	SMD blablabla	Some concerns	High	Low	High	Low	High

RoB 2.0 not integrated in to current Revman

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Low risk / Unclear risk / High risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	



Included studies

RoB 2.0

Apply?

臺中榮民總醫院
Taichung Veterans General Hospital