Introduction to the ROBUST-RCT

(Risk Of Bias instrument for Use in SysTematic reviews-for Randomised Controlled Trials)

Ying Wang, PhD
EBM center of Beijing University of Chinese Medicine

ROBUST-RCT

- **A rigorously developed, simply structured, and user-friendly instrument for assessing RoB of RCTs in SRs**

- Led by team from McMaster University (Gordon Guyatt, Ying Wang, Romina Brignardello-Petersen, Reed AC Siemieniuk, and Dena Zeraatkar)

- International collaboration: panel included 19 experts (16 methodologists and 3 EBM educators) from 12 countries

- Criteria for selecting methodologists: first/last/corresponding author of at least one RoB methodological paper, and co-author of at least two other papers

  (most RoB methodological papers identified from references of existing RCT RoB instruments)

Ground rules for development / Characteristics of ROBUST-RCT

- Aims to assess RoB of RCTs in the context of SRs
- A user-friendly instrument: item presentation simple and straightforward; making judgments not overly complex or difficult
- Bias: a systematic error or systematic deviation from the truth
- Assume systematic reviewers will use the GRADE approach to assess certainty of evidence
- Distinguish RoB from imprecision (random error), indirectness (applicability), publication bias, and reporting quality
- Currently addresses only individually randomized parallel group trials
- Not include items for the detection of fraud

Assembled panel

16 RoB methodologists, 3 EBM educators

↓

Collected candidate items

Systematic survey of existing RoB instruments

↓

Collected empirical evidence

Systematic survey of meta-epidemiological studies

↓

Held sixteen 1.5-hour panel meetings

Item selection

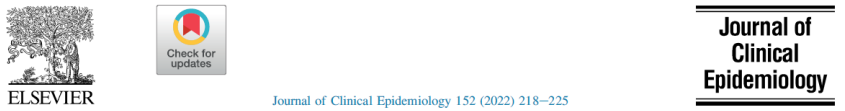
Instructions for included items

Presentation of the instrument

↓

Conducted user testing

15 junior systematic reviewers, 8 review experts



Journal of Clinical Epidemiology 152 (2022) 218–225

ORIGINAL ARTICLE

Instruments assessing risk of bias of randomized trials frequently included items that are not addressing risk of bias issues

Ying Wang[a,*], Maryam Ghadimi[a], Qi Wang[b], Liangying Hou[b], Dena Zeraatkar[a,c], Atiya Iqbal[a], Cameron Ho[d], Liang Yao[a], Malini Hu[e], Zhikang Ye[a], Rachel Couban[f], Susan Armijo-Olivo[g,h], Dirk Bassler[i], Matthias Briel[a,j], Lise Lotte Gluud[k], Paul Glasziou[l], Rod Jackson[m], Sheri A. Keitz[n], Luz M. Letelier[o], Philippe Ravaud[p], Kenneth F. Schulz[q], Reed A.C. Siemieniuk[a], Romina Brignardello-Petersen[a], Gordon H. Guyatt[a]

Journal of Clinical Epidemiology 165 (2024) 111211

ORIGINAL ARTICLE

Compelling evidence from meta-epidemiological studies demonstrates overestimation of effects in randomized trials that fail to optimize randomization and blind patients and outcome assessors

Ying Wang[a,*], Sameer Parpia[b], Rachel Couban[c], Qi Wang[d], Susan Armijo-Olivo[e,f], Dirk Bassler[g], Matthias Briel[h], Romina Brignardello-Petersen[a], Lise Lotte Gluud[i], Sheri A. Keitz[j], Luz M. Letelier[k], Philippe Ravaud[l], Kenneth F. Schulz[m], Reed A.C. Siemieniuk[a], Dena Zeraatkar[a], Gordon H. Guyatt[a]

RESEARCH METHODS AND REPORTING

Check for updates

Development of ROBUST-RCT: Risk Of Bias instrument for Use in SysTematic reviews-for Randomised Controlled Trials

Ying Wang,[1,2] Sheri Keitz,[3] Matthias Briel,[2,4] Paul Glasziou,[5] Romina Brignardello-Petersen,[2] Reed A C Siemieniuk,[2] Dena Zeraatkar,[2,6] Elie A Akl,[2,7] Susan Armijo-Olivo,[8,9] Dirk Bassler,[10] Carrol Gamble,[11] Lise Lotte Gluud,[12] Jane Luise Hutton,[13] Luz M Letelier,[14] Philippe Ravaud,[15] Kenneth F Schulz,[16] David J Torgerson,[17] Gordon H Guyatt[2,18,19]

User testing confirmed simplicity and ease of practical application of ROBUST-RCT: junior systematic reviewers are able to assess core items correctly

Criteria for item selection

- Clearly a risk of bias problem rather than imprecision, indirectness, publication bias, or reporting quality
- Theoretical or logical argument for why the item is important
- Information required to make judgment on the item is commonly reported in trials
- Non-expert systematic reviewers can make the judgment easily
- Problem occurs more often than rarely
- Empirical evidence supports item influence on effect estimates

Risk Of Bias instrument for Use in SysTematic reviews-for Randomized Controlled Trials (ROBUST-RCT)

Study reference:

State the outcome(s) that are being assessed for risk of bias:

Six core items – each includes two steps

Core items and response options	Step 1 Evaluate what happened	Step 2 Judge risk of bias
Core items:		
Item 1 Random sequence generation	Was the allocation sequence adequately generated?	Judge risk of bias related to sequence generation
Item 2 Allocation concealment	Was the allocation adequately concealed?	Judge risk of bias related to allocation concealment
Item 3 Blinding of participants	Were participants blinded?	Judge risk of bias related to blinding of participants
Item 4 Blinding of healthcare providers	Were healthcare providers blinded?	Judge risk of bias related to blinding of healthcare providers
Item 5 Blinding of outcome assessors	Were outcome assessors blinded?	Judge risk of bias related to blinding of outcome assessors
Item 6 Outcome data not included in analysis	Extract the number of participants who were not included in analysis in each group	Judge risk of bias related to the overall percentage of participants not included in analysis
Response options	Definitely yes, probably yes, probably no, definitely no (except for item 6)	Definitely low, probably low, probably high, definitely high

Items 1-5, who complete which step?

Approach 1: front-line reviewers complete both steps

Approach 2: front-line reviewers (if less experienced) complete only step 1 and review leaders (more experienced) complete step 2

Item 4: Blinding of healthcare providers

Step 1: Were healthcare providers blinded

☐ **Definitely Yes**	Trial explicitly stated that healthcare providers were blinded.
☐ **Probably Yes**	No explicit statement about blinding of healthcare providers, and: - it is a placebo-controlled drug trial; or - it is an active control drug trial (A vs. B) and mention of "double dummy" or that medications were identical or matched; or - trial was described as "single blinded", "double blinded" or "triple blinded", and the best judgment is that one of the blinded groups is the healthcare providers.
☐ **Probably No**	No explicit statement about blinding of healthcare providers, and: - it is an active control drug trial (A vs. B) but no mention of "double dummy" or that medications were identical or matched; or - it is a non-drug trial; or - trial was described as "single blinded" and the best judgement is that the single blinded group is someone other than the healthcare providers.
☐ **Definitely No**	• Trial explicitly stated that healthcare providers were not blinded. • Trial was described as "open-label" or "unblinded".

Support for judgement:

Step 2: Judge risk of bias related to blinding of healthcare providers

Issues to consider:

i) Were healthcare providers blinded (step 1)

ii) *If unblinded, how likely unblinding of healthcare providers has influenced the outcome*

- *How likely healthcare provider-initiated co-interventions have influenced the outcome*

☐ **Definitely Low**	Healthcare providers were definitely blinded.
☐ **Probably Low**	• Healthcare providers were probably blinded; OR • Unblinding of healthcare providers unlikely to have influenced the outcome because: - Unlikely there is any healthcare provider-initiated co-intervention that could potentially influence the outcome; or - Investigators have documented all healthcare provider-initiated co-interventions that could potentially influence the outcome and demonstrated similarity in use of all these co-interventions between groups.
☐ **Probably High**	• Healthcare providers were definitely or probably not blinded, AND unblinding of healthcare providers likely to have influenced the outcome because there are healthcare provider-initiated co-interventions that could potentially influence the outcome.
☐ **Definitely High**	• Healthcare providers were definitely or probably not blinded, AND unblinding of healthcare providers very likely to have influenced the outcome because there are healthcare provider-initiated co-interventions that could potentially influence the outcome and investigators have documented dissimilarity in any of these co-interventions between groups.

Support for judgement:

Six core items – each includes two steps

Core items and response options	Step 1 Evaluate what happened	Step 2 Judge risk of bias
Core items:		
Item 1 Random sequence generation	Was the allocation sequence adequately generated?	Judge risk of bias related to sequence generation
Item 2 Allocation concealment	Was the allocation adequately concealed?	Judge risk of bias related to allocation concealment
Item 3 Blinding of participants	Were participants blinded?	Judge risk of bias related to blinding of participants
Item 4 Blinding of healthcare providers	Were healthcare providers blinded?	Judge risk of bias related to blinding of healthcare providers
Item 5 Blinding of outcome assessors	Were outcome assessors blinded?	Judge risk of bias related to blinding of outcome assessors
Item 6 Outcome data not included in analysis	Extract the number of participants who were not included in analysis in each group	Judge risk of bias related to the overall percentage of participants not included in analysis
Response options	Definitely yes, probably yes, probably no, definitely no (except for item 6)	Definitely low, probably low, probably high, definitely high

Two approaches for assessing item 6:

Approach 1: deciding RoB associated with this item for each individual trial – *need to complete both steps*

Approach 2: assessing RoB associated with missing data across the entire body of evidence at the meta-analysis level – *need to complete only step 1*

Item 6: Outcome data not included in analysis

Step 1: Extract the number of participants who were not included in analysis in each group

Note: For time-to-event outcomes, also count the participants who were censored because of missing follow-up data in 'N not analyzed'.

	N not analyzed	N total (usually N randomized)	Percentage not analyzed (N not analyzed / N total)
Intervention group			
Control group			
Overall			

Step 2: Judge risk of bias related to the overall percentage of participants not included in analysis

Issue to consider: Was the overall percentage of participants not included in analysis acceptably low

Note: Systematic review teams need to set and fill in the threshold for each response option. See manual for instructions and example thresholds.

☐ **Definitely Low**	Percentage of participants not included in analysis is < %
☐ **Probably Low**	• Percentage of participants not included in analysis is % to < % • If the trial did not mention whether there were participants not included in analysis, a substantial loss to follow-up is unlikely (e.g., ICU mortality)
☐ **Probably High**	• Percentage of participants not included in analysis is % to < % • If the trial did not mention whether there were participants not included in analysis, a substantial loss to follow-up is likely (e.g., 1-year quality of life)
☐ **Definitely High**	Percentage of participants not included in analysis is ≥ %

Support for judgement:

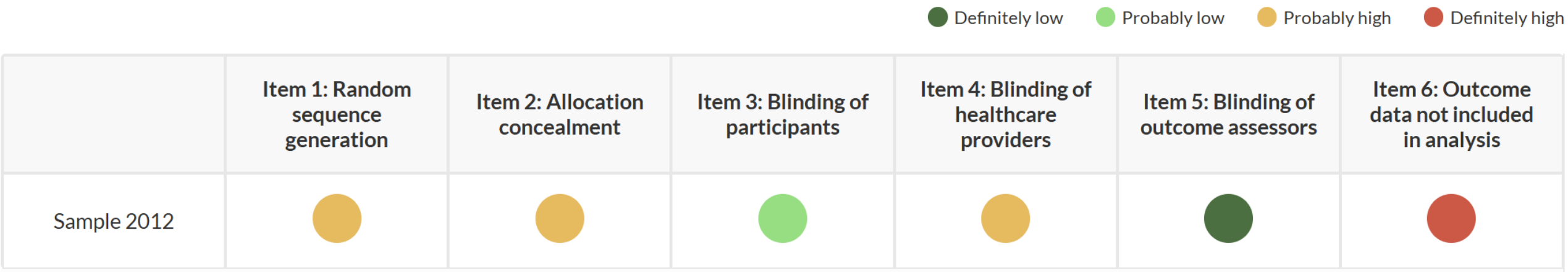
Eight optional items

Optional items	Titles
Item 1	Whether baseline prognostic factors were balanced between groups
Item 2	Whether co-interventions were balanced between groups in blinded trials
Item 3	Whether outcome assessment or data collection differed between groups
Item 4	Whether follow-up time, frequency, or intensity of outcome assessment differed between groups
Item 5	Whether outcome measurement method was valid (ie, validity of outcome measurement)
Item 6	When investigators conducted an as treated analysis, was the percentage of participants not analysed in the groups to which they were randomised sufficiently low
Item 7	Whether there was selective reporting
Item 8	Whether the trial was terminated early for benefit

- Information required to make judgements is not commonly reported or problems with these items occurs infrequently, or both
- However, these items may still be worth considering in certain circumstances
- **Review leaders consider whether the optional items are relevant in their specific circumstances; decide whether include any of them**

Visualization

- https://www.clarityresearch.ca/ebm-implementation-tools
- https://magicevidence.org/robust-rct



Thanks!

Ying Wang