

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

## TEMPLATE FOR COMPLETION

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on behalf of the RoB2 Development Group

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### Study details

#### Reference

Fawzy M et al, 2018

### Study design

- ☒ Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

### For the purposes of this assessment, the interventions being compared are defined as

Experimental: Artificial oocyte activation

Comparator: Routine ICSI

### Specify which outcome is being assessed for risk of bias

Still birth rate

**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.

Pooled results

### Is the review team's aim for this result...?

- ☒ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

**If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):**

- ✓ 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) 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- ☐ "Grey literature" (e.g. unpublished thesis)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 or Research Councils UK Gateway to Research)
- ☐ Personal communication with trialist
- ☐ Personal communication with the sponsor

## Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in **red** are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

### Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	1.1 <u>Yes</u>	<u>Y</u> / <u>PY</u> / <b>PN</b> / <b>N</b> / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	1.2 <u>Yes</u>	<u>Y</u> / <u>PY</u> / <b>PN</b> / <b>N</b> / NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	1.3 <u>No</u>	<b>Y</b> / <b>PY</b> / <u>PN</u> / <u>N</u> / NI
Risk-of-bias judgement	<b>Low concerns</b>	Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?	Not applicable	NA / Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*) **participant behaviour contamination**)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	2.1 <u>No</u>	Y / PY / <u>PN</u> / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	2.2 <u>Probably yes (while the clinicians were not aware, the embryologist were aware)</u>	Y / PY / <u>PN</u> / N / NI
2.3. If <u>Y/PY/NI</u> to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	2.3 <u>Probably no (no contamination)</u>	NA / Y / PY / <u>PN</u> / N / NI
2.4 If <u>Y/PY</u> to 2.3: Were these deviations likely to have affected the outcome?	2.4 NA	NA / Y / PY / <u>PN</u> / N / NI
2.5. If <u>Y/PY/NI</u> to 2.4: Were these deviations from intended intervention balanced between groups?	2.5 NA	NA / <u>Y/PY</u> / <u>PN</u> / N / NI
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	2.6 <u>Yes</u>	<u>Y</u> / <u>PY</u> / <u>PN</u> / N / NI
2.7 If <u>N/PN/NI</u> 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?	2.7 NA	NA / Y / PY / <u>PN</u> / N / NI
Risk-of-bias judgement	<u>Low concerns</u>	Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?	NA	NA / Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*) (**performance bias**)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	2.1 <b>No</b>	<b>Y</b> / <b>PY</b> / <b>PN</b> / <b>N</b> / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	2.2 <b>Yes</b> (while the clinicians were blinded, the embryologist were aware)	<b>Y</b> / <b>PY</b> / <b>PN</b> / <b>N</b> / NI
2.3. [If applicable:] If <b>Y/PY/NI</b> to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	2.3 <b>Probably Yes</b>	NA / <b>Y</b> / <b>PY</b> / <b>PN</b> / <b>N</b> / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	2.4 <b>Probably No</b>	NA / <b>Y</b> / <b>PY</b> / <b>PN</b> / <b>N</b> / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	2.5 <b>No</b>	NA / <b>Y</b> / <b>PY</b> / <b>PN</b> / <b>N</b> / NI
2.6. If <b>N/PN/NI</b> to 2.3, or <b>Y/PY/NI</b> to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	2.6 NA	NA / <b>Y</b> / <b>PY</b> / <b>PN</b> / <b>N</b> / NI
Risk-of-bias judgement	<b>Low concerns</b>	Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?	NA	NA / Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable

### Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	3.1 Yes	<u>Y</u> / <u>PY</u> / <u>PN</u> / <u>N</u> / NI
3.2 If <u>N/PN/NI</u> to 3.1: Is there evidence that the result was not biased by missing outcome data?	3.2 NA	NA / <u>Y</u> / <u>PY</u> / <u>PN</u> / <u>N</u>
3.3 If <u>N/PN</u> to 3.2: Could missingness in the outcome depend on its true value?	3.3 NA	NA / <u>Y</u> / <u>PY</u> / <u>PN</u> / <u>N</u> / NI
3.4 If <u>Y/PY/NI</u> to 3.3: Is it likely that missingness in the outcome depended on its true value?	3.4 NA	NA / <u>Y</u> / <u>PY</u> / <u>PN</u> / <u>N</u> / NI
Risk-of-bias judgement	Low concerns	Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?	NA	NA / Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome (Detection bias)

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	4.1 No	Y / PY / <u>PN</u> / <u>N</u> / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	4.2 No	Y / PY / <u>PN</u> / <u>N</u> / NI
4.3 If <u>N/PN/NI</u> to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	4.3 Yes	NA / Y / PY / <u>PN</u> / <u>N</u> / NI
4.4 If <u>Y/PY/NI</u> to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	4.4 Probably no	NA / Y / PY / <u>PN</u> / <u>N</u> / NI
4.5 If <u>Y/PY/NI</u> to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	4.5 NA	NA / Y / PY / <u>PN</u> / <u>N</u> / NI
Risk-of-bias judgement	Low concerns	Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable



Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
<b>5.1</b> 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?	5.1 <b>Probably yes</b> (even though not clearly specified in the trial protocol, the authors have reported all the standard expected outcomes for fertility trial)	<b>Y / PY / PN / N / NI</b>
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
<b>5.2.</b> ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	5.2 <b>Probably no</b>	<b>Y / PY / PN / N / NI</b>
<b>5.3</b> ... multiple eligible analyses of the data?	5.3 <b>Probably no</b>	<b>Y / PY / PN / N / NI</b>
<b>Risk-of-bias judgement</b>	<b>Low concerns</b>	Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement	Low concerns	Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?	NA	NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable



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