Supplementary Data: Syrcle risk of bias tool for *in vivo* animal studies

Mastbergen et al. (1):

Was the allocation sequence adequately generated and applied?

1. Did the investigators describe a random component in the sequence generation process?

   No

Were the groups similar at baseline, or were they adjusted for the confounders in the analysis?

1. Was the distribution of relevant baseline characteristics balanced for the intervention and control groups?

   Unclear

2. If relevant, did the investigators adequately adjust for unequal distribution of some relevant baseline characteristics in the analysis?

   Unclear

3. Was the timing of disease induction adequate?

   Yes

Was the allocation to the different groups adequately concealed during?

Could the investigator allocating the animals to intervention or control group not foresee assignment due to one of the following or equivalent methods?

Unclear

Were the animals randomly housed during the experiment?

1. Did the authors randomly place the cages or animals within the animal room/facility?

   Unclear

2. Is it unlikely that the outcome or the outcome measurement was influenced by not randomly housing the animals?

No

5) Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?

Was blinding of caregivers and investigators ensured, and was it unlikely that their blinding could have been broken?

Unclear

6) Were animals selected at random for outcome assessment?

Did the investigators randomly pick an animal during outcome assessment, or did they use a random component in the sequence generation for outcome assessment?

Unclear

7) Was the outcome assessor blinded?

1. Was blinding of the outcome assessor ensured, and was it unlikely that blinding could have been broken?

   Yes

2. Was the outcome assessor not blinded, but do review authors judge that the outcome is not likely to be influenced by lack of blinding?

   No

8) Were incomplete outcome data adequately addressed? (*)

1. Were all animals included in the analysis?

   Yes

2. Were the reasons for missing outcome data unlikely to be related to true outcome? (e.g., technical failure)

   No

3. Are missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups?

   No missing data

4. Are missing outcome data imputed using appropriate methods?

   No missing data

9. **Are reports of the study free of selective outcome reporting? (*)**

1. Was the study protocol available and were all of the study's pre-specified primary and secondary outcomes reported in the current manuscript?

   Yes

2.. Was the study protocol not available, but was it clear that the published report included all expected outcomes (i.e. comparing methods and results section)?

   Not applicable

10. **Was the study apparently free of other problems that could result in high risk of bias?**

1. Was the study free of contamination (pooling drugs)?

   No, but risk of biasing of the drugs used is low.

2. Was the study free of inappropriate influence of funders

   Yes

3. Was the study free of unit of analysis errors?

   Yes

4. Were design-specific risks of bias absent?

   Yes

Huh et al. (2) :

Was the allocation sequence adequately generated and applied?

1. Did the investigators describe a random component in the sequence generation process?

   No

Were the groups similar at baseline, or were they adjusted for the confounders in the analysis?

1. Was the distribution of relevant baseline characteristics balanced for the intervention and control groups?

   Unclear

2. If relevant, did the investigators adequately adjust for unequal distribution of some relevant baseline characteristics in the analysis?

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2. Is it unlikely that the outcome or the outcome measurement was influenced by not randomly housing the animals?

   No

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1. Was the study free of contamination (pooling drugs)?

   Unclear

2. Was the study free of inappropriate influence of funders

   Yes

3. Was the study free of unit of analysis errors?

   Yes

4. Were design-specific risks of bias absent?

   Yes

Jones et al. (3) :

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Not applicable

Was the study apparently free of other problems that could result in high risk of bias?

1. Was the study free of contamination (pooling drugs)?

   No, but risk of bias of the used drugs is unlikely

2. Was the study free of inappropriate influence of funders

   Yes

3. Was the study free of unit of analysis errors?

   Yes

4. Were design-specific risks of bias absent?

   Yes

Fukai et al. (4):

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2. Was the study free of inappropriate influence of funders

   Yes

3. Was the study free of unit of analysis errors?

   Yes

4. Were design-specific risks of bias absent?

   Yes

Ou et al.(5):

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2. Was the outcome assessor not blinded, but do review authors judge that the outcome is not likely to be influenced by lack of blinding?

   No, outcome may be influenced due to lack of blinding

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Unclear

2. Was the study free of inappropriate influence of funders

Yes

3. Was the study free of unit of analysis errors?

Yes

4. Were design-specific risks of bias absent?

Yes

Ashkavand et al. (6):

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2. Was the study free of inappropriate influence of funders

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3. Was the study free of unit of analysis errors?

Yes

4. Were design-specific risks of bias absent?

Yes

Moon et al. (7)

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   Unclear, but outcome influence will be influenced if blinding is not performed.

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Unclear

2. Was the study free of inappropriate influence of funders

Yes

3. Was the study free of unit of analysis errors?

Yes

4. Were design-specific risks of bias absent?

Yes

Panahifar et al. (8)

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3. Was the study free of unit of analysis errors?

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Nagy et al. (9)

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4. Were design-specific risks of bias absent?

   Yes

Tu et al. (10)

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   Unclear

2. Was the outcome assessor not blinded, but do review authors judge that the outcome is not likely to be influenced by lack of blinding?

   Unclear, if blinding in primary outcome assessment was not performed, this will influence outcome.

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3. Was the study free of unit of analysis errors?

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Wen et al. (11)

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Li et al. (12)

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   No missing data.

Are reports of the study free of selective outcome reporting? (*)

1. Was the study protocol available and were all of the study's pre-specified primary and secondary outcomes reported in the current manuscript?

   Yes

2.. Was the study protocol not available, but was it clear that the published report included all expected outcomes (i.e. comparing methods and results section)?

   Not applicable

Was the study apparently free of other problems that could result in high risk of bias?

1. Was the study free of contamination (pooling drugs)?

   Unclear

2. Was the study free of inappropriate influence of funders

   Yes

3. Was the study free of unit of analysis errors?

   Yes

4. Were design-specific risks of bias absent?

   Yes

Liu et al. (13)

Was the allocation sequence adequately generated and applied?

1. Did the investigators describe a random component in the sequence generation process?

   Yes

Were the groups similar at baseline, or were they adjusted for the confounders in the analysis?

1. Was the distribution of relevant baseline characteristics balanced for the intervention and control groups?

   Unclear

2. If relevant, did the investigators adequately adjust for unequal distribution of some relevant baseline characteristics in the analysis?

   Unclear

3. Was the timing of disease induction adequate?

   Yes

Was the allocation to the different groups adequately concealed during?

Could the investigator allocating the animals to intervention or control group not foresee assignment due to one of the following or equivalent methods?

Unclear

Were the animals randomly housed during the experiment?

1. Did the authors randomly place the cages or animals within the animal room/facility?

   Unclear

2. Is it unlikely that the outcome or the outcome measurement was influenced by not randomly housing the animals?

   No

Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?

Was blinding of caregivers and investigators ensured, and was it unlikely that their blinding could have been broken?

Unclear

Were animals selected at random for outcome assessment?

Did the investigators randomly pick an animal during outcome assessment, or did they use a random component in the sequence generation for outcome assessment?

Unclear

Was the outcome assessor blinded?

1. Was blinding of the outcome assessor ensured, and was it unlikely that blinding could have been broken?

   Unclear

2. Was the outcome assessor not blinded, but do review authors judge that the outcome is not likely to be influenced by lack of blinding?

   Unclear, but outcome influence will be influenced if blinding is not performed.

Were incomplete outcome data adequately addressed? (*)

1. Were all animals included in the analysis?

   Unclear

2. Were the reasons for missing outcome data unlikely to be related to true outcome? (e.g., technical failure)

   Unclear

3. Are missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups?

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2.. Was the study protocol not available, but was it clear that the published report included all expected outcomes (i.e. comparing methods and results section)?

   Not applicable

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1. Was the study free of contamination (pooling drugs)?

   Unclear

2. Was the study free of inappropriate influence of funders

   Yes

3. Was the study free of unit of analysis errors?

   Yes

4. Were design-specific risks of bias absent?

   Yes

Dai et al. (14)

Was the allocation sequence adequately generated and applied?

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Yes

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   Not applicable

Was the study apparently free of other problems that could result in high risk of bias?

1. Was the study free of contamination (pooling drugs)?

   No, but unlikely that the drugs used will influence the results

2. Was the study free of inappropriate influence of funders

   Yes

3. Was the study free of unit of analysis errors?

   Yes

4. Were design-specific risks of bias absent?

   Yes

Jean et al. (15)

Was the allocation sequence adequately generated and applied?

1. Did the investigators describe a random component in the sequence generation process?

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2. Was the distribution of relevant baseline characteristics balanced for the intervention and control groups?

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   Not applicable

Was the study apparently free of other problems that could result in high risk of bias?

1. Was the study free of contamination (pooling drugs)?

   No, but risk of biasing of the drugs used is low

2. Was the study free of inappropriate influence of funders

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3. Was the study free of unit of analysis errors?

   Yes

4. Were design-specific risks of bias absent?

   Yes

Jiang et al. (16)

Was the allocation sequence adequately generated and applied?

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2. Was the study free of inappropriate influence of funders

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   Yes

4. Were design-specific risks of bias absent?

   Yes

Dong et al. (17)

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Was the study apparently free of other problems that could result in high risk of bias?

1. Was the study free of contamination (pooling drugs)?

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2. Was the study free of inappropriate influence of funders

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3. Was the study free of unit of analysis errors?

   Yes

4. Were design-specific risks of bias absent?

   Yes

Wen et al. (18)

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1. Was the study free of contamination (pooling drugs)?

No, but risk of biasing of the drugs lis low

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3. Was the study free of unit of analysis errors?

Yes

4. Were design-specific risks of bias absent?

Yes

Janssen et al. (19)

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   Not applicable

Was the study apparently free of other problems that could result in high risk of bias?

1. Was the study free of contamination (pooling drugs)?

   No but low risk of bias of the drugs used

2. Was the study free of inappropriate influence of funders

   Yes

3. Was the study free of unit of analysis errors?

   Yes

4. Were design-specific risks of bias absent?

   Yes

Tellegen et al. (20)

Was the allocation sequence adequately generated and applied?

1. Did the investigators describe a random component in the sequence generation process?

   Yes

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7. Was the distribution of relevant baseline characteristics balanced for the intervention and control groups?

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8. If relevant, did the investigators adequately adjust for unequal distribution of some relevant baseline characteristics in the analysis?

   Not applicable

9. Was the timing of disease induction adequate?

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Not applicable

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