Risk assessment of cross-over RCTs

Haidar (2020)

Study design

- [ ] Individually-randomized parallel-group trial
- [ ] Cluster-randomized parallel-group trial
- [X] Individually randomized cross-over (or other matched) trial

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.

Time in range: 3.9-10.0 mmol/L

Is the review team's aim for this result…?

- [X] 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)

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

- [X] Journal article(s) with results of the trial
- [ ] Trial protocol
- [ ] Statistical analysis plan (SAP)
- [X] 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- [ ] "Grey literature" (e.g. unpublished thesis)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

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	"We used blocked randomization to generate allocation sequences" Pag. 598.	Yes
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	"which were disclose after the admission visit.."	Yes
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		No information
Risk-of-bias judgement		Low
Domain S: S: Risk of bias arising from period and carryover effects in a crossover trial		
S.1 Was the number of participants allocated to each of the two sequences equal or nearly equal?	The number of participants allocated in each sequence has been the same.	Yes
S.2 If N/PN/NI to S.1: Were period effects accounted for in the analysis?		No applicable
S.3 Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period?	A period of 21 days is left between each intervention.	Probably yes
Risk-of-bias judgement		Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)		
2.1. Were participants aware of their assigned intervention during the trial?	"Participants and investigators were not blinded to the allocation Pag. 598	Yes
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	They were supposed to know the allocation. "Study personnel delivered basal insulin and pramlintide manually by programming a new temporary basal every 10 min". Page. 598.	Yes
2.3. <u>If Y/PY/NI to 2.1 or 2.2</u>: Were there deviations from the intended intervention that arose because of the experimental context?	There is no information to suggest that there were deviations from the initial allocation.	Not information
2.4. <u>If Y/PY to 2.3</u>: Were these deviations from intended intervention balanced between groups?		No applicable
2.5 <u>If N/PN/NI to 2.4</u>: Were these deviations likely to have affected the outcome?		No applicable
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	"Our analyses were on a modified intention-to-treat basis. Participants who did not complete the rapid insulin-alone artificial pancreas intervention and at least one insulin-and-pramlintide intervention were not included in the analysis and were replaced in the enrollment process". Pag. 599.	Yes

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?		No applicable
Risk-of-bias judgement		Some concerns
Domain 3: Missing outcome data		
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Losses exceed 5% of data	Probably not
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		Probably not
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		Probably not
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		Not apliccable
Risk-of-bias judgement		Some concerns
Domain 4: Risk of bias in measurement of the outcome		
4.1 Was the method of measuring the outcome inappropriate?	The glucose profile is an appropriate method to determine the time in range of each of the interventions.	Not
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	There is no mention of differences in the procedure for assessing the outcome.	Probably no
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	It is likely that those who evaluated the results were aware of the assignment of the participants. "Participants and investigators were not blinded to the allocation Pag. 598	Yes
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	There is no evidence to suggest that the assessment of the outcome may have been influenced by knowledge of the assignment.	Not
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		No applicable
Risk-of-bias judgement		Low
Domain 5: Risk of 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?	NCT02814123.	Yes
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	There is no evidence to suggest this.	Probably not
5.3 ... multiple eligible analyses of the data?	There is no evidence to suggest this.	Probably no
Risk-of-bias judgement		Low
Overall risk of bias		
Risk-of-bias judgement		Some concerns

Tsoukas (2021)

Study design

- [ ] Individually-randomized parallel-group trial
- [ ] Cluster-randomized parallel-group trial
- [X] Individually randomized cross-over (or other matched) trial

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Time in range: 3·9–10·0 mmol/L (with a 6% non-inferiority margin).

Is the review team's aim for this result…?

- [X] 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)

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

X	Journal article(s) with results of the trial
	Trial protocol
	Statistical analysis plan (SAP)
X	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

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	"We used block randomisation (block size of four) for the allocation sequences, which were allocated by a computer after the completion of the admission visit". Pag 3.	Yes
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	We used block randomisation (block size of four) for the allocation sequences, which were allocated by a computer after the completion of the admission visit". Pag 3.	Yes
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	.	No information
Risk-of-bias judgement		Low
Domain S: S: Risk of bias arising from period and carryover effects in a crossover trial		
S.1 Was the number of participants allocated to each of the two sequences equal or nearly equal?	The number of participants has been almost the same in the interventions.	Yes
S.2 If N/PN/NI to S.1: Were period effects accounted for in the analysis?		No applicable
S.3 Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period?	There is a period of 9 days between interventions	Probably yes
Risk-of-bias judgement		Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)		
2.1. Were participants aware of their assigned intervention during the trial?	"Participants and investigators were not masked to the allocation because it was practically challenging to do so". Pag.3	Yes
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	It is expected, as it is an open label trial.	Yes
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?	There is no information to suggest that there were deviations from the initial allocation.	No information
2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?		No applicable
2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?		No applicable
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	The analysis to estimate the allocation effect seems appropriate.	Probably yes
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?		No applicable
Risk-of-bias judgement		Some concerns
Domain 3: Missing outcome data		
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Data were available for almost all randomised participants.	Yes
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		No applicable
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		No applicable
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		No applicable
Risk-of-bias judgement		Low
Domain 4: Risk of bias in measurement of the outcome		

4.1 Was the method of measuring the outcome inappropriate?	The glucose profile is an appropriate method to determine the time in range of each of the interventions.	Not
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	There is no mention of differences in the procedure for assessing the outcome.	Probably no
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	It is likely that those who evaluated the results were aware of the assignment of the participants. "Participants and investigators were not blinded to the allocation" Pag. 598	Yes
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	There is no evidence to suggest that the assessment of the outcome may have been influenced by knowledge of the assignment.	Probably no
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		No applicable
Risk-of-bias judgement		Low
Domain 5: Risk of 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?	NCT03800875	Yes
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	NCT03800875	Probably not
5.3 ... multiple eligible analyses of the data?	NCT03800875	Probably not
Risk-of-bias judgement		Low
Overall risk of bias		
Risk-of-bias judgement		Some concerns

Estudio: Tsoukas (2021) Pilot study

Study design

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[ ] Cluster-randomized parallel-group trial
[X] Individually randomized cross-over (or other matched) trial

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Time in range: 3.9-10 mmol/L

Is the review team's aim for this result…?

[X] 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)

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

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[ ] Trial protocol
[ ] Statistical analysis plan (SAP)
[X] Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
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[ ] Personal communication with trialist
[ ] Personal communication with the sponsor

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	The pilot study had a 12-day, three-way, randomized, blinded, crossover design that compared a FiASP-and-placebo closed-loop system with FCC, a FiASP-and-pramlintide closed-loop system with SMA, and a FiASP-and-placebo closed-loop system with SMA. Pag 2091	No information

1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		No information
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	There are no data to suggest a problem with randomisation	No information
Risk-of-bias judgement		Some concerns
Domain S: S: Risk of bias arising from period and carryover effects in a crossover trial		
S.1 Was the number of participants allocated to each of the two sequences equal or nearly equal?	The allocation of participants is expected to have been the same.	No information
S.2 If N/PN/NI to S.1: Were period effects accounted for in the analysis?		No information
S.3 Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period?	There was a 14-45-day washout period between each intervention to cognitively separate the arms for qualitative assessment. Pag. 2092	Yes
Risk-of-bias judgement		Some concerns
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)		
2.1. Were participants aware of their assigned intervention during the trial?	"This was necessary to mask participants and research staff to the study drug in the interventions with SMA"	Probably not
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	This was necessary to mask participants and research staff to the study drug in the interventions with SMA	Probably not
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?		No applicable
2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?		No applicable
2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?		No applicable
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Tthe analysis is appropriate	Probably yes
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?		No applicable
Risk-of-bias judgement		Low
Domain 3: Missing outcome data		
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Data were available for all participants.	Yes
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		No applicable
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		No applicable
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		No applicable
Risk-of-bias judgement		Low
Domain 4: Risk of bias in measurement of the outcome		
4.1 Was the method of measuring the outcome inappropriate?	The glucose profile is an appropriate method to determine the time in range of each of the interventions.	Not
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	There is no mention of differences in the procedure for assessing the outcome.	Probably not
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	It is likely that those who evaluated the results were unaware of the allocation of participants, as the researchers were blinded in the allocation procedure.	Not
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		No applicable
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		No applicable
Risk-of-bias judgement		Low
Domain 5: Risk of 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?	"We performed an eight-participant inpatient feasibility study, and a four-participant outpatient pilot study internal to a larger, main trial.	Yes

	The feasibility and main outpatient studies are registered with ClinicalTrials.gov (NCT03993366 and NCT04163874, respectively)". Pag. 2091	
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	There is no data to suggest that multiple assessments were made.	Not
5.3 ... multiple eligible analyses of the data?	There is no evidence to suggest that multiple analyses were carried out.	Not
Risk-of-bias judgement		Low
Overall risk of bias		
Risk-of-bias judgement		Some concerns

Estudio: Tsoukas (2021) Feasibility study

Study design

- [ ] Individually-randomized parallel-group trial
- [ ] Cluster-randomized parallel-group trial
- [X] Individually randomized cross-over (or other matched) trial

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Is the review team's aim for this result…?

- [X] to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
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Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		No information
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		No information
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	There are no data to suggest a problem with randomisation.	No information
Risk-of-bias judgement		Some concerns
Domain S: S: Risk of bias arising from period and carryover effects in a crossover trial		
S.1 Was the number of participants allocated to each of the two sequences equal or nearly equal?	The allocation of participants is expected to have been the same.	No information
S.2 If N/PN/NI to S.1: Were period effects accounted for in the analysis?		No information
S.3 Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period?	"Each 24-hour closed-loop intervention was preceded by a 3-day, at-home, run-in period, during which participants used the study medications on open-loop therapy,	Probably yes

	with carbohydrate counting". Pg. 2092.	
Risk-of-bias judgement		Some concerns
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)		
2.1. Were participants aware of their assigned intervention during the trial?	During the interventions, every 10 minutes a member of the research staff entered glucose sensor readings into a laptop that ran the dosing algorithms, recommending adjusted basal rates that were manually programed into the pumps.	Probably not
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		No information
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?		No information
2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?		No applicable
2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?		No applicable
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Probably yes
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?		No applicable
Risk-of-bias judgement		Some concerns
Domain 3: Missing outcome data		
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Data were available for all participants.	Yes
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		No applicable
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		No applicable
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		No applicable
Risk-of-bias judgement		Low
Domain 4: Risk of bias in measurement of the outcome		
4.1 Was the method of measuring the outcome inappropriate?	The glucose profile is an appropriate method to determine the time in range of each of the interventions.	Not
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	There is no mention of differences in the procedure for assessing the outcome	Probably not
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		Not information
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		Probably not
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		No applicable
Risk-of-bias judgement		Some concerns
Domain 5: Risk of 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?	"We performed an eight-participant inpatient feasibility study, and a four-participant outpatient pilot study internal to a larger, main trial. The feasibility and main outpatient studies are registered with ClinicalTrials.gov (NCT03993366 and NCT04163874, respectively)". Pag. 2091	Yes
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	There is no data to suggest that multiple assessments were made.	Not
5.3 ... multiple eligible analyses of the data?	There is no evidence to suggest that multiple analyses were carried out.	Not
Risk-of-bias judgement		Low
Overall risk of bias		
Risk-of-bias judgement		Hight