1 Se orienta el ensayo a una pregunta claramente definida? SÍ / NO SÉ / NO

Una pregunta debe definirse en términos de: - La población de estudio; - La intervención realizada; - La comparación, los desenlaces (+ y -). Puntúa desenlaces según GRADE.

2 Fue aleatoria la asignación de los pacientes a los tratamientos? SÍ / NO SÉ / NO

- ¿Se generó adecuadamente? ¿Se mantuvo oculta la secuencia de aleatorización? ¿Son iguales en línea basal?

3 ¿Se mantuvo la comparabilidad de los grupos a través del estudio? SÍ / NO SÉ / NO

Desviaciones de la intervención por problemas en la asignación

Desviaciones de la intervención por problemas de adhesión al tratamiento.

¿Cómo se realizó el análisis, ITT, mITT (excluyendo perdidos), PP, AT (as treated)?

4 ¿Son importantes las pérdidas ocurridas durante el estudio? SÍ / NO SÉ / NO

¿Difieren según el grupo?¿Las pérdidas podrían depender de su valor o resultado?¿Se hace análisis de sensibilidad?

5 ¿Fue adecuada la medición de los desenlaces? SÍ / NO SÉ / NO

Tipo de desenlace medido y método usado. Cegamiento del paciente, clínico, evaluador, estadístico Si hay problema ¿es diferencial entre los grupos?

6 ¿Se evitó la comunicación selectiva de resultados? SÍ / NO SÉ / NO

Mirar registro de ensayos. ¿Hay reporte selectivo de desenlaces o reporte selectivo de análisis?

7 ¿Cuál es el efecto del tratamiento para cada desenlace?

¿Qué desenlaces se han medido? Detalla los positivos y los negativos

8 ¿Cuál es la precisión de este efecto? SÍ / NO SÉ / NO

¿Cuáles son sus intervalos de confianza?

9 ¿Puede aplicarse estos resultados en tu medio o población local? SÍ / NO SÉ / NO

¿Crees que los pacientes incluidos en el ensayo son demasiado distintos a tus pacientes? ¿Hay algún otro ensayo parecido a este? ¿Es consistente con este?

10 ¿Se han tenido en cuenta todos los resultados y su importancia clínica? SÍ / NO SÉ / NO

Utilidades y disutilidades de cada desenlace. Balance de efectos + y -. Preferencias del paciente, costes, etc

11 ¿Los beneficios a obtener justifican los riesgos y los costes? SÍ / NO SÉ / NO

Es improbable que pueda deducirse del ensayo pero, ¿qué piensas tú al respecto?

PLANTILLA CASPE REVISIÓN SISTEMÁTICA

PARTE A: ¿LOS RESULTADOS DE LA REVISIÓN SON VÁLIDOS?

1 ¿Se hizo la revisión sobre un tema claramente definido? SÍ / NO SÉ / NO

Una pregunta debe definirse en términos PICO: - La población de estudio; - La intervención realizada; - La comparación, los desenlaces

2 ¿Buscaron los autores el tipo de artículos adecuado? SÍ / NO SÉ / NO

-El mejor tipo de estudio es el que a) se dirige a la pregunta objeto de la revisión y b) tiene un diseño apropiado para la pregunta (puede ser óptimo o subóptimo por razones diversas)

3 ¿Crees que estaban incluidos los estudios importantes y pertinentes? SÍ / NO SÉ / NO

Pista 1:

¿qué bases de datos bibliográficos se han usado? ¿Qué estrategia de búsqueda?
Seguimiento de las referencias. Contacto personal con los autores. Búsqueda de estudios no publicados y de resultados no publicados – control de protocolos originales.
Idiomas distintos del inglés
Pista 2: ¿Criterios de inclusión y exclusión. Selección de estudios. Extracción de datos.

4 ¿Crees que los autores de la revisión han hecho suficiente esfuerzo para valorar la calidad de los estudios y de los resultados incluidos? SÍ / NO SÉ / NO

Pista 1: el riesgo de sesgo depende de los 5 dominios de Cochrane RoB2.
Pista 2: valorar para cada desenlace, en cada estudio y en el conjunto de estudios

5 Si los resultados de los diferentes estudios han sido mezclados para obtener un resultado combinado, ¿era razonable hacer eso? SÍ / NO SÉ / NO

Pista 1: la heterogeneidad puede ser clínica, metodológica o estadística (i2)

PARTE B: ¿CUÁLES SON LOS RESULTADOS?

6 ¿Cuál es el resultado global de la revisión?

Pista 1 Considera:
valora para los desenlaces + y –
¿Cuáles son los resultados para cada desenlace?
¿Cómo están expresados los resultados? RR, HR, etc
¿Muestran gráficos forest-plot?

7 Para el conjunto de los estudios (en cada desenlace concreto) SÍ / NO SÉ / NO

Riesgo de sesgo en los desenlaces
¿Cuál es la precisión de los resultados?
¿Son consistentes los resultados de los estudios para cada desenlace?
¿Es indirecta la evidencia en algún desenlace?
Sesgo de publicación para desenlace incluido en el protocolo pero no mostrado

PARTE C: ¿SON LOS RESULTADOS APLICABLES EN TU MEDIO?

8 ¿Se pueden aplicar los resultados en tu medio? SÍ / NO SÉ / NO

Pista 1 Considera si: Los pacientes cubiertos por la revisión pueden ser suficientemente diferentes de los de tu áre. Y si tu medio parece ser muy diferentes al del estudio

9 ¿Se han considerado todos los resultados importantes para la decisión? SÍ/NO SÉ / NO

Utilidades y disutilidades
Balance de efectos positivo y negativos
Preferencias del paciente, costes, etc

PARTE A ¿Son válidos los resultados?

Preguntas de eliminación

1 ¿Fue una muestra representativa y bien definida de pacientes en un momento similar en el curso de la enfermedad? SÍ / NO SÉ / NO

Pistas: ¿De qué ámbito son los pacientes, primaria o especializada?
En qué punto de su curso clínico se incluyen en el estudio?

2 ¿Fue el seguimiento lo suficientemente prolongado y completo? SÍ / NO SÉ / NO

Pistas: El intervalo temporal entre un factor pronóstico y un resultado es variable y puede ser muy largo. ¿Se pierden pacientes? ¿Se investigan sus características?

Preguntas detalladas

3 ¿Se utilizaron criterios objetivos y no sesgados para los resultados? SÍ / NO SÉ / NO

Pistas: Los resultados a veces son objetivos (ej: muerte) y otras no tanto (ej: calidad de vida).
¿Se valoraron de modo 'ciego'?

4 ¿Se hizo un ajuste por los factores pronósticos importantes? SÍ / NO SÉ / NO

Pistas: En muchos estudios de pronóstico al grupo de pacientes se le divide en subgrupos de factores pronósticos (o tratamiento) sospechados. Si se hizo esto, ¿se controlaron por otros factores?

PARTE B ¿Cuáles son los resultados?

5 ¿Cuál es la probabilidad del(los) evento(s) en un periodo de tiempo determinado?

Pistas: La probabilidad varía en el tiempo.
¿Se presentan 'curvas de supervivencia'?
¿Se presentan para los distintos factores pronósticos?

6 ¿Cuán precisas son las estimaciones?

Pistas: ¿Se dan intervalos de confianza?

PARTE C ¿Son los resultados aplicables en tu medio?

7 ¿Son los pacientes del estudio similares a los míos? SÍ / NO SÉ / NO

Pistas: considera si:
los pacientes del estudio pueden ser suficientemente diferentes de los de tu área
tu medio parece ser muy diferente al del estudio

8 ¿Conducen los resultados a seleccionar o a evitar un tratamiento? SÍ / NO SÉ / NO

9 ¿Son útiles los resultados para tranquilizar o aconsejar a los pacientes? SÍ / NO SÉ / NO

PARTE A ¿Son válidos los resultados del estudio?

Preguntas de eliminación

1 ¿Existió una comparación con una prueba de referencia adecuada? SÍ / NO SÉ / NO
Pista: ¿es correcto el gold estándar? No siempre se puede aplicar el mismo gold estándar a todos los pacientes.

2 ¿Incluyó la muestra un espectro adecuado de pacientes? SÍ / NO SÉ / NO
Pistas: ¿están adecuadamente descritos los pacientes, y cómo se seleccionaron?
Casi cualquier prueba distingue entre sanos y gravemente enfermos.

3 ¿Existe una adecuada descripción de la prueba? SÍ / NO SÉ / NO
Pistas: ¿se describe con claridad qué es un resultado positivo y qué es un resultado negativo? ¿se especifica la reproducibilidad de la prueba? Esto puede ser un aspecto clave en pruebas que dependen del observador, tales como las pruebas de imagen.

Preguntas detalladas

4 ¿Hubo evaluación ciega de los resultados? SÍ / NO SÉ / NO
Pista: ¿las personas que interpretaron la prueba conocían los resultados del gold estándar y viceversa?

5 ¿La decisión de realizar el gold standard fue independiente del resultado del test índice? SÍ / NO SÉ / NO
Pistas: ¿se incluyeron preferentemente los resultados positivos en la prueba que se iba a evaluar?¿se utilizaron diferentes gold estándar en los pacientes con test índice + y en los pacientes con test -?

PARTE B ¿Cuáles son los resultados?

6 ¿Se pueden calcular los cocientes de probabilidad (Likelihood Ratios)? SÍ / NO SÉ / NO
Pista: ¿se han tenido en cuenta los pacientes 'no concluyentes'? ¿se pueden calcular los cocientes de probabilidad para distintos niveles de la prueba, si procede?.

7 ¿Cuál es la precisión de los resultados? SÍ / NO SÉ / NO
Pista: buscar o calcular los 95%IC de los cocientes de probabilidad (LR+, LR-) (ej. Openepi)

PARTE C ¿Son los resultados aplicables al escenario?

8 ¿Serán satisfactorias en el ámbito del escenario la reproducibilidad de la prueba y su interpretación? SÍ / NO SÉ / NO
Pista: considera si el ámbito de la prueba es demasiado diferente al del escenario

9 ¿Es aceptable la prueba en este caso? SÍ / NO SÉ / NO
Pista: considera la disponibilidad de la prueba, los riesgos y las molestias de la prueba y los costes

10 ¿Modificarán los resultados de la prueba la decisión sobre cómo actuar? SÍ / NO SÉ / NO
Pista: desde la perspectiva del escenario, si la actitud no va a cambiar, la prueba es inútil. Considera el umbral de acción y la probabilidad de enfermedad antes y después de la prueba

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)
TEMPLATE FOR COMPLETION

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne
on behalf of the RoB2 Development Group

Version of 22August 2019

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.

Study details

Reference

Study design

X 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: Comparator:

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 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 <u>obtained</u> 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?		Y / PY/ PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y / PY/ PN / N / NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		Y / PY / PN / N/ NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		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*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N/ NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY/ PN / N/ NI
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NA / Y / PY / PN / N/ NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA / Y / PY / PN / N/ NI
2.5. If Y/PY/NIto 2.4: Were these deviations from intended intervention balanced between groups?		NA / Y / PY/ PN / N / NI
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y / PY/ PN / N / NI
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?		NA / Y / PY / PN / N/ NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		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*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N/ NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N/ NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY/ PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY/ PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		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?		Y / PY/ PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA / Y / PY/ PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA / Y / PY/ PN / N/ NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N/ NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		Y / PY / PN / N/ NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		Y / PY / PN / N/ NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		NA /Y / PY / PN / N/ NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N/ NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N/ NI
Risk-of-bias judgement		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
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?		Y / PY/ PN / N/ NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		Y / PY / PN / N/ NI
5.3 ... multiple eligible analyses of the data?		Y / PY / PN / N/ NI
Risk-of-bias judgement		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 / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

ROBIS: Tool to assess risk of bias in systematic reviews

Phase 1: Assessing relevance (Optional)

ROBIS is designed to assess the risk of bias in reviews with questions relating to interventions, aetiology, diagnosis and prognosis. State your overview/guideline question (target question) and the question being addressed in the review being assessed:

Intervention reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients/Population(s):		
Intervention(s):		
Comparator(s):		
Outcome(s):		

For aetiology reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients/Population(s):		
Exposure(s) and comparator(s):		
Outcome(s):		

For DTA reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients):		
Index test(s):		
Reference standard:		
Target condition:		

For prognostic reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients:		
Outcome to be predicted:		
Intended use of model:		
Intended moment in time:		

Does the question addressed by the review match the target question?	YES/NO/UNCLEAR

Phase 2: Identifying concerns with the review process

DOMAIN 1: STUDY ELIGIBILITY CRITERIA	
Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Y/PY/PN/N/NI
1.2 Were the eligibility criteria appropriate for the review question?	Y/PY/PN/N/NI
1.3 Were eligibility criteria unambiguous?	Y/PY/PN/N/NI
1.4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Y/PY/PN/N/NI
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Y/PY/PN/N/NI
Concerns regarding specification of study eligibility criteria	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES	
Describe methods of study identification and selection (e.g. number of reviewers involved):	
2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y/PY/PN/N/NI
2.2 Were methods additional to database searching used to identify relevant reports?	Y/PY/PN/N/NI
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Y/PY/PN/N/NI
2.4 Were restrictions based on date, publication format, or language appropriate?	Y/PY/PN/N/NI
2.5 Were efforts made to minimise error in selection of studies?	Y/PY/PN/N/NI
Concerns regarding methods used to identify and/or select studies	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL	
Describe methods of data collection, what data were extracted from studies or collected through other means, how risk of bias was assessed (e.g. number of reviewers involved) and the tool used to assess risk of bias:	
3.1 Were efforts made to minimise error in data collection?	Y/PY/PN/N/NI
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Y/PY/PN/N/NI
3.3 Were all relevant study results collected for use in the synthesis?	Y/PY/PN/N/NI
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Y/PY/PN/N/NI
3.5 Were efforts made to minimise error in risk of bias assessment?	Y/PY/PN/N/NI
Concerns regarding methods used to collect data and appraise studies	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 4: SYNTHESIS AND FINDINGS	
Describe synthesis methods:	
4.1 Did the synthesis include all studies that it should?	Y/PY/PN/N/NI
4.2 Were all pre-defined analyses reported or departures explained?	Y/PY/PN/N/NI
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Y/PY/PN/N/NI
4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Y/PY/PN/N/NI
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Y/PY/PN/N/NI
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Y/PY/PN/N/NI
Concerns regarding the synthesis and findings Rationale for concern:	LOW/HIGH/UNCLEAR

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

Phase 3: Judging risk of bias

Summarize the concerns identified during the Phase 2 assessment:

Domain	Concern	Rationale for concern
1. Concerns regarding specification of study eligibility criteria		
2. Concerns regarding methods used to identify and/or select studies		
3. Concerns regarding methods used to collect data and appraise studies		
4. Concerns regarding the synthesis and findings		

RISK OF BIAS IN THE REVIEW	
Describe whether conclusions were supported by the evidence:	
A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	Y/PY/PN/N/NI
B. Was the relevance of identified studies to the review's research question appropriately considered?	Y/PY/PN/N/NI
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Y/PY/PN/N/NI
Risk of bias in the review Rationale for risk:	RISK: LOW/HIGH/UNCLEAR

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ⍰
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ⍰
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ⍰
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ⍰
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ⍰
   b) study controls for any additional factor ⍰ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ⍰
   b) structured interview where blind to case/control status ⍰
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ⍰
   b) no

3) Non-Response rate
   a) same rate for both groups ⍰
   b) non respondents described
   c) rate different and no designation

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ☐
   b) somewhat representative of the average _____ in the community ☐
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ☐
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ☐
   b) structured interview ☐
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ☐
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ☐
   b) study controls for any additional factor ☐ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ☐
   b) record linkage ☐
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ☐
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ☐
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ☐
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

PROBAST

(Prediction model study Risk Of Bias Assessment Tool)

Published in Annals of Internal Medicine (freely available):

1. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies
2. PROBAST: A Tool to Assess Risk of Bias and Applicability of Prediction Model Studies: Explanation and Elaboration

What does PROBAST assess?

PROBAST assesses both the *risk of bias* and *concerns regarding applicability* of a study that evaluates (develops, validates or updates) a multivariable diagnostic or prognostic prediction model. It is designed to assess primary studies included in a systematic review.

Bias occurs if systematic flaws or limitations in the design, conduct or analysis of a primary study distort the results. For the purpose of prediction modelling studies, we have defined *risk of bias* to occur when shortcomings in the study design, conduct or analysis lead to systematically distorted estimates of a model's predictive performance or to an inadequate model to address the research question. Model predictive performance is typically evaluated using calibration, discrimination and sometimes classification measures, and these are likely inaccurately estimated in studies with high risk of bias. *Applicability* refers to the extent to which the prediction model from the primary study matches your systematic review question, for example in terms of the participants, predictors or outcome of interest.

A primary study may include the development and/or validation or update of more than one prediction model. A PROBAST assessment should be completed for each distinct model that is developed, validated or updated (extended) for making individualised predictions. Where a publication assesses multiple prediction models, only complete a PROBAST assessment for those models that meet the inclusion criteria for your systematic review. Please note that subsequent use of the term "model" includes derivatives of models, such as simplified risk scores, nomograms, or recalibrations of models.

PROBAST is not designed for all multivariable diagnostic or prognostic studies. For example, studies using multivariable models to identify predictors associated with an outcome but not attempting to develop a model for making individualised predictions are not covered by PROBAST.

PROBAST includes four steps.

Step	Task	When to complete
1	Specify your systematic review question(s)	Once per systematic review
2	Classify the type of prediction model evaluation	Once for each model of interest in each publication being assessed, for each relevant outcome
3	Assess risk of bias and applicability	Once for each development and validation of each distinct prediction model in a publication
4	Overall judgment	Once for each development and validation of each distinct prediction model in a publication

If this is your first time using PROBAST, we strongly recommend reading the detailed explanation and elaboration (E&E, see link above) paper and to check the examples on www.probast.org

Step 1: Specify your systematic review question

State your systematic review question to facilitate the assessment of the applicability of the evaluated models to your question. *The following table should be completed once per systematic review.*

Criteria	Specify your systematic review question
Intended use of model:	
***Participants** including selection criteria and setting:*	
***Predictors** (used in prediction modelling), including types of predictors (e.g. history, clinical examination, biochemical markers, imaging tests), time of measurement, specific measurement issues (e.g., any requirements/ prohibitions for specialized equipment):*	
Outcome to be predicted:	

Step 2: Classify the type of prediction model evaluation

Use the following table to classify the evaluation as model development, model validation or model update, or combination. Different signalling questions apply for different types of prediction model evaluation. If the evaluation does not fit one of these classifications then PROBAST should not be used.

Classify the evaluation based on its aim			
Type of prediction study	**PROBAST boxes to complete**	**Tick as appropriate**	**Definition for type of prediction model study**
Development only	Development		Prediction model development without external validation. These studies may include internal validation methods, such as bootstrapping and cross-validation techniques.
Development and validation	Development and validation		Prediction model development combined with external validation in other participants in the same article.
Validation only	Validation		External validation of existing (previously developed) model in other participants.

This table should be completed once for each publication being assessed and for each relevant outcome in your review.

Publication reference	
Models of interest	
Outcome of interest	

Step 3: Assess risk of bias and applicability

PROBAST is structured as four key domains. Each domain is judged for risk of bias (low, high or unclear) and includes signalling questions to help make judgements. Signalling questions are rated as yes (Y), probably yes (PY), probably no (PN), no (N) or no information (NI). All signalling questions are phrased so that "yes" indicates absence of bias. Any signalling question rated as "no" or "probably no" flags the potential for bias; you will need to use your judgement to determine whether the domain should be rated as "high", "low" or "unclear" risk of bias. The guidance document contains further instructions and examples on rating signalling questions and risk of bias for each domain.

The first three domains are also rated for concerns regarding applicability (low/ high/ unclear) to your review question defined above.

Complete all domains separately for each evaluation of a distinct model. Shaded boxes indicate where signalling questions do not apply and should not be answered.

DOMAIN 1: Participants			
A. Risk of Bias			
Describe the sources of data and criteria for participant selection:			
		Dev	Val
1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?			
1.2 Were all inclusions and exclusions of participants appropriate?			
Risk of bias introduced by selection of participants	**RISK:** *(low/ high/ unclear)*		
Rationale of bias rating:			
B. Applicability			
Describe included participants, setting and dates:			
Concern that the included participants and setting do not match the review question	**CONCERN:** *(low/ high/ unclear)*		
Rationale of applicability rating:			

DOMAIN 2: Predictors			
A. Risk of Bias			
List and describe predictors included in the final model, e.g. definition and timing of assessment:			
		Dev	Val
2.1 Were predictors defined and assessed in a similar way for all participants?			
2.2 Were predictor assessments made without knowledge of outcome data?			
2.3 Are all predictors available at the time the model is intended to be used?			
Risk of bias introduced by predictors or their assessment	**RISK:** *(low/ high/ unclear)*		
Rationale of bias rating:			
B. Applicability			
Concern that the definition, assessment or timing of predictors in the model do not match the review question	**CONCERN:** *(low/ high/ unclear)*		
Rationale of applicability rating:			

DOMAIN 3: Outcome			
A. Risk of Bias			
Describe the outcome, how it was defined and determined, and the time interval between predictor assessment and outcome determination:			
		Dev	Val
3.1 Was the outcome determined appropriately?			
3.2 Was a pre-specified or standard outcome definition used?			
3.3 Were predictors excluded from the outcome definition?			
3.4 Was the outcome defined and determined in a similar way for all participants?			
3.5 Was the outcome determined without knowledge of predictor information?			
3.6 Was the time interval between predictor assessment and outcome determination appropriate?			
Risk of bias introduced by the outcome or its determination	**RISK:** *(low/ high/ unclear)*		
Rationale of bias rating:			
B. Applicability			
At what time point was the outcome determined: *If a composite outcome was used, describe the relative frequency/distribution of each contributing outcome:*			
Concern that the outcome, its definition, timing or determination do not match the review question	**CONCERN:** *(low/ high/ unclear)*		
Rationale of applicability rating:			

DOMAIN 4: Analysis			
Risk of Bias			
Describe numbers of participants, number of candidate predictors, outcome events and events per candidate predictor:			
Describe how the model was developed (for example in regards to modelling technique (e.g. survival or logistic modelling), predictor selection, and risk group definition):			
Describe whether and how the model was validated, either internally (e.g. bootstrapping, cross validation, random split sample) or externally (e.g. temporal validation, geographical validation, different setting, different type of participants):			
Describe the performance measures of the model, e.g. (re)calibration, discrimination, (re)classification, net benefit, and whether they were adjusted for optimism:			
Describe any participants who were excluded from the analysis:			
Describe missing data on predictors and outcomes as well as methods used for missing data:			
		Dev	Val
4.1 Were there a reasonable number of participants with the outcome?			
4.2 Were continuous and categorical predictors handled appropriately?			
4.3 Were all enrolled participants included in the analysis?			
4.4 Were participants with missing data handled appropriately?			
4.5 Was selection of predictors based on univariable analysis avoided?			
4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of controls) accounted for appropriately?			
4.7 Were relevant model performance measures evaluated appropriately?			
4.8 Were model overfitting and optimism in model performance accounted for?			
4.9 Do predictors and their assigned weights in the final model correspond to the results from multivariable analysis?			
Risk of bias introduced by the analysis	**RISK:** *(low/ high/ unclear)*		
Rationale of bias rating:			

Step 4: Overall assessment

Use the following tables to reach overall judgements about risk of bias and concerns regarding applicability of the prediction model evaluation (development and/or validation) across all assessed domains.
Complete for each evaluation of a distinct model.

Reaching an overall judgement about risk of bias of the prediction model evaluation	
Low risk of bias	If all domains were rated low risk of bias. If a prediction model was developed without any external validation, and it was rated as low risk of bias for all domains, consider downgrading to **high risk of bias**. Such a model can only be considered as low risk of bias, if the development was based on a very large data set and included some form of internal validation.
High risk of bias	If at least one domain is judged to be at **high risk of bias**.
Unclear risk of bias	If an unclear risk of bias was noted in at least one domain and it was low risk for all other domains.

Reaching an overall judgement about applicability of the prediction model evaluation	
Low concerns regarding applicability	If low concerns regarding applicability for all domains, the prediction model evaluation is judged to have **low concerns regarding applicability**.
High concerns regarding applicability	If high concerns regarding applicability for at least one domain, the prediction model evaluation is judged to have **high concerns regarding applicability**.
Unclear concerns regarding applicability	If unclear concerns (but no "high concern") regarding applicability for at least one domain, the prediction model evaluation is judged to have **unclear concerns regarding applicability** overall.

Overall judgement about risk of bias and applicability of the prediction model evaluation		
Overall judgement of risk of bias	**RISK:** *(low/ high/ unclear)*	
Summary of sources of potential bias:		
Overall judgement of applicability	**CONCERN:** *(low/ high/ unclear)*	
Summary of applicability concerns:		

The Risk Of BiasIn Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

Version 19 September 2016

ROBINS-I tool (Stage I): At protocol stage

Specify the review question

Participants	
Experimental intervention	
Comparator	
Outcomes	

List the confounding domains relevant to all or most studies

List co-interventions that could be different between intervention groups and that could impact on outcomes

ROBINS-I tool (Stage II): For each study

Specify a target randomized trial specific to the study

Design	Individually randomized / Cluster randomized / Matched (e.g. cross-over)
Participants	
Experimental intervention	
Comparator	

Is your aim for this study…?

☐ to assess the effect of *assignment to* intervention

☐ to assess the effect of *starting and adhering to* intervention

Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

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.

Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

"Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

(i) Confounding domains listed in the review protocol				
Confounding domain	Measured variable(s)	Is there evidence that controlling for this variable was unnecessary?*	Is the confounding domain measured validly and reliably by this variable (or these variables)?	OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator?
			Yes / No / No information	Favour experimental / Favour comparator / No information

(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important				
Confounding domain	Measured variable(s)	Is there evidence that controlling for this variable was unnecessary?*	Is the confounding domain measured validly and reliably by this variable (or these variables)?	OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator?
			Yes / No / No information	Favour experimental / Favour comparator / No information

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.

(i) Co-interventions listed in the review protocol		
Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information

(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important		
Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information

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.

Signalling questions	Description	Response options
Bias due to confounding		
1.1 Is there potential for confounding of the effect of intervention in this study? **If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered		Y / PY / PN / N
If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:		
1.2. Was the analysis based on splitting participants' follow up time according to intervention received? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, go to question 1.3.		NA / Y / PY / PN / N / NI
1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)		NA / Y / PY / PN / N / NI

Questions relating to baseline confounding only		
1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?		NA / Y / PY / PN / N / NI
1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?		NA / Y / PY / PN / N / NI
1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?		NA / Y / PY / PN / N / NI
Questions relating to baseline and time-varying confounding		
1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?		NA / Y / PY / PN / N / NI
1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?		NA / Y / PY / PN / N / NI
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to confounding?		Favours experimental / Favours comparator / Unpredictable

Bias in selection of participants into the study		
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? **If N/PN to 2.1:** go to 2.4		Y / PY / PN / N / NI
2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention?		NA / Y / PY / PN / N / NI
2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?		NA / Y / PY / PN / N / NI
2.4. Do start of follow-up and start of intervention coincide for most participants?		Y / PY / PN / N / NI
2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases?		NA /Y / PY / PN / N / NI
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to selection of participants into the study?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Bias in classification of interventions		
3.1 Were intervention groups clearly defined?		Y / PY / PN / N / NI
3.2 Was the information used to define intervention groups recorded at the start of the intervention?		Y / PY / PN / N / NI
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?		Y / PY / PN / N / NI
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to classification of interventions?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Bias due to deviations from intended interventions		
If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2		
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?		Y / PY / PN / N / NI
4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?		NA / Y / PY / PN / N / NI
If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6		
4.3. Were important co-interventions balanced across intervention groups?		Y / PY / PN / N / NI
4.4. Was the intervention implemented successfully for most participants?		Y / PY / PN / N / NI
4.5. Did study participants adhere to the assigned intervention regimen?		Y / PY / PN / N / NI
4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to deviations from the intended interventions?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Bias due to missing data		
5.1 Were outcome data available for all, or nearly all, participants?		Y / PY / PN / N/ NI
5.2 Were participants excluded due to missing data on intervention status?		Y / PY / PN / N / NI
5.3 Were participants excluded due to missing data on other variables needed for the analysis?		Y / PY / PN / N / NI
5.4 **IfPN/Nto 5.1, orY/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?		NA / Y / PY / PN / N / NI
5.5 **If PN/Nto 5.1, orY/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data?		NA / Y / PY / PN / N / NI
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to missing data?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Bias in measurement of outcomes		
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?		Y / PY / PN / N / NI
6.2 Were outcome assessors aware of the intervention received by study participants?		Y / PY / PN / N / NI
6.3 Were the methods of outcome assessment comparable across intervention groups?		Y / PY / PN / N / NI
6.4 Were any systematic errors in measurement of the outcome related to intervention received?		Y / PY / PN / N / NI
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to measurement of outcomes?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Bias in selection of the reported result		
Is the reported effect estimate likely to be selected, on the basis of the results, from... 7.1. ... multiple outcome *measurements* within the outcome domain?		Y / PY / PN / N / NI
7.2 ... multiple *analyses* of the intervention-outcome relationship?		Y / PY / PN / N / NI
7.3 ... different *subgroups*?		Y / PY / PN / N / NI
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to selection of the reported result?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall bias		
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the overall predicted direction of bias for this outcome?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

QUADAS-2 TOOL FOR DIAGNOSIS TEST

QUADAS-2 tool: Risk of bias and applicability judgments

Domain 1: Patient selection	
A. Risk of bias	
Describe methods of patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting):	
• **Was a consecutive or random sample of patients enrolled?**	Yes/No/Unclear
• **Was a case-control design avoided?**	Yes/No/Unclear
• **Did the study avoid inappropriate exclusions?**	Yes/No/Unclear
Could the selection of patients have introduced bias?	RISK: LOW/HIGH/UNCLEAR
B. Concerns regarding applicability	
Describe included patients (prior testing, presentation, intended use of index test and setting):	
Is there concern that the included patients do not match the review question?	CONCERN: LOW/HIGH/UNCLEAR

Domain 2: Index test(s) ***(if more than 1 index test was used, please complete for each test)***	
A. Risk of bias	
Describe the index test and how it was conducted and interpreted: Describe the index test and how it was conducted and interpreted	
• **Were the index test results interpreted without knowledge of the results of the reference standard?**	Yes/No/Unclear
• **If a threshold was used, was it pre-specified?**	Yes/No/Unclear
Could the conduct or interpretation of the index test have introduced bias?	RISK: LOW/HIGH/UNCLEAR
B. Concerns regarding applicability	
Is there concern that the index test, its conduct, or interpretation differ from the review question?	CONCERN: LOW/HIGH/UNCLEAR

Domain 3: Reference standard	
A. Risk of bias	
Describe the reference standard and how it was conducted and interpreted: Describe the reference standard and how it was conducted and interpreted:	
• **Is the reference standard likely to correctly classify the target condition?**	Yes/No/Unclear
• **Were the reference standard results interpreted without knowledge of the results of the index test?**	Yes/No/Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	RISK: LOW/HIGH/UNCLEAR
B. Concerns regarding applicability	
Is there concern that the target condition as defined by the reference standard does not match the review question?	CONCERN: LOW/HIGH/UNCLEAR

Domain 4: Flow and timing	
A. Risk of bias	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram):	
Describe the time interval and any interventions between index test(s) and reference standard:	
• **Was there an appropriate interval between index test(s) and reference standard?**	Yes/No/Unclear
• **Did all patients receive a reference standard?**	Yes/No/Unclear
• **Did patients receive the same reference standard?**	Yes/No/Unclear
• **Were all patients included in the analysis?**	Yes/No/Unclear
Could the patient flow have introduced bias?	RISK: LOW/HIGH/UNCLEAR