

**Appendix 2:** detailed ROBIS assessment of the included systematic reviews.**Ahmed 2016**

Item	Author's judgment	Support for judgment
------	-------------------	----------------------

**DOMAIN 1: study eligibility criteria**

#1 Did the review adhere to pre-defined objectives and eligibility criteria?	PN	The authors specified that the objectives were to summarize the diagnostic accuracy of glaucoma diagnostic technologies compared to white on white perimetry. However, they originally included optic disc photographs as a parallel gold standard and later excludes this reference standard because few studies used such method as reference standard. The actual objectives of the review seem to have been chosen Post Hoc, based on the selected studies
#2 Were the eligibility criteria appropriate for the review question?	NI	The eligibility criteria were appropriate to the review question as stated in the introduction. However, in the methods the authors stated that "We organized the review to answer both primary and second research question. The primary research question addressed the diagnostic accuracies of five index technologies for glaucoma screening". For such research question the inclusion criteria used in this review would not be completely appropriate
#3 Were eligibility criteria unambiguous?	PN	There were concerns about the comparator accepted as reference standard for the included studies: white on white perimetry as it seemed from the text, or white on white perimetry or a composite gold standard (which include white on white perimetry) as it seemed from figure 1
#4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Y	The restrictions applied such as the number of participants included in primary studies or the outcome measures reported in the original study, appeared appropriate
#5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	NI	Published and unpublished human studies of any design were considered. No details about restrictions based on study language were provided
<u>Concerns regarding specification of study eligibility criteria</u>	High	There are concern as to whether the objectives were chosen a priori or post hoc, after the studies' selection. There were ambiguous details regarding the reference standard and the research question (screening or not screening studies)

**DOMAIN 2: identification and selection of studies**

#1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	PY	MEDLINE, EMBASE, BIOSIS Previews, CINAHL, PubMed, and the Cochrane Library were searched. This was judged to be an appropriate range
#2 Were methods additional to database searching used to identify relevant reports?	Y	Additional methods such as handsearching bibliographies, web based materials, contacting experts, abstracts of key papers and conference proceedings, have been performed

#3. Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	NI	The authors reported that a specific search terms tailored for diagnostic testing have been studied but details of the search terms used as well as the methodological filters applied, were not reported
#4 Were restrictions based on date, publication format, or language appropriate?	PY	The search strategy was restricted from 1993 onward and it seems appropriate
#5 Were efforts made to minimize error in selection of studies?	Y	Selection has been conducted independently by at least two reviewers, and this was applied to both screening search results and assessing full text articles
<u>Concerns regarding specification of study eligibility criteria</u>	Unclear	All signaling questions but one were judged at low risk of bias, however no details of the search terms were reported. No details on methodological filters applied were reported as well, therefore remains unclear whether the review have included high proportion of relevant studies

**DOMAIN 3: data collection and study appraisal**

#1 Were efforts made to minimize error in data collection?	Y	One person abstracted data, and a second reviewer independently verified the data using an electronic data abstraction form developed a priori
#2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	PN	The authors reported that data collection included study identification data, research methods data, population baseline variables, clinical variables, VF variables and index technology variables. However only details on age, sex and (partially) ethnic were reported in the text. No further details were reported
#3 Were all relevant study results collected for use in the synthesis?	NI	The authors stated that "The parameters of interest included sensitivities, specificities, likelihood ratios, ROC curves, and DORs". Sensitivities and specificities were extracted from each study, but despite DORs was used as primary outcome, no further details about data needed to calculate other parameters of interest (such as likelihood ratio and ROC curve), were reported
#4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Y	QUADAS was used to assess the risk of bias
#5 Were efforts made to minimize error in risk of bias assessment?	NI	How the risk of bias assessment was conducted (i.e. how many assessors), was not reported
<u>Concerns regarding specification of study eligibility criteria</u>	Unclear	There were insufficient study details about the characteristics of the included studies, the study results collected and the risk of bias assessment. So there is unclear risk of bias in both data collection and study appraisal process

**DOMAIN 4: synthesis and findings**

#1 Did the synthesis include all studies that it should?	PY	Despite no details on how many studies for each imaging technologies were included in the review were reported, from figure 1 seems that all the included studies were combined in the quantitative synthesis
#2 Were all pre-defined analyses reported or departures explained?	PN	No protocol were available for this review. However the authors reported a list of parameters of interest including sensitivity, specificity, likelihood ratio, ROC curve and DORs. Likelihood ratio were not reported. AUC were

		displayed in table 3 but not reported or mentioned at all in the text
#3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	PY	Quote "Random-effects meta-analysis was performed for each diagnostic instrument where possible and stratified by the type of summary statistics available from eligible studies."
#4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	PY	Statistical heterogeneity was assessed and a random-effects model has been appropriately used to allow for heterogeneity. Subgroup analysis were conducted to explore some sources of heterogeneity despite the main reason of heterogeneity suggested by the authors (methods and cut-off used in each study), were not assessed
#5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	PN	The authors reported that the level of heterogeneity was very high. And that "When methods of outcome analysis, as well as cutoffs are this varied, it is very difficult to be certain about the accuracy and effectiveness of a test". No funnel plot or sensitivity analysis were used
#6 Were biases in primary studies minimal or addressed in the synthesis?	PY	The risk of bias of the included studies as assessed with QUADAS was overall good for 75% of the included studies. No discussion about studies with lower quality were reported
<u>Concerns regarding specification of study eligibility criteria</u>	High	Methodology was adequate and risk of bias of the included studies was (for the most part) low, however parameters of interest were partially reported and not included in the discussion and the robustness of the results was weak due to very high level of heterogeneity

**Risk of Bias in the Review**

A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	PN	Among limitations identified by the Phase 2 assessment, only the high level of heterogeneity was addressed by the review authors
B. Was the relevance of identified studies to the review's research question appropriately considered?	PN	The authors did not consider the relevance of the included studies to the review question and there were insufficient details for the reader (with respect to study design, reference standard and characteristics of the included studies) to make this assessment
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Y	The results of predefined parameters of interest, were partially reported or discussed, however the findings emphasized in the discussion is properly based on the results, and the limitations related to the high level of heterogeneity and its suggested causes were addressed.
<u>Risk of bias in the review</u>	High	The phase 2 assessment identified a number of areas of concern with the review process which were not completely addressed by the authors. These include lack of clarity in the inclusion criteria (i.e. reference standard), no details on the search term strategy, insufficient details on data of included studies collected and the risk of bias assessment.

**Fallon 2017**

Item	Author's judgment	Support for judgment
------	-------------------	----------------------

**DOMAIN 1: study eligibility criteria**

#1 Did the review adhere to pre-defined objectives and eligibility criteria?	Y	A protocol including details on study design, study participants, type of intervention and reference standard, was available
#2 Were the eligibility criteria appropriate for the review question?	PY	The details of studies eligible for inclusion were properly reported in the review
#3 Were eligibility criteria unambiguous?	Y	Study design, study participant, and index /reference test, were clearly stated
#4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	PY	Study with less than 50 participants and studies involving juvenile subjects were excluded
#5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	PY	Language restrictions to studies published in English, Spanish or French, were applied
<u>Concerns regarding specification of study eligibility criteria</u>	Low	No concerns about eligibility criteria were identified

**DOMAIN 2: identification and selection of studies**

#1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	PY	MEDLINE, EMBASE, and the Cochrane library were searched
#2 Were methods additional to database searching used to identify relevant reports?	PN	Additional methods for study searching (handsearching bibliographies or citations) as well as gray literature (posters, communications, and theses) was not taken into account.
#3. Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	PY	A detailed search strategy was provided in a web appendix as well as in the protocol
#4 Were restrictions based on date, publication format, or language appropriate?	PY	The search strategy was restricted from January 2004, to February, 2015 and this seemed appropriate considering the technology improvement. Publications in English, Spanish, or French were included
#5 Were efforts made to minimize error in selection of studies?	PY	One reviewer screened the abstract to identify the potential relevant studies, and assessed the full text of the relevant studies to include in the review. A second reviewer was only consulted in doubtful cases
<u>Concerns regarding specification of study eligibility criteria</u>	Low	Range of database and electronic sources as well as the specific terms of the search strategy were appropriate. Only one assessor (who consulted a second assessor only for doubtful cases) evaluated the abstract and the full text of the studies to judge their inclusion

**DOMAIN 3: data collection and study appraisal**

#1 Were efforts made to minimize error in data collection?	PN	An open source software was used to create an abstraction form, but only one abstractor collected the data, while a second abstractor were consulted only for doubtful cases
#2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Y	Study characteristics and result tables were provided in the manuscript and appendices
#3 Were all relevant study results collected for use in the synthesis?	PY	Sensitivities and specificities were extracted from each study to calculate the diagnostic accuracy measures and perform meta-analysis
#4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Y	QUADAS-2 was used to assess the risk of bias and applicability concern of all the included studies
#5 Were efforts made to minimize error in risk of bias assessment?	PN	Only one reviewer assessed the risk of bias, while a second reviewer was consulted only for doubtful cases
<u>Concerns regarding specification of study eligibility criteria</u>	High	There were completed details about the characteristics of the included studies and an appropriate tool was used to assess the risk of bias in individual studies. Both data abstraction

		and risk of bias assessment were performed by one assessor, who consulted a second reviewer in doubtful cases
--	--	---

**DOMAIN 4: synthesis and findings**

#1 Did the synthesis include all studies that it should?	PY	All the eligible studies were included in the synthesis
#2 Were all pre-defined analyses reported or departures explained?	PY	A protocol was available as supplementary information. All analyses in methods section were addressed in the results
#3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	PY	Quote: "The diagnostic odds ratio was calculated for each study. To compare diagnostic accuracy among instruments and among parameters within each instrument, a meta-analysis considering the hierarchical summary receiver-operating characteristic model was performed."
#4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	PY	Statistical heterogeneity was assessed by forest plot, and addressed using a random effects model. Subgroup analyses were performed to examine the effect of potential effect modifiers
#5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	PN	The authors did not conduct a sensitivity analysis neither explored a funnel plot. However, there was a discussion around the case control design of the included studies
#6 Were biases in primary studies minimal or addressed in the synthesis?	PY	Biases were assessed using the QUADAS-2 tool. This assessment indicated that patient selection and flow and timing were at high risk of bias. Other aspects of QUADAS-2 were not of major concern. No subgroup analysis were conducted
<u>Concerns regarding specification of study eligibility criteria</u>	Low	Despite the lack of a sensitivity analysis and subgroup analysis for risk of bias of the individual studies, the synthesis seemed unlikely to produce biased results

**Risk of Bias in the Review**

D. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	PY	Limitations identified by the Phase 2 assessment, specifically the fact that study selection, risk of bias assessment and data abstraction were performed by one reviewer alone, were recognized and addressed by the authors in the discussion
E. Was the relevance of identified studies to the review's research question appropriately considered?	PY	Quote: "...all studies were considered to match the question being addressed by the review." The implications of the study design of the included studies was discussed in detail. The potential sources of bias in terms of patient selection and flow and timing available from the included studies, were discussed in detail
F. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Y	The findings/conclusions of the review seems to properly reflect the review' results
<u>Risk of bias in the review</u>	Low	The phase 2 assessment identified areas of concern with regard to the process of study selection, data abstraction and risk of bias assessment, being all these phases conducted mainly by one reviewer (with a second reviewer involved only in doubtful cases). No sensitivity analysis were performed to assess the robustness of the findings. However, the potential limitation of the review and the included studies in term of risk of bias were addressed and discussed. The review conclusions appropriately reflect the results of the review

## Kansal 2018

Item	Author's judgment	Support for judgment
<b>DOMAIN 1: study eligibility criteria</b>		
#1 Did the review adhere to pre-defined objectives and eligibility criteria?	PY	A protocol for this review was not available. The authors provided details of eligibility criteria in the related section organized by population, index test, reference standard, study design and outcome. Some concerns is about the measure of diagnostic accuracy
#2 Were the eligibility criteria appropriate for the review question?	PY	The eligibility criteria reported in the related section seems to be appropriate for the research question
#3 Were eligibility criteria unambiguous?	NI	A protocol for this review is lacking. The eligibility criteria were to some extent unambiguous. However in data synthesis and statistical analysis section, the authors stated that "the AUROC was found to be more consistently reported in the included studies." This is confusing because the early in the manuscript the authors also stated that "...articles were included if they reported area under receiver operating characteristic curve (AUROC) statistics". So it should be obvious that all the included studies reported AUROC "consistently"
#4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	PY	No particular restrictions were applied
#5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	PN	Only clinical study originally published in English were accepted for inclusion. Moreover, 31 studies have been excluded because the full text manuscript was unable to be obtained
<u>Concerns regarding specification of study eligibility criteria</u>	High	No protocol was available for this review. The objectives and eligibility criteria were to some extent clearly specify. Concerns for potential risk of bias is related to the amount of potential relevant studies not included due to full text manuscript not recovered

**DOMAIN 2: identification and selection of studies**

#1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	PY	MEDLINE, EMBASE, CINAHL, Cochrane Library (Wiley Library), Web of Science, and BIOSIS, databases were searched. Authors stated that "Published and unpublished studies were considered" Despite no details about unpublished reports search was reported
#2 Were methods additional to database searching used to identify relevant reports?	PN	No additional methods than database searching was used
#3. Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	PY	The search strategy was provided in a web appendix and appeared to be sensitive
#4 Were restrictions based on date, publication format, or language appropriate?	PN	Search strategy was limited to English language
#5 Were efforts made to minimize error in selection of studies?	PY	Study selection was conducted by two independent screeners through a two phases process
<u>Concerns regarding specification of study eligibility criteria</u>	Low	Search strategy was limited to English study, and no additional methods were used to retrieve relevant study. An appropriate search strategy

		has been used and two independent screeners selected the study to be included
--	--	---

**DOMAIN 3: data collection and study appraisal**

#1 Were efforts made to minimize error in data collection?	NI	Data collection was conducted by using an electronic data extraction form but no details about the number of abstractors involved in this process, was reported
#2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Y	Detailed study characteristics were provided in the text and web appendix
#3 Were all relevant study results collected for use in the synthesis?	PY	AUROC curve data were extracted from each study which is sufficient to calculate the relative measures of diagnostic accuracy
#4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Y	QUADAS-2 was used to assess the risk of bias
#5 Were efforts made to minimize error in risk of bias assessment?	NI	How the study quality assessment was conducted (i.e. how many assessors), was not reported.
<u>Concerns regarding specification of study eligibility criteria</u>	Unclear	The characteristics of the included studies and relevant study results were sufficiently collected but no details about the data collection and the risk of bias assessment were reported

**DOMAIN 4: synthesis and findings**

#1 Did the synthesis include all studies that it should?	PY	All the included studies were combined in the quantitative synthesis
#2 Were all pre-defined analyses reported or departures explained?	PY	No protocol was available for this review. The analysis specified in the methods section was addressed in the results
#3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	PY	The authors stated that "Individual measures of AUROC from each study were pooled into a weighted summary AUROC"
#4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	PY	The authors stated that "Heterogeneity among included studies was tested by computing the $I^2$ , Z-value and $\chi^2$ statistics." and a fixed effect model or a random effects model were used when appropriate, based on the results of the testing. The level of heterogeneity was reported as forest plot
#5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	NI	No sensitivity analysis were reported or mentioned. Several funnel plots were constructed to evaluate the publication bias, but none was displayed and reported in the manuscript
#6 Were biases in primary studies minimal or addressed in the synthesis?	PY	Biases were assessed using QUADAS-2. Patient selection and flow and timing were at high risk of bias. No related subgroup analysis were conducted. Risk of bias was partially addressed in the discussion
<u>Concerns regarding specification of study eligibility criteria</u>	Low	Nevertheless some findings are partially reported (funnel plot detail, sensitivity analysis), the synthesis is unlikely to produce biased results, with between-study variation taken into account with appropriate methodology

**Risk of Bias in the Review**

G. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	PN	Among limitations identified by the Phase 2 assessment, concerns related to the data abstraction and risk of bias assessment were not addressed in the discussion. The high level of heterogeneity (as suggested by the forest plot) was not discussed as well. Heterogeneity was
---	----	---

		addressed by random effects model but robustness of the results was not explored with sensitivity analysis
H. Was the relevance of identified studies to the review's research question appropriately considered?	PY	The authors did consider the relevance of the included studies to the review question mainly by highlighting the different reference standards accepted for a study to be included
I. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	N	The authors stated that "Overall, there were no statistically significance differences between devices for any particular area imaged." It is unclear were these findings came from, because no statistical comparison analysis was mentioned in the methods, or reported in the text/table. If so, the interpretation of the results seems not to be guided by statistical strong comparison between AUROC. The conclusion as reported along the discussion seemed to come from a rough correlation between the absolute AUROC value. If so, the interpretation of the results risk to be not consistently for all the comparison. The same difference between AUROC value, is sometimes reported as similar, other time as higher vs lower
<u>Risk of bias in the review</u>	high	The phase 2 assessment identified some concerns with the review process, specifically related to the data abstraction and risk of bias assessment process. However the potential limitations related to these concerns as well as the robustness of the findings with respect to the high level of heterogeneity, were not addressed

**Michelessi 2015**

Item	Author's judgment	Support for judgment
------	-------------------	----------------------

**DOMAIN 1: study eligibility criteria**

#1 Did the review adhere to pre-defined objectives and eligibility criteria?	Y	A protocol for this review was available
#2 Were the eligibility criteria appropriate for the review question?	PY	The details of eligibility criteria provided in the protocol/article appeared appropriate to the review question
#3 Were eligibility criteria unambiguous?	PY	The types of study design were clearly stated. Details of the population of interest, the index test, outcome and any reference standard were provided
#4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	PY	The restrictions based on types of study design (no population-based screening study) were explained. The restrictions appeared to be appropriate to the research question
#5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	PY	No language restrictions were applied. Restrictions were applied to studies providing data to allow calculation of sensitivity and specificity. This is common in DTA reviews and was clearly explained
<u>Concerns regarding specification of study eligibility criteria</u>	Low	No potential concerns with regard to the eligibility criteria were identified. A protocol pre specify the review question and objectives

**DOMAIN 2: identification and selection of studies**

#1 Did the search include an appropriate range of databases/electronic sources for published and unpublished	PY	DARE, HTA, NHSEED (Cochrane Library), Ovid MEDLINE, Ovid MEDLINE In-Process and Other
--	----	---



reports?		Non-Indexed Citations, Ovid MED- LINE Daily, Ovid OLDMEDLINE, EMBASE, MEDION and the Aggressive Research Intelligence Facility database (ARIF) database were search.
#2 Were methods additional to database searching used to identify relevant reports?	PY	The authors stated that “We hand searched the reference lists of the included studies for further relevant studies.”
#3. Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	PY	Five appendices specify the search strategy terms for different database
#4 Were restrictions based on date, publication format, or language appropriate?	PY	No date or language restrictions were applied, and searches included steps to identify grey literature
#5 Were efforts made to minimize error in selection of studies?	Y	The process for both screening titles and abstracts and assessment of full text papers included pairs of reviewers, working independently. Any disagreement were solved by discussion or by referral to a third author
<u>Concerns regarding specification of study eligibility criteria</u>	Low	No area of potential concerns were recognized

**DOMAIN 3: data collection and study appraisal**

#1 Were efforts made to minimize error in data collection?	PY	Pairs of review authors independently extracted and collected the data
#2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	PY	The summary table included details on patient sampling, patient characteristics and setting, index test, target condition and reference standard
#3 Were all relevant study results collected for use in the synthesis?	Y	A flow diagram reported that results of all the included studies were used in the synthesis.
#4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Y	QUADAS -2 tool
#5 Were efforts made to minimize error in risk of bias assessment?	PY	Pairs of review authors independently assessed the methodological quality of included studies using the QUADAS-2 checklist. Any disagreement were solved by discussion or by referral to a third author
<u>Concerns regarding specification of study eligibility criteria</u>	Low	All signaling questions were rated as “Yes” or “Probably yes”, so the data collection and study appraisal phase is unlikely not have introduced bias in this review

**DOMAIN 4: synthesis and findings**

#1 Did the synthesis include all studies that it should?	PY	One hundred and six studies were considered relevant for this review and 106 studies were included in the synthesis
#2 Were all pre-defined analyses reported or departures explained?	PY	A protocol was available for this review. All predefined analysis were addressed in the results or explained accordingly (i.e. sensitivity analysis for type of study design by omitting case control study was impossible having nearly all the included studies, a case control design)
#3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	PY	To assess the diagnostic accuracy of the tests authors calculated summary sensitivity/specificity using data from 2 x 2 tables and synthesized it by using a bivariate model
#4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	PY	A large amount of heterogeneity emerged from the forest plot and this was largely investigated
#5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	PY	No sensitivity analysis was conducted, neither a funnel plot was constructed. Both decision were addressed and clarify in the text
#6 Were biases in primary studies minimal or addressed in the synthesis?	PY	By using QUADAS-2 tool, a high risk of bias was identified for patient selection domain and flow and timing domain. The case-control design was

		considered the main issue of the included studies and this was broadly addressed in the synthesis.
<u>Concerns regarding specification of study eligibility criteria</u>	Low	The authors comprehensively addressed heterogeneity in their analysis and used a subgroup analysis to explore it. Risk of bias of the individual studies was evaluated and addressed in the discussion

**Risk of Bias in the Review**

J. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	PY	The main concerns is related to the high risk of bias of the included study and the large heterogeneity emerged between studies. Both issues were addressed in the finding's interpretation
K. Was the relevance of identified studies to the review's research question appropriately considered?	Y	The relevance of the included study to the research question and the consequent applicability of the result in a well defined clinical pattern were properly considered
L. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	PY	The review conclusions reflect both the statistically significant and non-significant review' findings
<u>Risk of bias in the review</u>	Low	The phase 2 assessment identified a high risk of bias of the included studies and a high level of heterogeneity as potential limitation of the review. Both issues were discussed and addressed in the discussion. Overall, the review included clear inclusion criteria, a detailed search strategy, and appropriate details of the characteristics of the included study.