UNIVERSITY OF BIRMINGHAM

Assessment of methodological quality and QUADAS-2

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October 2015

Based on slides developed by Mariska Leeflang, Penny Whiting, Hans Reitsma and Sue Mallett

Learning objectives

- To be familiar with QUADAS-2
- To understand the need to adapt QUADAS-2 for the review
- To appreciate presenting and incorporating results of quality assessment

Outline

- Introduction to quality assessment of test accuracy studies
- QUADAS-2 tool
- Presenting and incorporating quality assessment results

Why assess quality?

- Problem 1: Bias in primary studies can lead to misleading summary estimates of accuracy
- Problem 2: The studies may not be applicable to the review question
- Problem 3: Results of primary studies may vary

Quality assessment to identify potential risk of bias and applicability to the review question and to guide interpretation of results

What do we mean by quality?

"both the risk of bias and applicability of a study;

(1) the degree to which estimates of diagnostic accuracy avoid risk of bias, and

(2) the extent to which primary studies are applicable to the review's research question"

Sources of bias and variation

- **Bias:** flaws in the design of the study may result in invalid estimates of accuracy

- **Applicability:** variation across studies mean that the results may not be applicable to your review question

Annals of Internal Medicine | Research and Reporting Methods

QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies

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In 2003, the QUADAS tool for systematic reviews of diagnostic accuracy studies was developed. Experience, anecdotal reports, and feedback suggested areas for improvement; therefore, QUADAS-2 was developed. This tool comprises 4 domains: patient selection, index test, reference standard, and flow and timing. Each domain is assessed in terms of risk of bias, and the first 3 domains are also assessed in terms of concerns regarding applicability. Signalling questions are included to help judge risk of bias.

The QUADAS-2 tool is applied in 4 phases: summarize the review question, tailor the tool and produce review-specific guidance, construct a flow diagram for the primary study, and judge bias and applicability. This tool will allow for more transparent rating of bias and applicability of primary diagnostic accuracy studies.

Ann Intern Med. 2011;155:529-536. www.annals.org

For author affiliations, see end of text.

* For members of the QUADAS-2 Group, see the **Appendix** (available at www.annals.org).

QUADAS-2

Three phased tool:

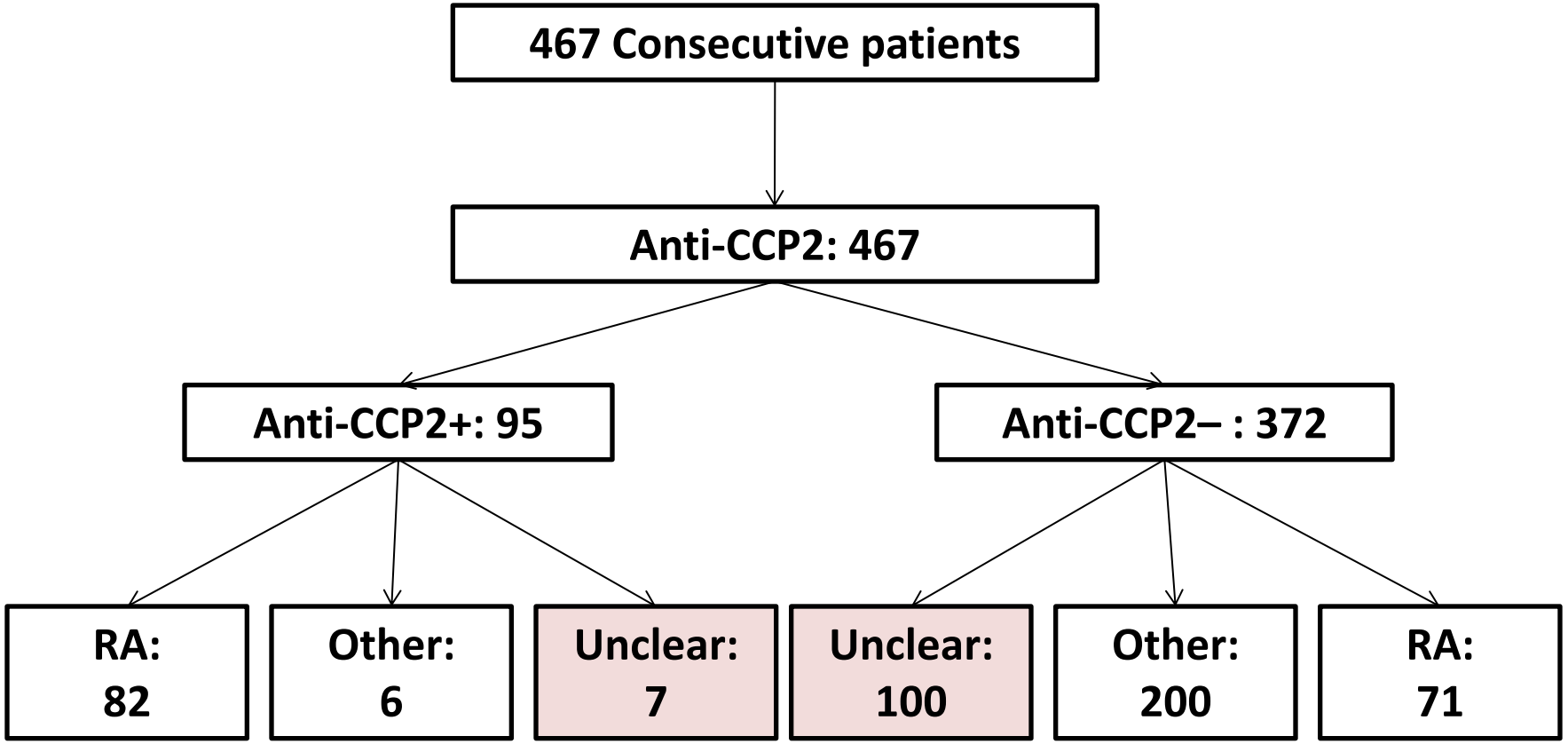
- Phase 1: Define the review question
- Phase 2: Draw a flow diagram
- Phase 3: Assessment of risk of bias and applicability
  - Four domains:
    - » Patient selection
    - » Index test
    - » Reference standard
    - » Flow and timing

Phase 1: Define the question

Define the question:

Patients: Patients with joint symptoms <12 months duration
Index test: Second generation anti-CCP test analysed by ELISA
Comparator test (if applicable): Rheumatoid factor detected by latex agglutination
Target condition: Rheumatoid arthritis
Reference Standard: American College of Rheumatology (ACR) criteria

Phase 2: Flow diagram



Phase 3: Assessment of domains

- Description:
  - Record information used to make judgement
- Signalling questions:
  - Used to inform rating of bias
  - Items phrased so that yes indicates absence of bias
- Domains:
  - Judgement of risk of bias/applicability made
  - A "**No**" on one or more signalling questions means that risk of bias should be considered, it does not necessarily imply that the risk should be judged as "**High**"
- Background document:
  - Provides general guidance on scoring
  - Scoring guidance, specific to your review should be produced to help ensure objective and consistent rating

QUADAS-2 domains

Domain	Source of Bias	Applicability
Patient selection	Study design Prospective/ retrospective Sample selection	Demographics Previous tests Presentation Intended use of test Setting
Index test	Blinding Threshold specification	Test technology Test execution Interpretation setting Interpreter expertise
Reference standard	Verification procedure Independence Blinding	Reference standard
Patient Flow and Timing	Appropriate time interval Intervention between tests Verification bias Appropriate exclusions Appropriate inclusions	NA

Signalling questions

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Describe methods of patient selection:

- ❖ 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 one index test was used, please complete for each test.

A. Risk of Bias

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:

- ❖ 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

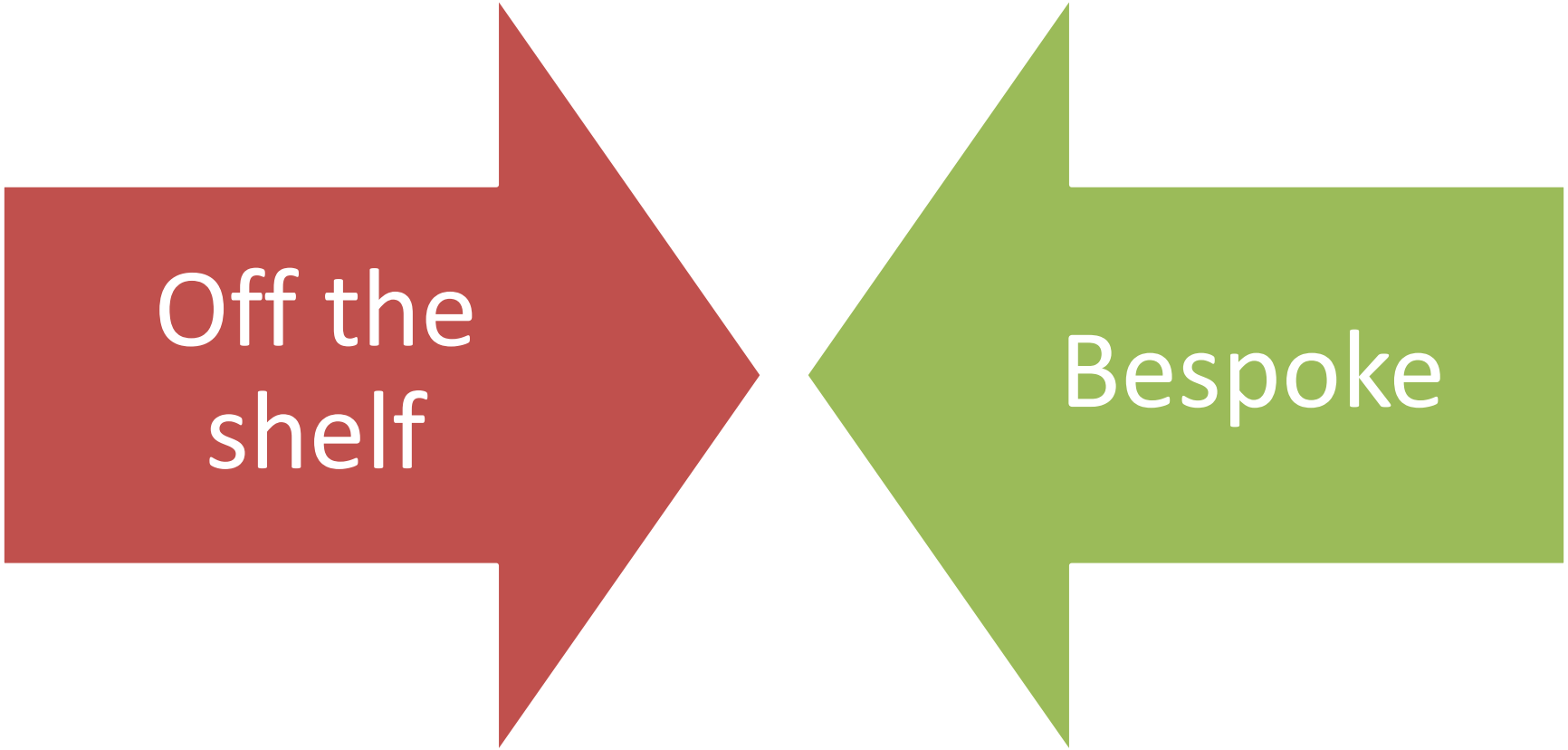
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram):

Describe the time interval and any interventions between index test(s) and reference standard:

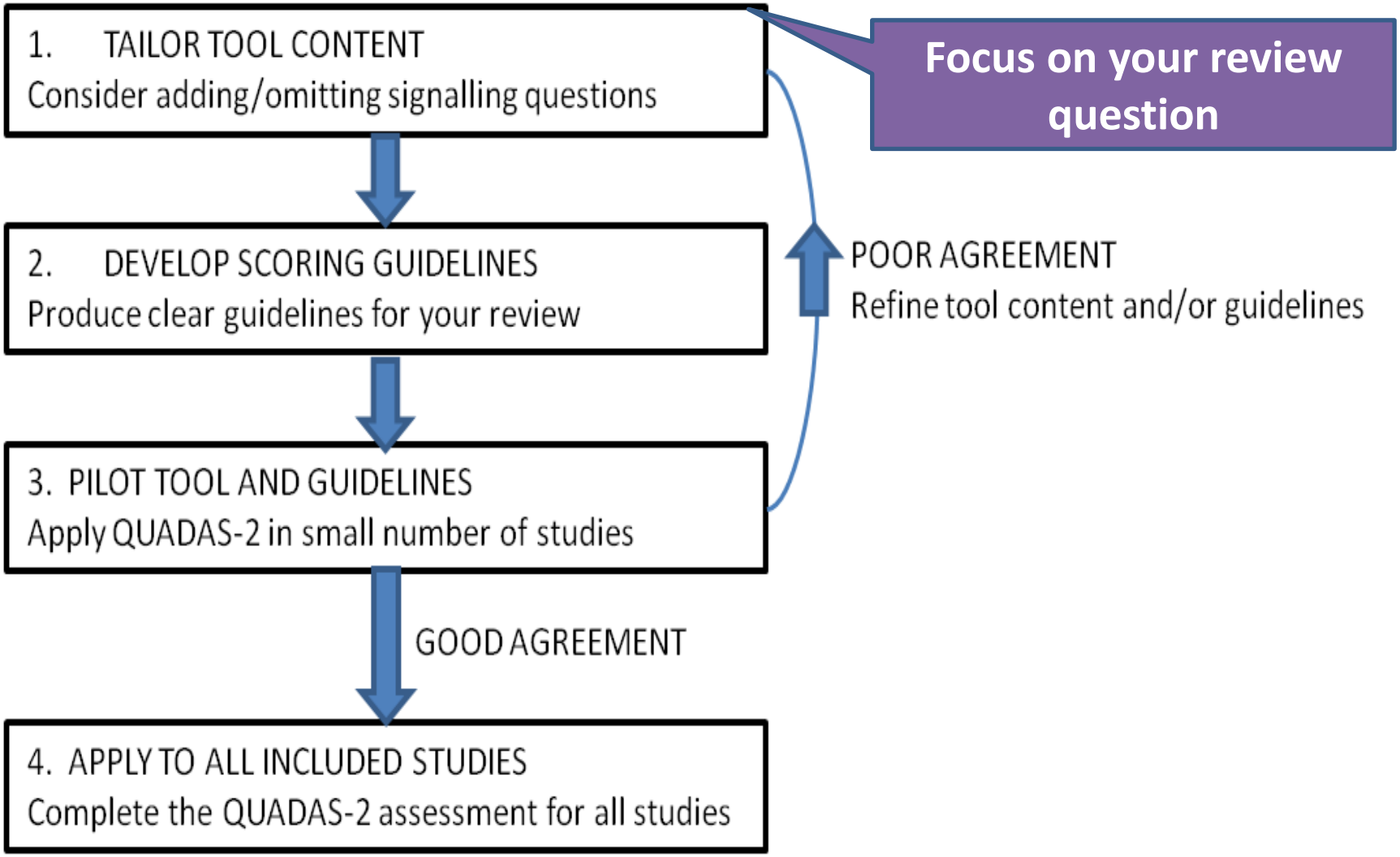
- ❖ Was there an appropriate interval between index test(s) and reference standard? Yes/No/Unclear
- ❖ Did all patients receive a reference standard? Yes/No/Unclear
- ❖ Did patients receive the same reference standard? Yes/No/Unclear
- ❖ Were all patients included in the analysis? Yes/No/Unclear

Could the patient flow have introduced bias? RISK: LOW /HIGH/UNCLEAR

Application of QUADAS-2



Tailoring QUADAS-2 to your review



DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Describe methods of patient selection:

- 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**

Patient selection - applicability

- Measures of accuracy may vary across patient groups:
  - Advanced versus early disease
  - Symptoms
  - Setting
  - Prior testing
  - Presence of alternative conditions
  - Demographic features
  - Intended use of the test

DOMAIN 2: INDEX TEST(S)

If more than one index test was used, please complete for each test.

A. Risk of Bias

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**

Index test

Bias: Blinding

- Knowledge of reference standard results when interpreting index test may lead to over-optimistic estimates of accuracy
- Less important for objective tests or if index test is interpreted prior to reference standard

Index test

Bias: Threshold selection

- Selecting threshold to maximise sensitivity and/or specificity may lead to overoptimistic measures of test performance.
- Performance of this cut-off in an independent set of patients will be likely to be lower, even if the study consists of patients from the same population.
- Important that the threshold is pre-specified rather than derived from the results of the study.

Index test

Applicability:

- If test conduct, technology, setting or interpretation differ from your review question the results may not be applicable

DOMAIN 3: REFERENCE STANDARD

A. Risk of Bias

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**

Reference standard

Bias: Reference standard

- How do we know the truth?
  - Post-mortem, histology, radiology, microbiology, chemical pathology

- Calculating accuracy assumes reference standard is 100% accurate – any disagreements assume index test is incorrect

Reference standard

Bias: Blinding

- Reference standard should be interpreted blind to index test results
- Related to degree of subjectiveness and order of tests.
- Index test should not form part of the reference standard

- Example:
  - ACR criteria for RA (reference standard) are applied some time after the anti-CCP test (Index test) and could therefore be influenced by knowledge of the test results

Reference standard

Applicability:

- Outcome of reference standard is decisive: if the reference standard does not detect the target condition defined in the review question results may not be applicable
- Critical to choose valid/optimal reference standard

Example:

- When defining UTI the reference standard is generally based on specimen culture but the threshold above which a result is considered positive may vary

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**

Flow and timing

Bias: Timing

- Delay between tests can cause misclassification due to recovery or progression to more advanced disease
- Length of time which may cause such bias will vary between conditions

Example

- For the evaluation of MRI for the early diagnosis of MS, a minimum follow-up period of around 10 years is required, for infectious disease e.g. UTI a delay of a few days may be important

Flow and timing

Bias: Work-up/verification Bias

- The reference standard may be expensive, risky or unpleasant – clinically unwilling to perform on "normals"
- If only cases who are test positive undergo reference standard may result in misclassifying false negatives as true negatives and will overestimate sensitivity and specificity.
- Alternative methods such as extended follow-up or random sample of test negatives may be appropriate

Example

- D-dimer test for diagnosis of PE, where ventilation perfusion scans are used (ref standard 1) in those testing positive and clinical follow-up in those testing negative (ref standard 2). Follow-up may miss some cases of PE and overestimate accuracy.

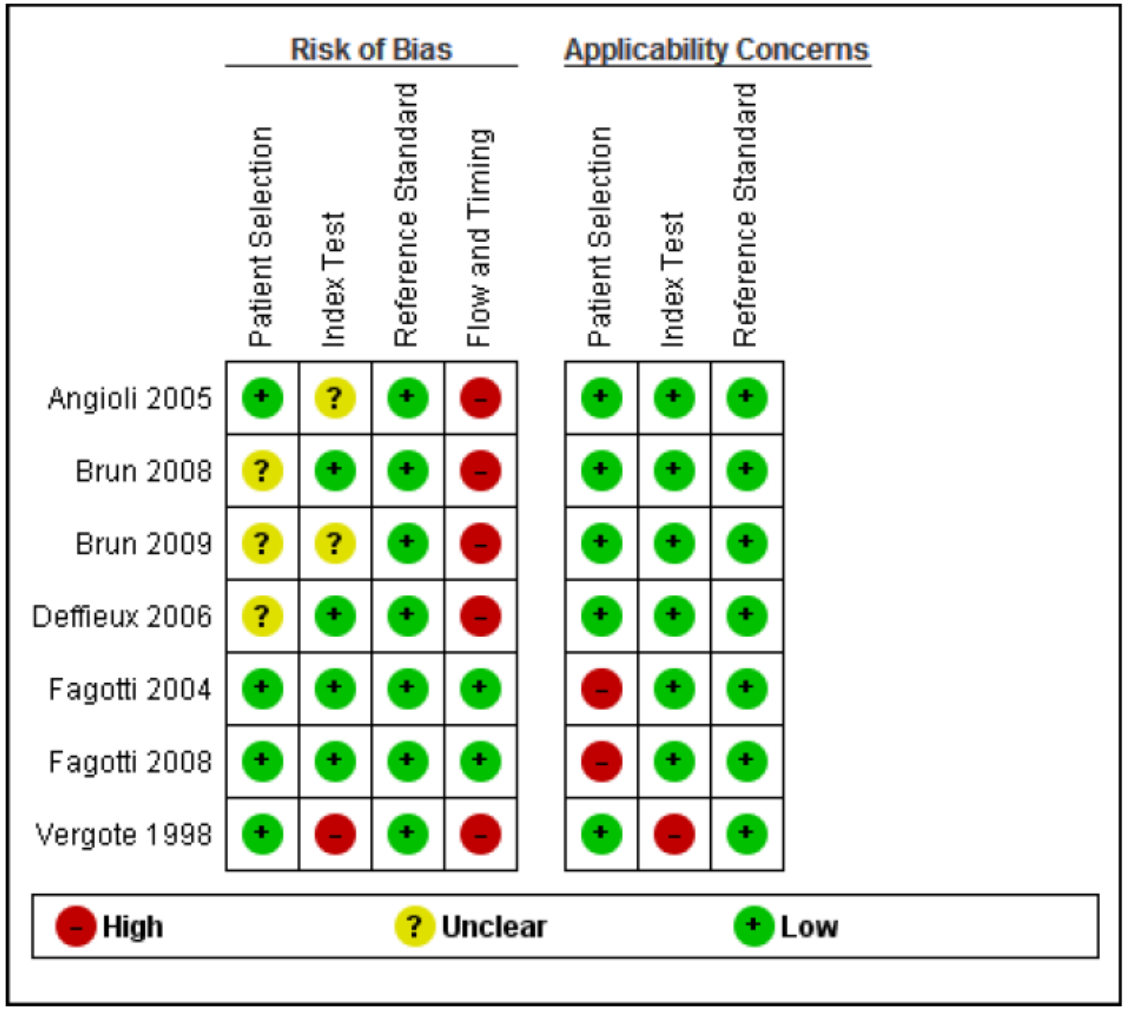
Incorporating study quality

- What do existing reviews do?

Incorporating study quality

- Present the results of the quality assessment:
  - In a table

Figure 5. 'Risk of bias' and applicability concerns summary: review authors' judgements about each domain for each included study

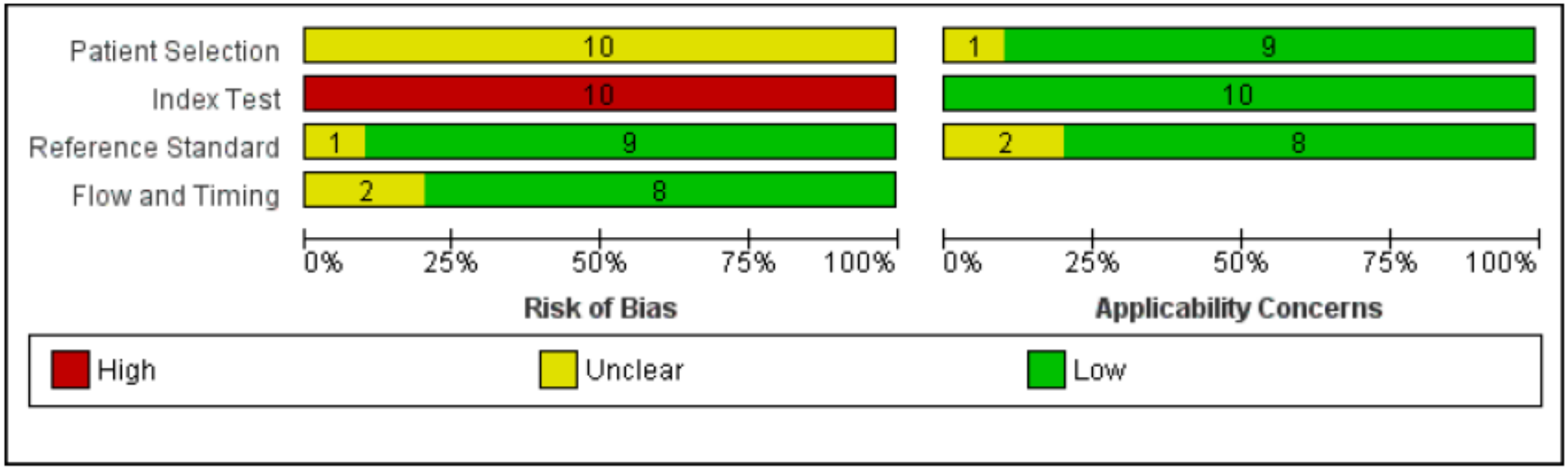


Citation: Rutten MJ, Leeflang MMG, Kenter GG, Mol BWJ, Buist M. Laparoscopy for diagnosing resectability of disease in patients with advanced ovarian cancer. *Cochrane Database of Systematic Reviews* 2014, Issue 2. Art. No.: CD009786. DOI: 10.1002/14651858.CD009786.pub2.

Incorporating study quality

- Present the results of the quality assessment:
  - In a table
  - Graphically

Figure 3. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies.



What do existing reviews do?

Table 3 Incorporation of quality assessment in main text of diagnostic reviews

Approach	Overall quality of included studies	Number N = 65
Quality mentioned in the main text		**60 (92%)[b]**
Results of quality assessment reported, no mention in discussion or conclusion		13 (20%)
Results of quality assessment reported and discussed, but quality not linked to conclusion		41 (63%)
Results of quality assessment reported and discussed, and conclusions regarding test accuracy linked to results of quality assessment		6 (9%)
Results of quality assessment reported and discussed, and recommendations based on general unspecified quality items		12 (18%)

[b]Quality was mentioned in one or more sections in the main text.

Ochodo *et al. BMC Medical Research Methodology* 2014, **14**:33

Incorporating study quality

- Present the results of the quality assessment:
  - In a table
  - Graphically
- Investigate individual quality items as potential sources of heterogeneity
- Basis for recommendations for future research

Investigation of heterogeneity

- Sensitivity analysis to see whether the overall estimate changes when excluding specific studies
- Stratified analysis according to presence/absence of specific quality criteria
- Analysis using meta-regression
- Define methodological criteria a priori

Problems with quality assessment

- Not as straightforward as it might sound!
- Hampered by poor reporting
- Quality assessment is subjective
- Statistical incorporation of quality problematic with limited studies

Take home message

- Quality assessment is essential
- The QUADAS-2 tool is recommended by Cochrane
- The specific items and scoring guidelines should be tailored to your review question
- The results of the quality assessment should be presented
- No quality scores and cut-offs for ‘good’ quality
- Study quality should be incorporated into all reviews

Website

- www.quadas.org

ACKNOWLEDGEMENTS

Materials for this presentation are based in part on material adapted from members of the Cochrane Screening and Diagnostic Test Methods Group

See http://dta.cochrane.org/dta-author-training-online-learning for additional training materials