Cochrane Systematic Reviews of Diagnostic Test Accuracy

Collecting data and assessing methodological quality

Thursday June 19th 2008

Mariska Leeflang

Amsterdam Medical Center, DTA working group,
Continental Europe Support Unit

Steps in a systematic review

1. Formulating the question
   (and defining criteria for inclusion of studies)
2. Searching for studies
3. Selecting studies
4. Collecting data
5. Assessment of methodological quality
6. Analysing and presenting results
7. Interpreting results

Data collection

- Principles same as for intervention reviews
- Data collection: bridge between what is reported in the primary studies and what reviewer reports in SR
- Challenge is to extract all essential data without extracting unnecessary data
- Data-extraction can be done by using a database or a paper form
- Piloting the data-extraction form and duplicate data collection is recommended to improve accuracy

Data collection form

- General study details, participants, reference standard, index test(s), comparator test(s), participant flow, test results, adverse events and patient acceptability.
- Results data extracted as 2 x 2 data
  - Various methods to calculate this data from data that may be reported in the review
- May also extract summary statistics and use this to check contingency data
- Problem of multiple sets of 2 x 2 data in single report:
  - extract all available results data unless specific reasons for exclusion (e.g. pre-specified in protocol that only particular test in certain patient group is of interest)

Quality assessment

Why assess quality?

- Problem 1: Bias in primary studies can lead to misleading summary estimates of accuracy
- Problem 2: Results of primary studies may vary
- Quality assessment to guide the interpretation of results in terms of potential for bias and sources of heterogeneity

Cochrane definition of quality

"the methodological quality of a study; the degree to which the design and conduct of a study fit to the study objectives"

Doing the quality assessment

- Quality assessment tools:
  - Large number of different tools
  - Styles: Quality scores/levels of evidence/ component approach
  - The handbook recommends a modified version of the QUADAS tool for Cochrane reviews

Sources of bias and variation

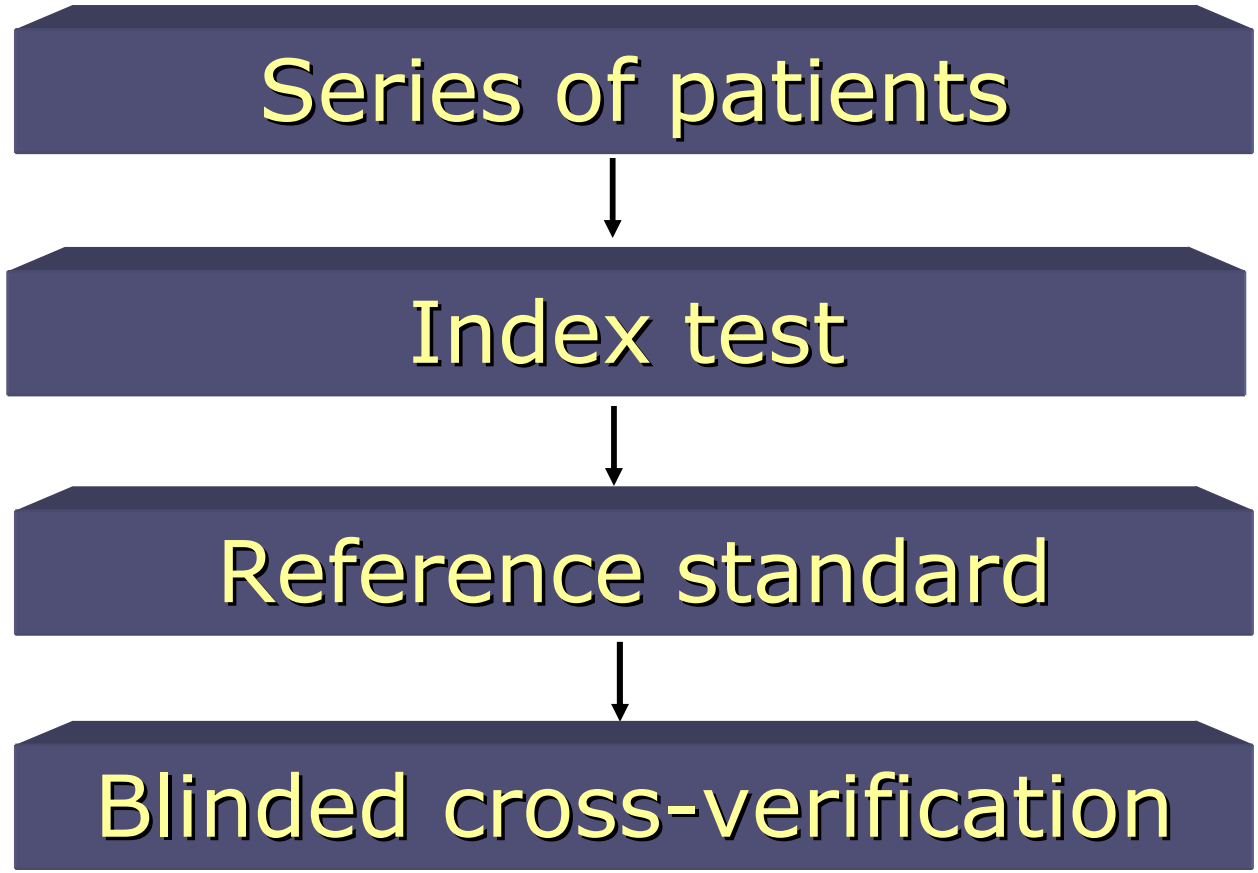
Whiting P et al. Ann Intern Med. 2004 ;140(3):189-202.
Whiting P et al. BMC Med Res Methodol. 2003;3:25.

Cochrane Handbook for Reviews of Diagnostic Test Accuracy

QUADAS

1	Was the spectrum of patients representative of the patients who will receive the test in practice?
2	Is the reference standard likely to correctly classify the target condition?
3	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
4	Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?
5	Did patients receive the same reference standard regardless of the index test result?
6	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?
7	Were the index test results interpreted without knowledge of the results of the reference standard?
8	Were the reference standard results interpreted without knowledge of the results of the index test?
9	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
10	Were uninterpretable/ intermediate test results reported?
11	Were withdrawals from the study explained?

Basic Test Accuracy Study

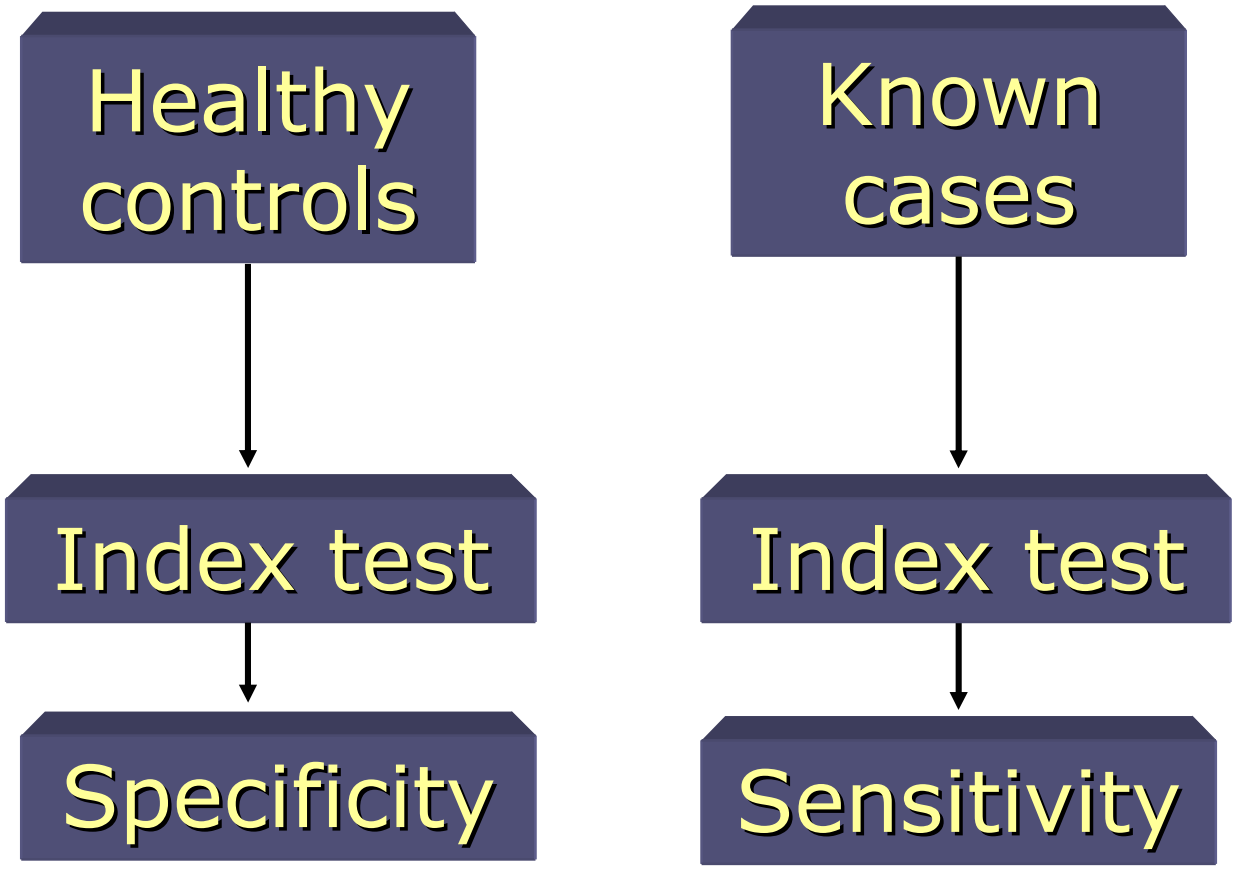


Problems with spectrum

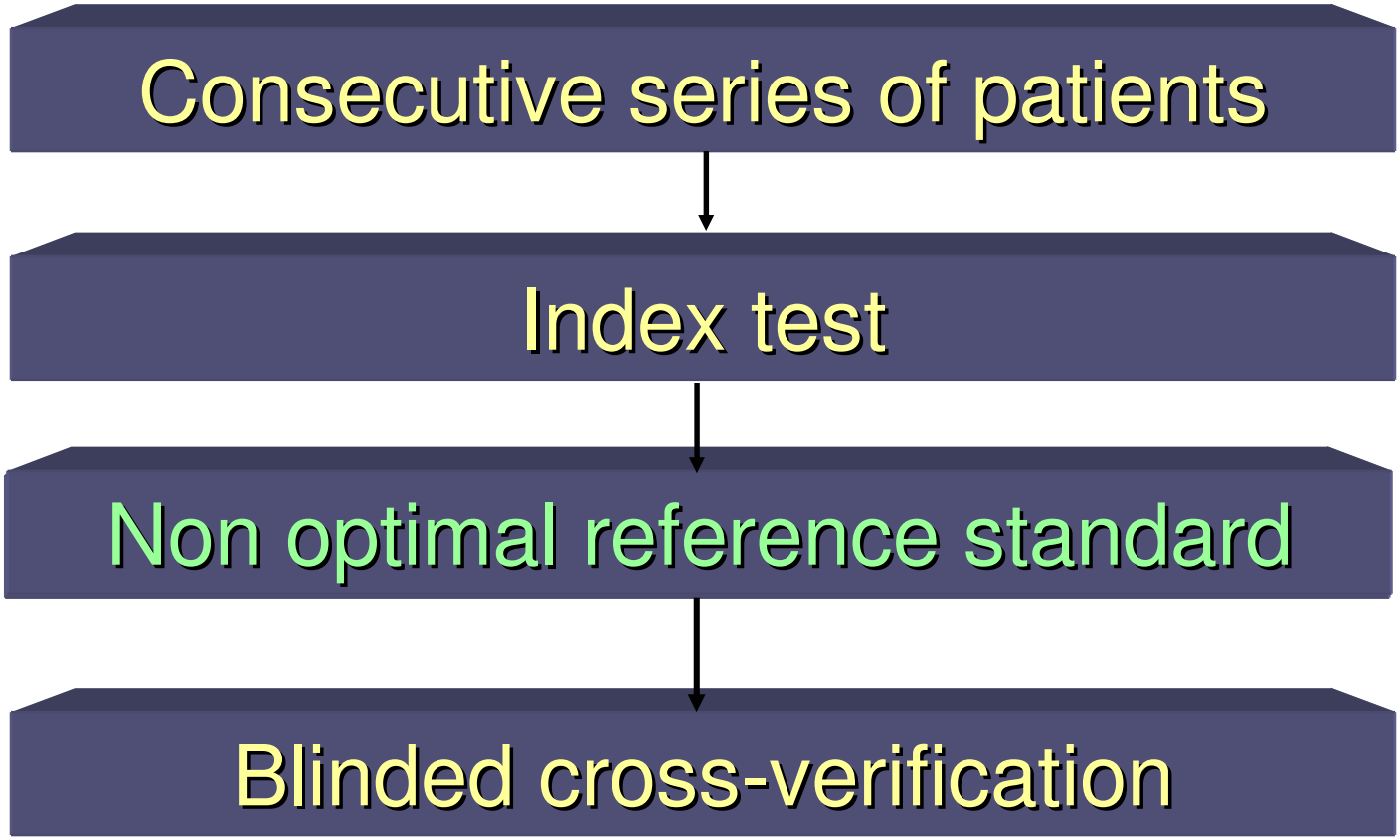
Measures of accuracy vary across patient groups:

- Patient characteristics e.g. age
- Patient selection/Study design
- Setting

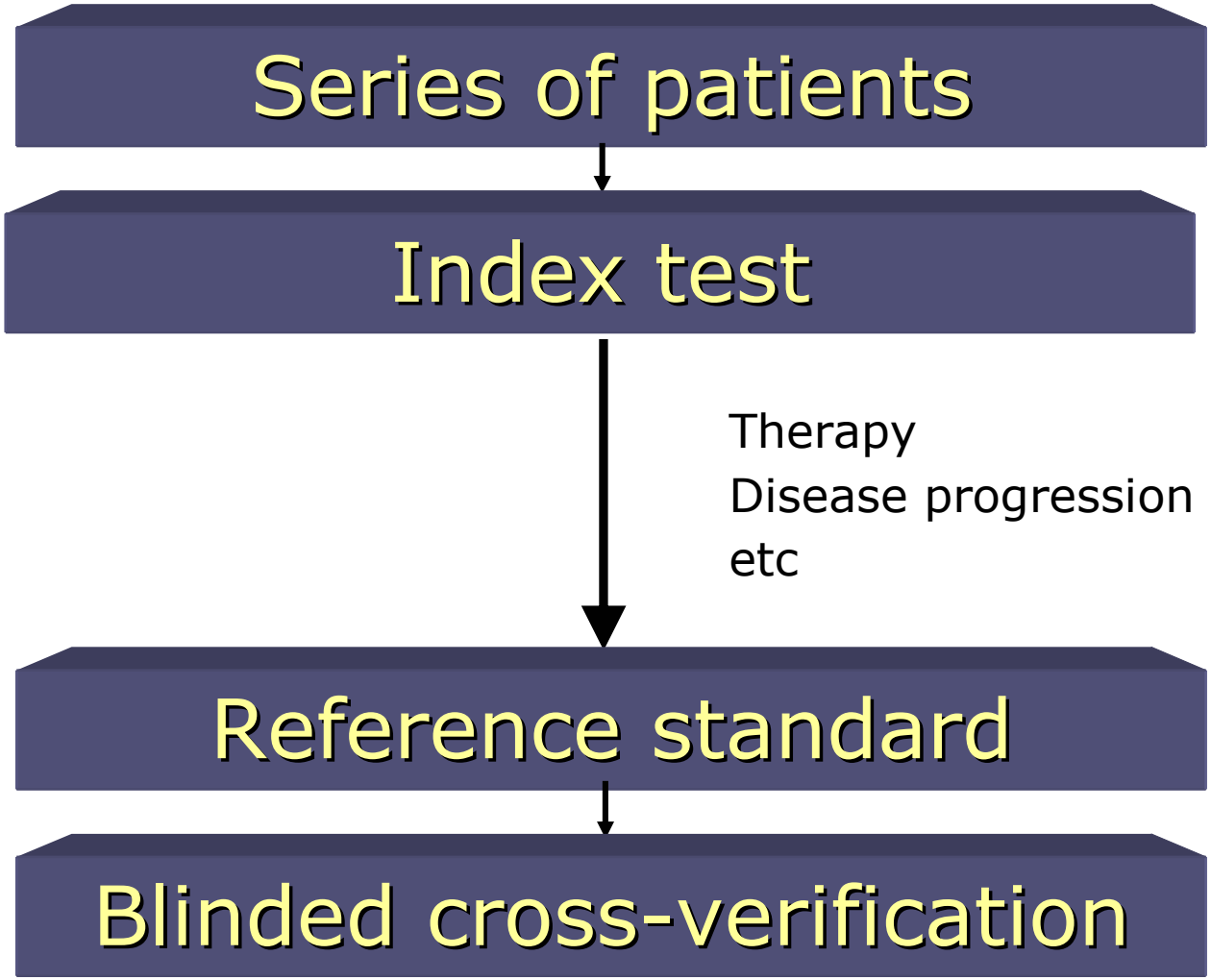
Diagnostic case-control design



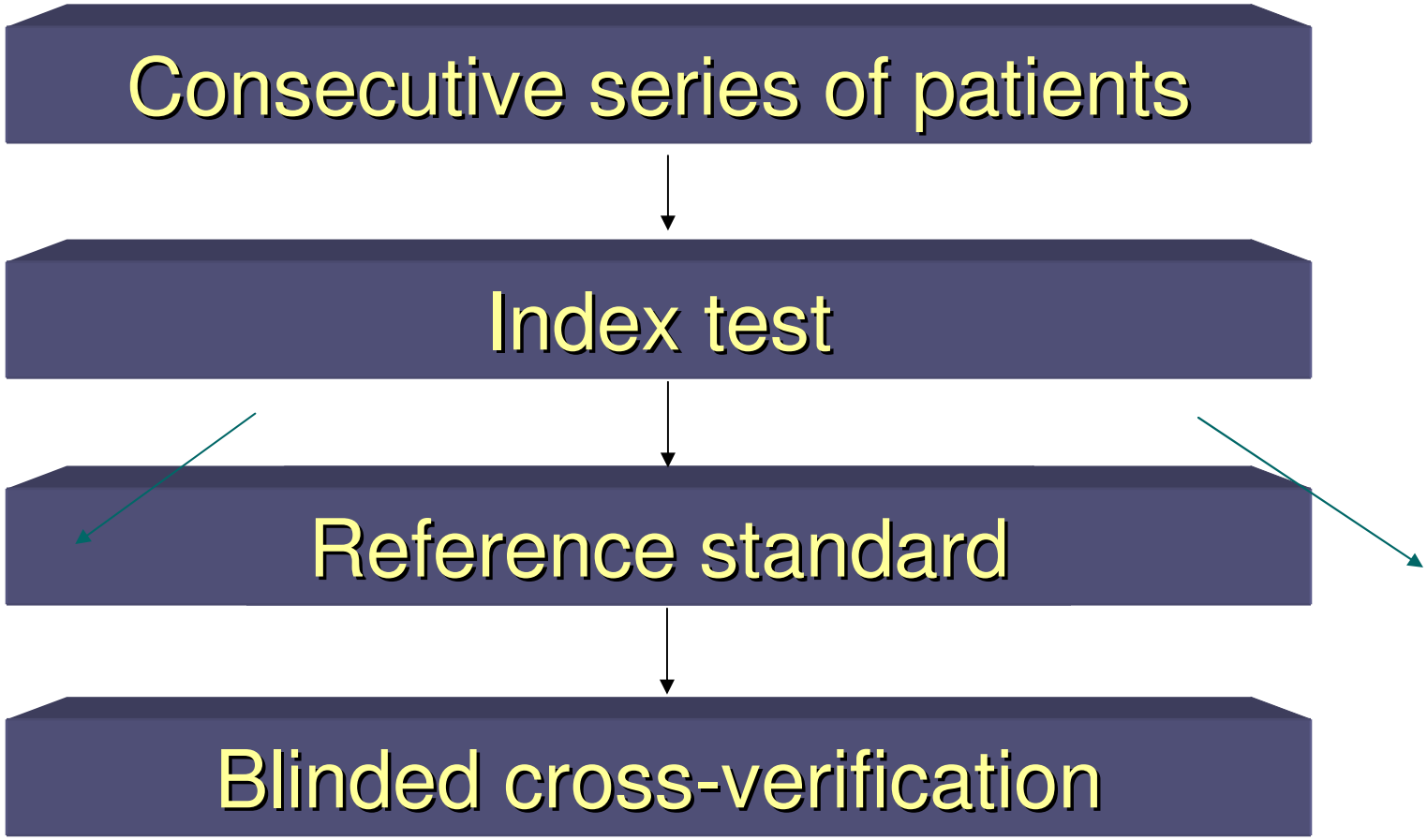
Reference standard bias



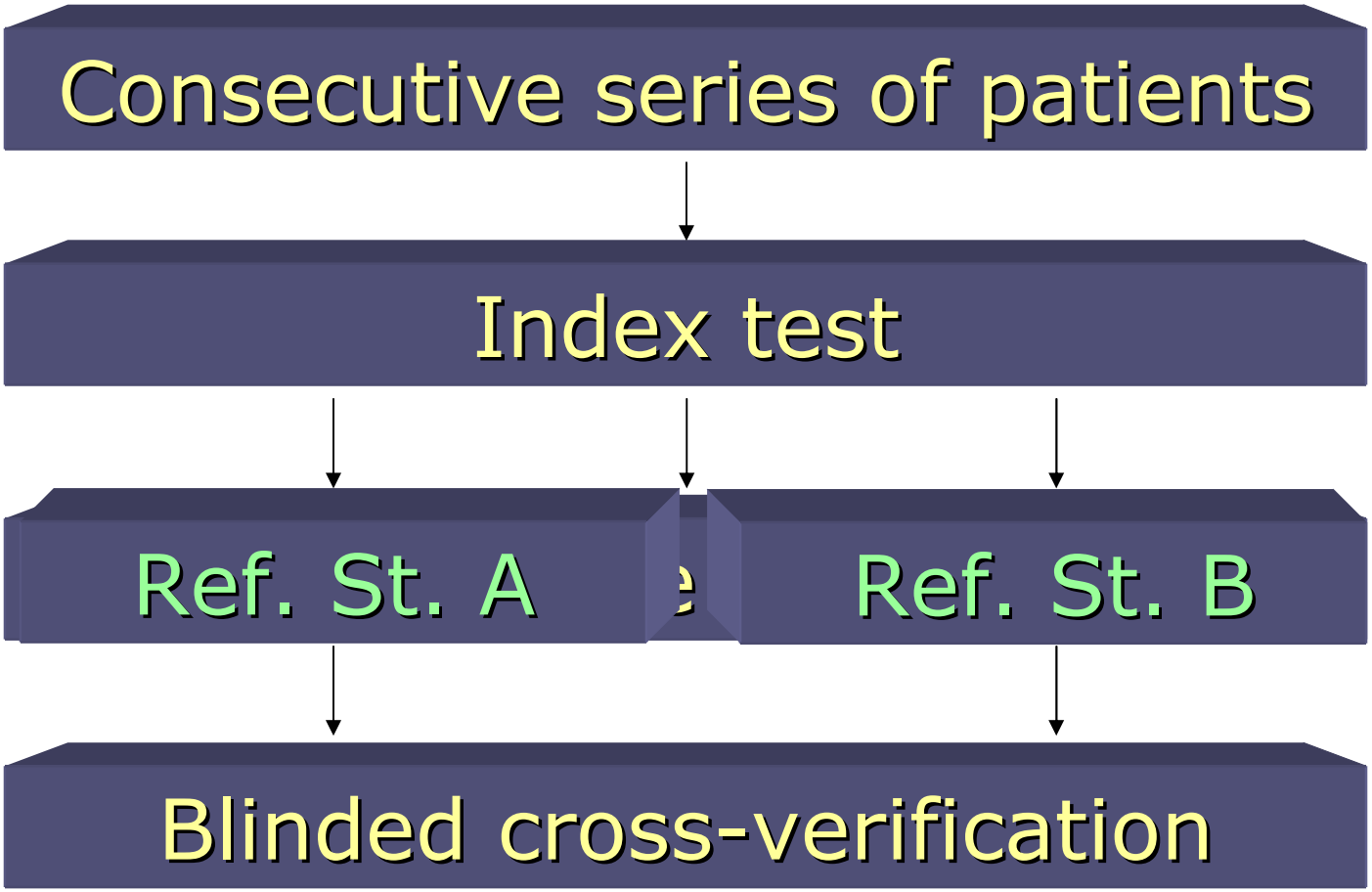
Time between index test and reference standard



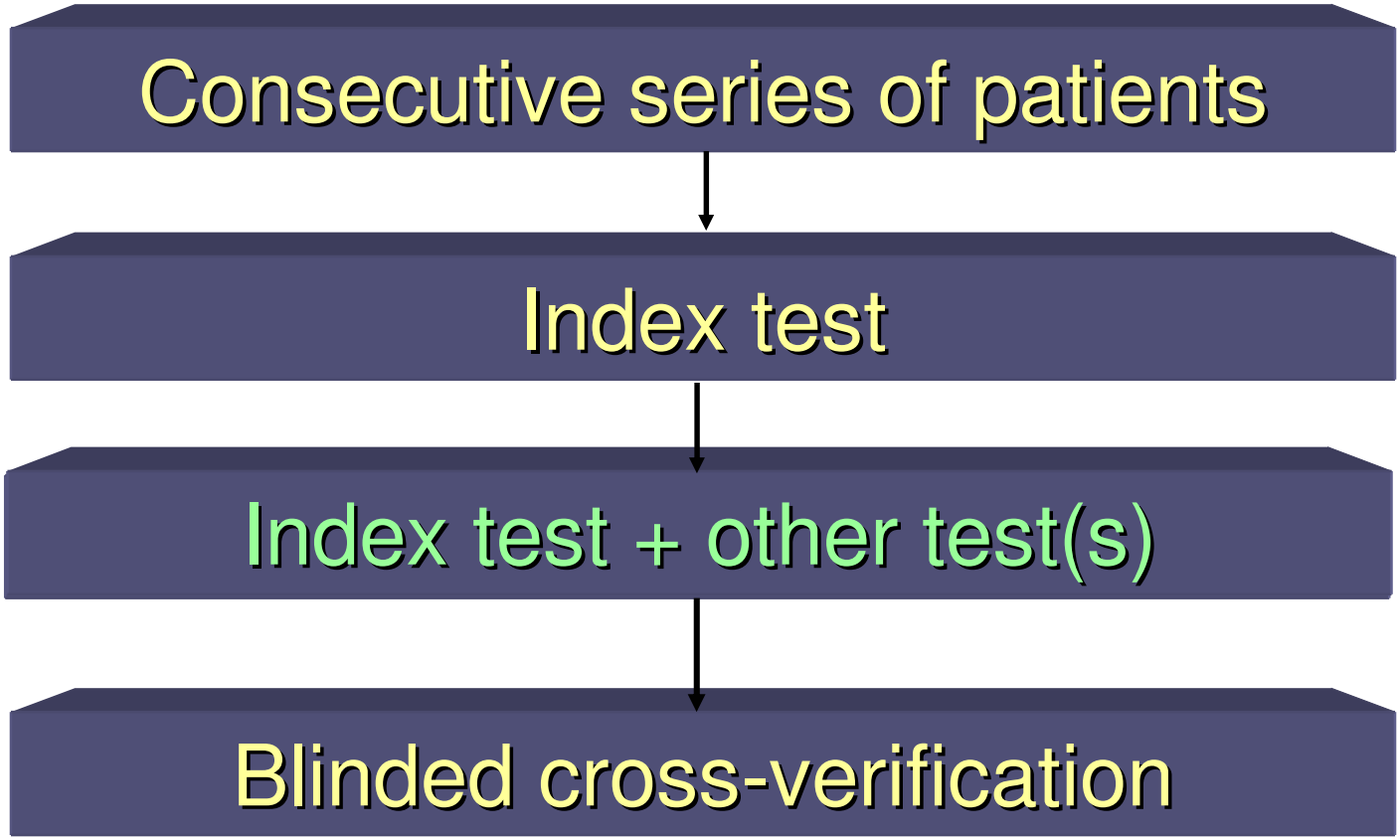
Partial verification bias



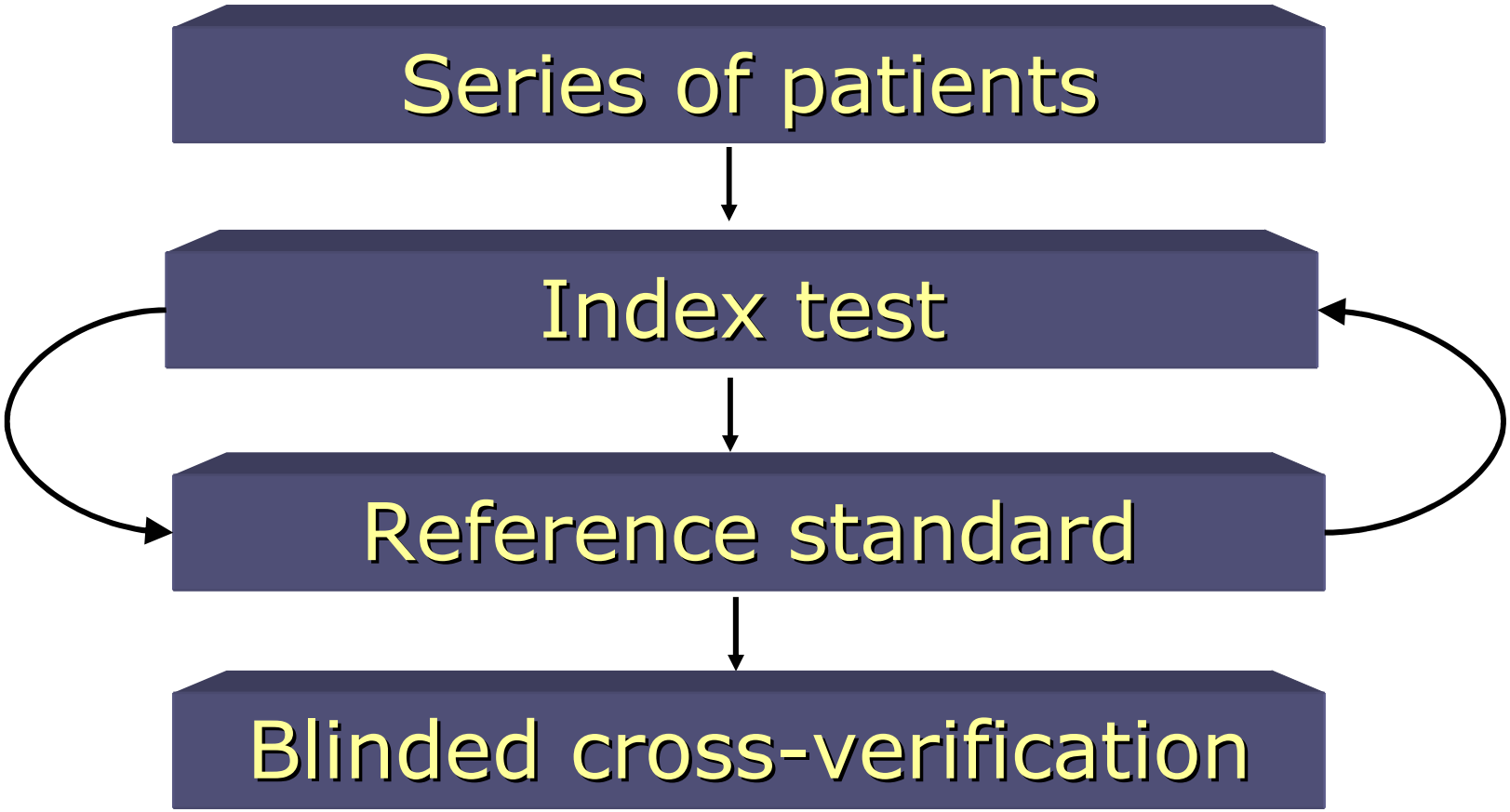
Differential verification bias



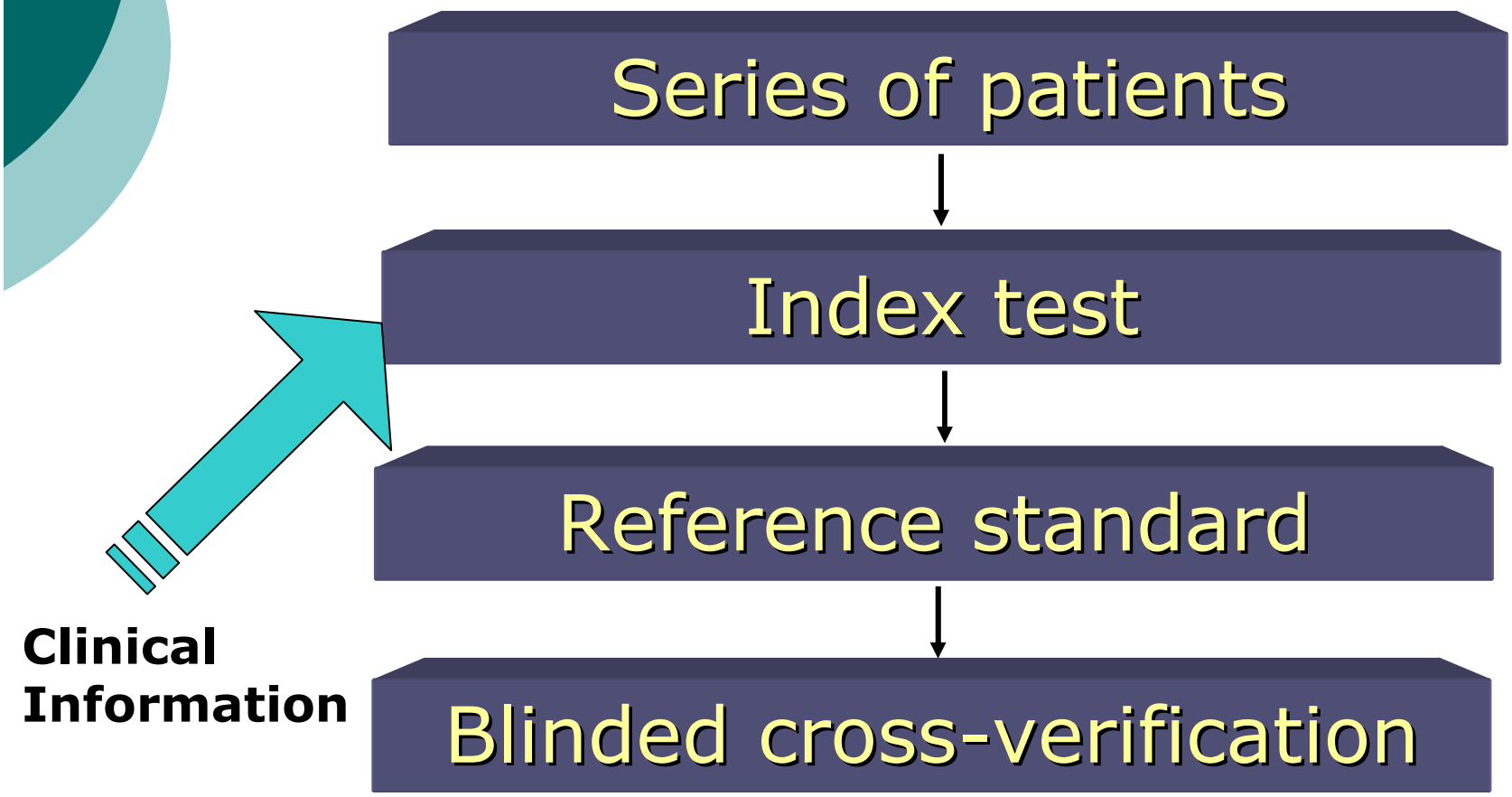
Incorporation bias



Blinding


Series of patients
Index test
Reference standard
Blinded cross-verification

Blinding


Series of patients
Index test
Reference standard
Blinded cross-verification
Clinical Information

Two important reporting items

- Reporting of uninterpretable/ intermediate test results
- Explanation of withdrawals

	biopsy		
	+	-	
HPV+	45	68	113
+/-	20	25	45
HPV-	7	161	198
	72	254	356

Additional items

12.	If a cut-off value has been used, was it established before the study was started (pre-specified cut-off value)?
13.	Is the technology of the index test likely to have changed since the study was carried out?
14.	Did the study provide a clear definition of what was considered to be a "positive" result?
15.	Was treatment started after the index test was carried out but before the reference standard was performed?
16.	Was treatment started after the reference standard was carried out but before the index test was performed?
17.	Were data on observer variation reported?
18.	Were data on instrument variation reported?
19.	Were data presented for appropriate patient sub-groups?
20.	Was an appropriate sample size included?
21.	Were objectives pre-specified?

Assessment of items

- All items scored as yes/no/unclear
- Items phrased so that yes indicates absence of bias
- Background document describes how items should be scored

Practical Issues

- Number of assessors
- Background of assessors
- Resolving disagreement
- Piloting the assessment process
- Develop your quality assessment tool

Your quality assessment tool

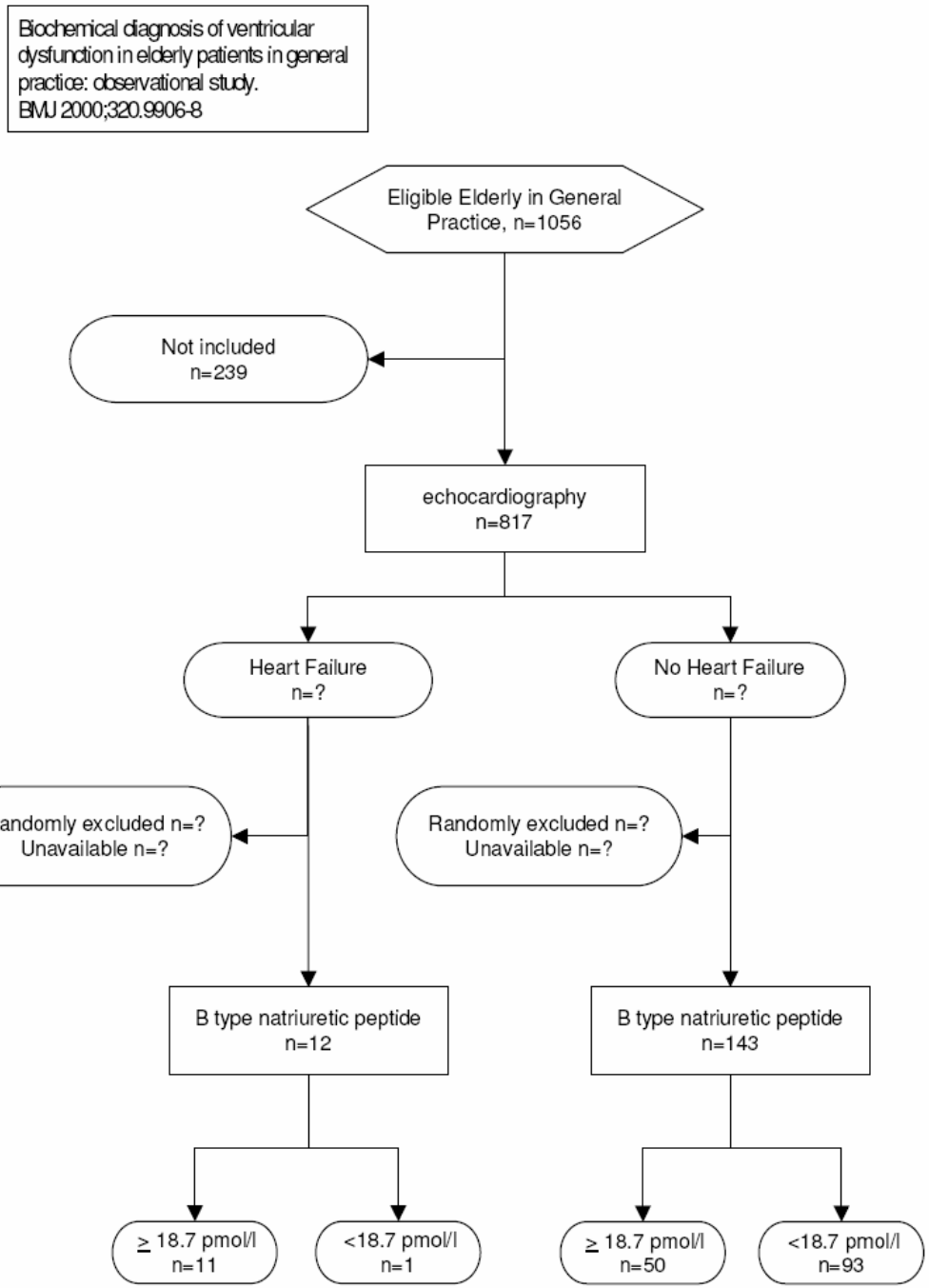
- Items to include
  - Core items
  - Additional items
    - select from suggested items
    - add your own if other items are important for your review topic
- Produce scoring guidelines specific to your review

Now it’s your turn!

Example: BNP for heart failure

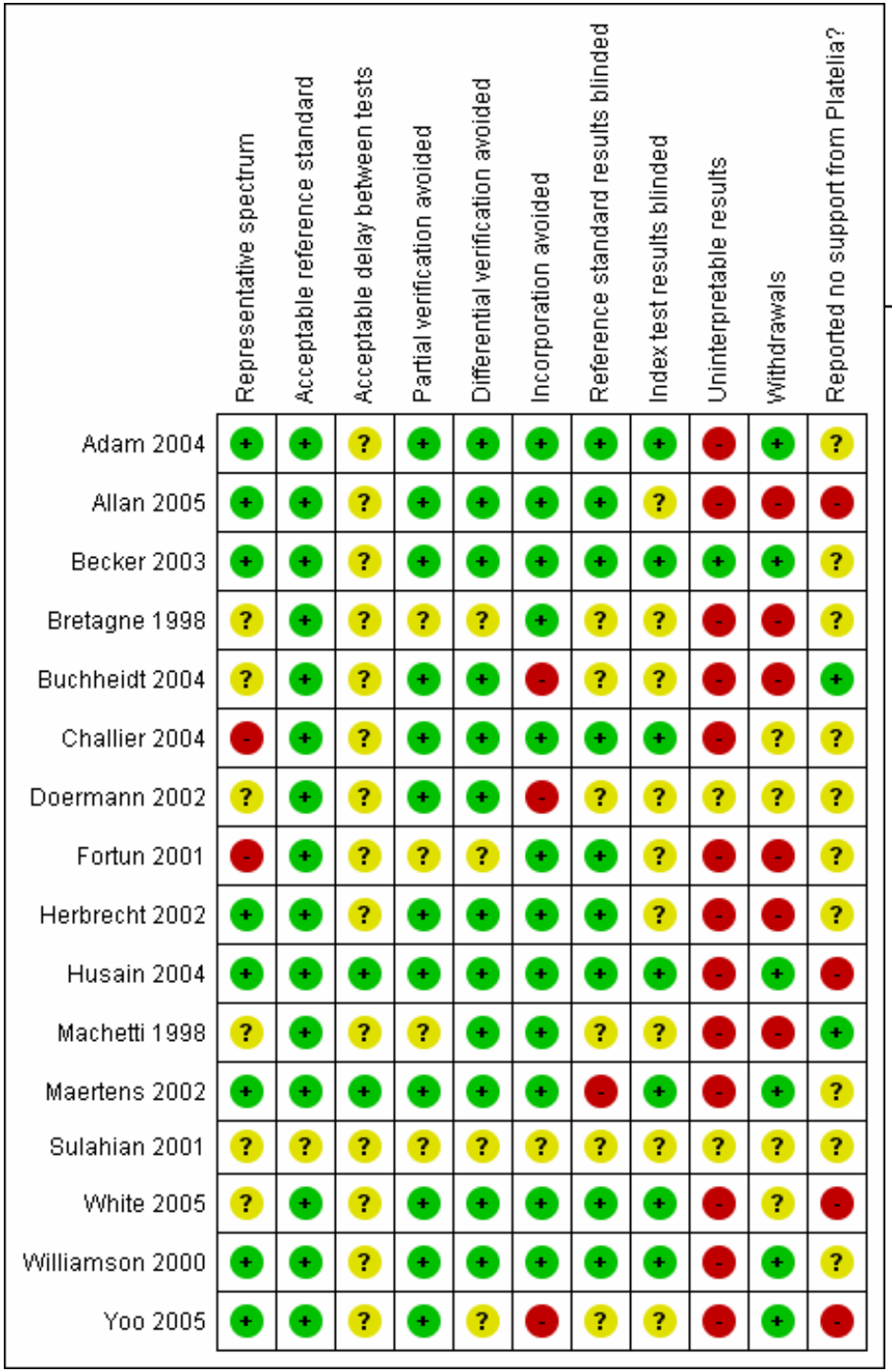
- **Aim:** To assess the accuracy of BNP for the diagnosis of heart failure
- In small groups:
  1. Produce a flow diagram for the study
  2. Discuss (attention to what has been done, what is missing and possible consequences):

     QUADAS item 1 (spectrum)
     QUADAS items 2, 4 and 5 (verification)
  3. Discuss the conclusion of the authors


Biochemical diagnosis of ventricular dysfunction in elderly patients in general practice: observational study. BMJ 2000;320.9906-8
Eligible Elderly in General Practice, n=1056
Not included n=239
echocardiography n=817
Heart Failure n=?
No Heart Failure n=?
Randomly excluded n=? Unavailable n=?
Randomly excluded n=? Unavailable n=?
B type natriuretic peptide n=12
B type natriuretic peptide n=143
≥ 18.7 pmol/l n=11
<18.7 pmol/l n=1
≥ 18.7 pmol/l n=50
<18.7 pmol/l n=93

Incorporating study quality

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



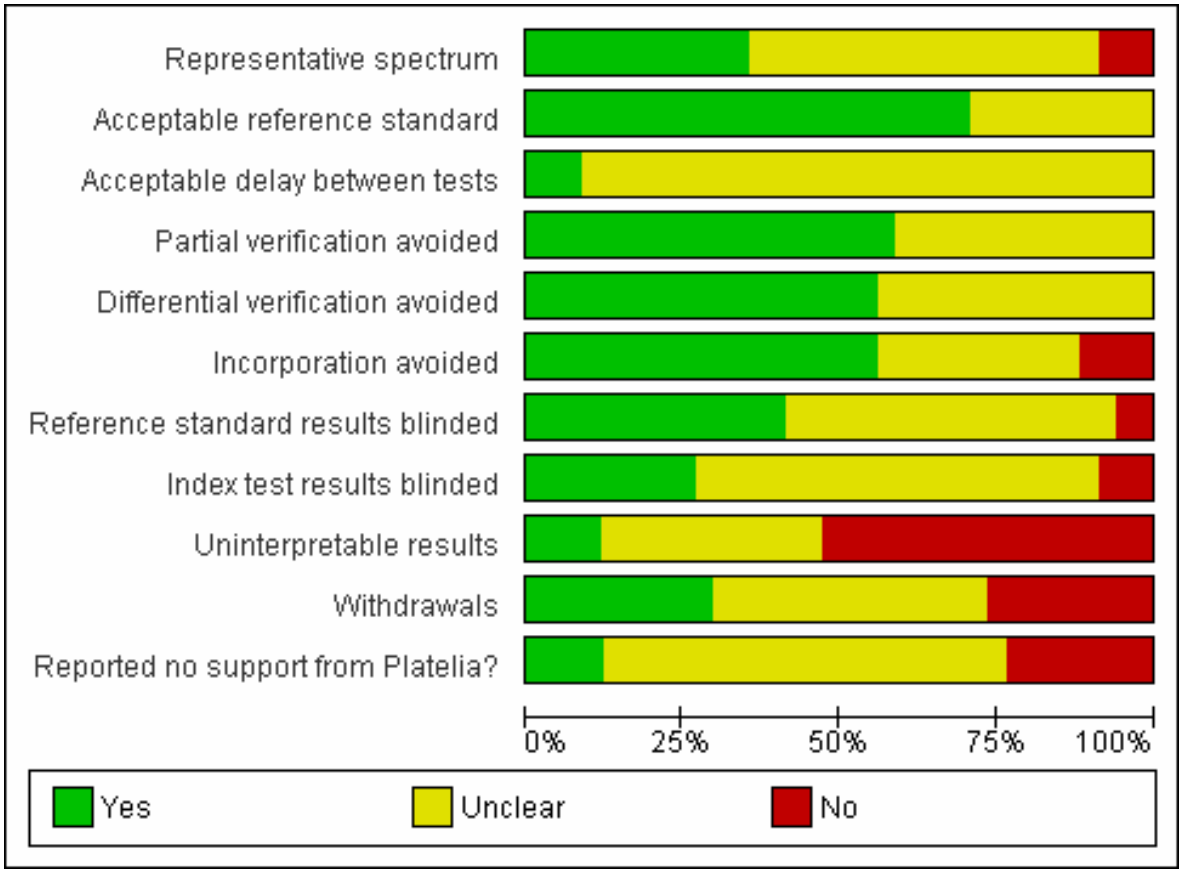
Methodological quality summary.

Review authors' judgments about each methodological quality item for each included study.

Incorporating study quality

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

Methodological Quality Graph



Review authors' judgments about each methodological quality item presented as percentages across all included studies.

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

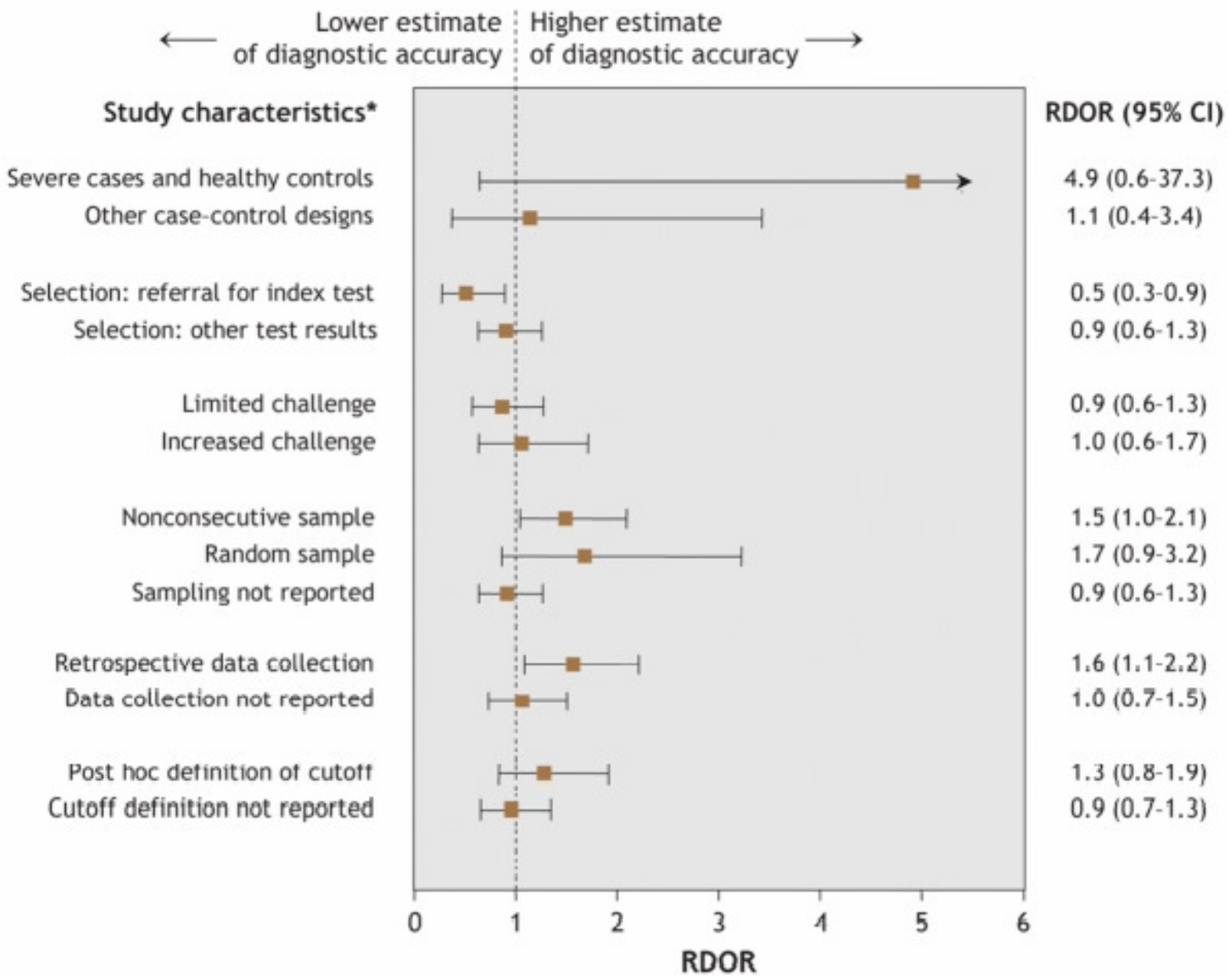
Investigation of heterogeneity

- Stratified analysis according to presence/absence of specific quality criteria
- Sensitivity analyses to investigate robustness of results
- Investigate several features simultaneously using meta-regression analysis

Always: define methodological criteria a priori

Problems with quality assessment

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


Lower estimate of diagnostic accuracy
Higher estimate of diagnostic accuracy
Study characteristics*
RDOR (95% CI)
Severe cases and healthy controls
4.9 (0.6-37.3)
Other case-control designs
1.1 (0.4-3.4)
Selection: referral for index test
0.5 (0.3-0.9)
Selection: other test results
0.9 (0.6-1.3)
Limited challenge
0.9 (0.6-1.3)
Increased challenge
1.0 (0.6-1.7)
Nonconsecutive sample
1.5 (1.0-2.1)
Random sample
1.7 (0.9-3.2)
Sampling not reported
0.9 (0.6-1.3)
Retrospective data collection
1.6 (1.1-2.2)
Data collection not reported
1.0 (0.7-1.5)
Post hoc definition of cutoff
1.3 (0.8-1.9)
Cutoff definition not reported
0.9 (0.7-1.3)
0
1
2
3
4
5
6
RDOR

Conclusions

- Data should be collected on:
  - General study details, participants, reference standard, index test(s), comparator test(s), participant flow, test results (2 x 2 data), adverse events and patient acceptability.
- Quality assessment is essential, but exact effects not (yet) known
- The QUADAS tool should be used as a starting point

Conclusions

- The quality 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