APPENDIX 2.

Risk of bias criteria for prognostic studies

Risk of bias assessment was made with QUIPS tool (1) presented at Cochrane colloquium in 2010 and adjusted for this review. Following six domains were used: representativeness of study population, adequateness of follow-up period and attrition, appropriateness of FeNO measurement, appropriateness of outcome measurement, adequateness of statistical analysis (including confounding factors and co-interventions) and reporting, and conflict of interests. Each element was classified as low, unclear or high risk of bias. To draw conclusions about the overall risk of bias within a study, we decided to classify the studies in three categories: studies with low, unclear or high risk of bias. If all the domains within a study were graded as low risk of bias, the overall judgement was low risk of bias, and if one of the domains was assessed as having high risk of bias, the overall risk of bias for a study was graded as high risk of bias. Explicit criteria of this review for assessment are presented at the end of this appendix.

Quality assessment of prognostic studies

Wolff R, Westwood M, Scheibler F, Schröer-Günther M, Janßen I, Kleijnen J. Assessment of risk of bias in prognostic studies. Presentation. 18th Cochrane Colloquium, 19/10/2010. Keystone, USA.

Study population

1. Were the selection criteria clearly defined?

☐ **yes**: Study inclusion/exclusion criteria clearly reported, description of selection process (e.g. consecutive patients with....)

☐ **no**: Not reported, or description of study participants only (e.g. numbers and types of participants described, but not the process of selection)

notes:

2. Similar point in the course of their disease?

☐ **yes**: It is clear that participants were recruited at a similar point in the course of their disease and this point is clearly defined

☐ **no**: There is potentially significant variation in disease stage, between participants

☐ **unclear**: Give reasons

notes:

3. Was the study population representative of the population of interest?

☐ **yes**: The study population represents the population of interest with respect to key characteristics (e.g. disease stage, demographics, previous treatments), sufficiently to limit potential bias in the results

☐ **no**: Study participants differ in potentially significant ways from the population of interest

☐ **unclear**: Give reasons

notes:

Follow-up/attrition

4. Was the follow-up period adequate?

☐ **yes**: Participants were followed-up for sufficient time for the target outcome to emerge (defined, a priori, by topic)

☐ **no**: Follow-up period too short to allow observation of the target outcome

☐ **unclear**: Follow-up period not reported

notes:

5. Was completeness of follow-up described?

☐ **yes**: Numbers lost to follow-up reported, or outcome data clearly available for all participants

☐ **no**: Participants not accounted for

☐ **unclear**: Results reported such that it is not clear whether all participants were accounted for (e.g. significance of a prognostic variable reported without per participant data)

notes:

6. Was completeness of follow-up adequate?

☐ **yes**: Follow-up was sufficiently complete to limit the potential for bias in the results (defined, a priori, by topic, e.g. 80%)

☐ **no**: Follow-up below the pre-defined threshold

☐ **unclear**: Results reported such that completeness of follow-up is not clear (e.g. significance of a prognostic variable reported without per participant data)

notes:

Prognostic factor measurement

7. Were prognostic factors clearly defined?

☐ **yes**: Prognostic factors were clearly described, including method or measurement and cut-offs (if used), such that an independent investigator could replicate the study

☐ **no**: Prognostic factors not described in sufficient detail to permit replication

☐ **unclear**: Give reasons

notes:

8. Were prognostic factors measured appropriately?

☐ **yes**: Prognostic factors were measured using appropriate methods (defined, a priori, by topic, e.g. methods routinely used in clinical practice, same methods used for included participants)

☐ **no**: Prognostic factors measured using methods other than those specified, or measurement method not clear

☐ **unclear**: Give reasons

notes:

9. Were prognostic data available for an adequate proportion of the included participants?

☐ **yes**: Prognostic data were available for all, or an adequate proportion (defined, a priori, by topic, e.g. 80%) of participants

☐ **no**: Prognostic data were available for less than the defined proportion of participants

☐ **unclear**: Results reported such that it is not clear whether data were for all (e.g. significance of a prognostic variable reported without per participant data)

notes:

Outcome measurement

10. Was the outcome of interest clearly defined?

☐ **yes**: Outcome was clearly described, including method or measurement and cut-offs (if used), such that an independent investigator could replicate the study

☐ **no**: Outcome was not described in sufficient detail to permit replication

☐ **unclear**: Give reasons

notes:

11. Was the outcome determined appropriately?

☐ **yes**: Outcome was determined, for all participants, using appropriate methods (defined, a priori, by topic, e.g. methods routinely used in clinical practice)

☐ **no**: Outcome was determined, for some or all participants, using methods other than those specified, or methods were not reported

notes:

12. Were outcomes determined blind to prognostic information?

☐ **yes**: It is clear that those determining outcome were not aware of key prognostic data/results of prognostic tests

☐ **no**: Those determining outcome were aware of key prognostic data/results of prognostic tests

☐ **unclear**: Not reported

notes:

Analysis/confounding

13. Were important confounding factors adequately accounted for?

☐ **yes**: Potential confounding factors/other prognostic variables were clearly described, measured and accounted for in statistical analyses

☐ **no**: Potential confounders were not considered, or were described and measured, but were not accounted for in the analyses

notes:

14. Were any treatments given to participants during the follow-up period standardised, or randomised?

☐ **yes**: Participants received the same, standardised treatment regimen, regardless of prognostic factor, or were randomised to different treatment options

☐ **no**: Treatments differed between patients, dependent upon prognostic variables

☐ **unclear**: Give reasons

notes:

15. Were the analysis methods adequate?

☐ **yes**:

☐ **no**: Give reasons

☐ **unclear**: Give reasons

notes:

16. Was the reporting independent of results?

☐ **yes**: Reporting was independent of results

☐ **no**: Give reasons (e.g. selective reporting of subgroups/ endpoints/ time points, reporting of unusual endpoints, primary endpoint underreported)

notes:

17. Study free of other aspects that have potential risk of bias?

☐ **yes**: No other aspects have potential risk of bias

☐ **no**: Give reasons (e.g. model underpowered)

☐ **unclear**: Give reasons

notes:

Risk of bias for this study

☐ **low**: Low risk of bias (plausible bias unlikely to seriously alter the results)

☐ **high**: High risk of bias (give reasons)

☐ **unclear:** (plausible bias that raises some doubt about results)

notes:

Criteria for low risk of bias defined for this review

Question 3.

Depending on study question / design: comparability of study groups at baseline, if not adjusted in analysis.

Question 4.

Required minimum follow-up time for each study question and outcome, based on estimated reasonable periods for possible group differences to appear. If significant difference emerged in a shorter period, risk of bias was graded low.
- study question 1: a) 4 weeks for symptoms or spirometry; b) 2 months for asthma exacerbation
- study question 2: 6 months

- study question 3: a) 4 weeks for symptoms; b) 2 months for asthma exacerbation
- study question 5: a) 4 weeks for symptoms or spirometry; b) 3 months for asthma exacerbation
- study question 6: a) 4 weeks for symptoms or spirometry; b) 3 months for asthma exacerbation

Question 6.

Attrition of study population (loss to follow-up) at maximum 20 %.

Question 7.

Exhalation flow rate (ml/s) in FeNO measurement must be reported.

Question 8.

FeNO measurement performed before spirometry.

Question 9.

FeNO measurement results available for at least 80 % of the entire study population. If not reported, the risk of bias was assessed to be low assuming that all participants were included in the data.

Question 12.

Patients blinded for FeNO measurement result or value when subjective outcome measures (e.g. symptoms) were used.

Question 13.

Proportion of atopic patients and smokers in study population reported.

Question 15.

FeNO value analysed as a continuous variable or, when dichotomised, this was based on reasonable cut-off values. Optimal cut-off values based on the study data were judged as unclear risk of bias if study population was under 200 (2,3).

Question 17.

Low risk of bias if there was no conflict of interest. Low risk of bias if any of the writers has a connection with manufacturer, but data was analysed independently. High risk of bias when study was carried out by FeNO device manufacturer.

References:

1. Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013; 158: 280-286.

2. Altman DG, Lausen B, Sauerbrei W, Schumacher M. Dangers of using "optimal" cutpoints in the evaluation of prognostic factors. *J Natl Cancer Inst* 1994; 86: 829-835.

3. Leeflang MM, Moons KG, Reitsma JB, Zwinderman AH. Bias in sensitivity and specificity caused by data-driven selection of optimal cutoff values: mechanisms, magnitude, and solutions. *Clin Chem* 2008; 54: 729-737.