Appendix 5 Risk of bias assessments for the studies

First author, Publication year	Representative study population	Adequate follow-up period and attrition	Appropriate prognostic factor (FeNO) measurement	Appropriate outcome measurement	Adequate statistical analysis (including confounding factors) and reporting	Free of concflict of interests	Overall risk of bias at study level	Comments
Study question 1: Does increased FeNO predict a favourable response to ICS in steroid-naïve asthmatics?								
Cowan 2010	yes	yes	yes	yes	yes	yes	low	
Szefler 2002	yes	no	yes	yes	yes	yes	high	In analyses 21/30 (70 %) participants (below the pre-defined threshold 80 %).
Szefler 2005	yes	no	yes	yes	yes	yes	high	It remains unclear, how many participants were included in the analyses, but the missing data were at least 23 % (over the pre-defined threshold 20 %).
Study question 2: Does increased FeNO predict risk of exacerbation in asthmatic patients on regular stabile ICS treatment?								
Gelb 2006	yes	yes	yes	?	?	yes	unclear	No reporting of blinding of participants (assessment of astma exacerbation might be based only on announcement of a participant). Analyses based on use of optimal cutoff value of FeNO derived from data, but the sample size was small for reliable analyses.
Kupczyk 2014	yes	yes	yes	?	?	yes	unclear	No reporting of blinding of outcome assessor (regarding FeNO value). It remains unclear what was the basis for the cutoff value of 45 ppb used in the analyses.
Ozier 2011	no	no	yes	?	?	yes	high	25 % of participants without ICS medication. Follow-up time too short (3 weeks). No reporting of blinding of participants (assessment of asthma control was made by phone). Analyses based on use of optimal cutoff value of FeNO derived from data, but the sample size was small for reliable analyses.
Study question 3: Does increased FeNO in asthmatic patients on regular stabile ICS treatment predict further benefit from augmenting the glucocorticoid treatment?								
Kupczyk 2013	yes	no	yes	yes	?	yes	high	Follow-up time too short (2 weeks). Analyses based on use of optimal cutoff value of FeNO derived from data.
Little 2000	yes	yes	yes	yes	yes	yes	low	
Michils 2008	yes	?	yes	?	?	yes	unclear	Follow-up time and number of participants at follow-up remain unclear. No reporting of blinding of participants (subjective outcome measure). Analyses based on use of optimal cutoff value of FeNO derived from data.
Perez-de-Llano 2010	yes	yes	yes	?	?	yes	unclear	No reporting of blinding of participants (subjective outcome measure). Analyses based on use of optimal cutoff value of FeNO derived from data.
Study questions 4: If an asthmatic patient on low dose ICS has good asthma control for at least 3 months, does low baseline FeNO predict successful withdrawal of ICS without asthma relapse?								
Pijnenburg 2005	yes	yes	yes	?	yes	yes	unclear	No reporting of blinding of participants (assessment of astma relapse might be based only on announcement of a participant).
Study questions 5: If an asthmatic patient on low dose ICS has good asthma control for at least 3 months and the ICS is withdrawn, does increased FeNO level during the follow-up predict asthma relapse?								
Ferrer 2010	yes	yes	yes	yes	?	yes	unclear	The cutoff value of 49 ppb for allocating study groups was based on median value of data and on results reported in the study by Pijnenburg 2005. The value is unreliable because both studies were very small.
Pijnenburg 2005	?	yes	yes	?	yes	yes	unclear	It remains unclear, whether the difference between the study groups regarding ICS dosage influenced on change of NO value after discontinuing the medication or not. No reporting of blinding of study participants.

? = unclear, not reported or reporting unclear