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Systematic review of health state utilities in children with asthma

Authors: Wei Sun Kua, Sarah Davis

Corresponding author: Wei Sun Kua

ScHARR, University of Sheffield,
Regent Court, 30 Regent Street
Sheffield, S1 4DA
Email: weisunkua@yahoo.com

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Systematic review of health state utilities in children with asthma

Wei Sun Kua
Sarah Davis

School of Health and Related Research (ScHARR), University of Sheffield, United Kingdom
Correspondence to Wei Sun Kua : weisunkua@yahoo.com

Keywords: Asthma, Exacerbation, Children, Health related quality of life (HRQoL)

Highlights

- Health state utilities are key parameters in cost utility analysis. In the absence of health related quality of life (HRQoL) data collected directly from clinical trials, published literature are relied upon for health utilities estimates.
- The review found few studies that reported preference-based health utilities in children with asthma. There is also a lack of robust estimates on utility decrement associated with asthma exacerbation in children.
- Future studies in children with asthma are encouraged to incorporate HRQoL data collection into the study design.
- This review also serves as an example on how health utilities are searched, identified and critically appraised for appropriateness to be used in an economic model.

ABSTRACT

Background:

Asthma exacerbations affect quality of life for children with asthma. A cost-utility analysis was performed alongside the PLEASANT clinical trial to assess the cost-effectiveness of a letter intervention in preventing and lessening exacerbations in school-aged children at the start of a new school term. The economic analysis relied on published literature for health utilities estimates as no patient reported outcome measures were collected in the trial.

Objective:

To identify preference-based utility values for children with day-to-day asthma symptoms (baseline utility) and children experiencing an asthma exacerbation, and to review the appropriateness of the utility values to be used in the PLEASANT economic analysis.

Methods:

A systematic review was performed in five electronic databases (Ovid MEDLINE, The Cochrane Library, EMBASE, ECONLIT and SCHARR Health Utilities Database) up to 5th July 2014 to identify studies that report preference-based utility values in children with asthma. Results were summarised narratively and utility data were assessed for quality, relevance to the economic analysis and compliance with the NICE reference case.

Results:

A total of 927 studies were identified from the search and 14 studies which met the inclusion criteria were included. Health utilities were elicited using various outcome measurements. EQ-5D was used in 5 studies (35.7%), HUI, PAHOM and direct valuation using vignettes were each reported in 2 studies (14.3%). Three (21.4%) studies estimated utility values from mapping between condition specific measures and the EQ-5D. None of the studies directly measured health utilities in children with asthma exacerbation using a preference-based measure.

Conclusions:

There is a lack of robust estimates on utility decrement in children with asthma exacerbation. Future studies in children with asthma should incorporate collection of health state utilities

into the study design, taking into account the ethical and methodological considerations of quality-of-life assessment during exacerbation.

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1.0 Introduction

A public health preventive strategy of a letter intervention sent to parents prior to the start of a new school year, to promote medication adherence was assessed in the Preventing and Lessening Exacerbation of Asthma in School-age children Associated with a New Term (PLEASANT) cluster randomised controlled trial. A cost utility analysis was performed alongside PLEASANT. Patient level data were obtained from CPRD which comprised of longitudinal medical records from primary care (1). This efficient design of the study allows a large amount of resource use to be captured without the need to collect information from practice sites. However, preference-based utility measures such as EQ-5D were not collected via CPRD. Given the absence of utility data collected directly from patients, a systematic review was performed to identify health state utility values for children with and without asthma exacerbation.

This review aimed to identify preference-based utility values for children with day-to-day asthma symptoms (baseline utility) and children experiencing an asthma exacerbation, and to review the appropriateness of the utility values for the PLEASANT economic analysis.

2.0 Methods

2.1 *Scoping*

A scoping search was conducted to establish the likely quantity and relevance of published literature. This was done by searching the MEDLINE, Cochrane HTA and NHS EED databases using a limited number of population terms in addition to a search filter for quality of life. It was found that there was a lack of utility data derived from EQ-5D in children with asthma. Although EQ-5D is the preferred outcome measure, the standard version of EQ-5D is not designed to be used in children. EQ-5D-Youth is available for children and adolescents, but there is not yet a validated UK tariff. In view of this, the NICE reference case states that other validated preference-based measures developed for children may be used instead, but does not specify the preferred quality of life instrument (2). Therefore, a broad approach was

taken in the search to identify utility values derived from EQ-5D, as well as other preference-based utility measures. EQ-5D values estimated from mapping studies were also considered.

2.2 Search strategy

2.2.1 Search terms

Both free text and MESH headings pertaining to children, asthma and asthma exacerbation were used in the search (see Appendix 1: Full search strategy
). The InterTASC Information Specialists' Sub-Group (ISSG) search filter was used to filter studies that report health-related quality of life (see Appendix 2: Quality of life filter
). The filter was adapted to include a newly-developed preference-based utility measure for children, Child Health Utility Index 9D (3), as well as other preference-based measures in asthmatic children, such as the Asthma Symptom Utility Index. Full search terms for this review are presented in Appendices 1 and 2.

2.2.2 Search limit

To increase sensitivity, the search was not limited by language, publication type, publication dates or study design.

2.2.3 Sources searched

The following clinical and economic databases were searched:

- Ovid MEDLINE (In-Process & Other Non-Indexed Citations) (1946 to 5th July, 2014)
- The Cochrane Library (includes Cochrane Database of Systematic Review (CDSR), NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) database) (up to 5th July, 2014)
- EMBASE (1974 to 5th July, 2014)
- ECONLIT (1886 to 5th July, 2014)
- SCHARR Health Utilities Database (up to 5th July, 2014).

In addition to the electronic database search, reference lists of the retrieved papers were screened for relevant papers.

2.3 Inclusion and exclusion criteria

The inclusion and exclusion criteria for the review are summarised in Table 1. Systematic reviews and protocols were not included, but were used to identify relevant papers.

Modelling studies were examined to determine the source of utility values used. Modelling studies which described utility data not reported elsewhere were included in the review. Non-English papers with English language abstracts were initially included but were excluded at full-text when English translations were not obtainable.

Table 1 Review inclusion and exclusion criteria

Criteria	**Inclusion**	**Exclusion**
Population	• Children with asthma • Population with mixed age groups but including some children	• Asthmatic patients aged 18 years and above • Non-asthma patients
Intervention		• Studies that only presented the utility change associated with a particular intervention
Outcomes	• Utility values from preference-based measures	• Non preference-based utility scores unless mapping to EQ-5D was performed • Studies which did not publish utility data
Publication type		• Qualitative study • Letters • Editorials • Case reports / case series • Systematic review • Protocols
Language	• English published papers	• Non-English published papers

2.4 Selection of studies

In the first stage of study selection, titles and abstract of the searched results were screened against the inclusion / exclusion criteria. Full articles were assessed if titles and abstracts were unclear. All studies identified during screening of titles and abstracts were further screened at full text.

2.5 Quality assessment

Quality assessment of articles in this review followed the criteria (sample size, number loss at follow up and handling of missing data) recommended by Papaioannou et al. (4) in the Decision Support Unit Technical Support Document on the identification, review and synthesis of health state utility values from the literature.

2.6 Data Extraction

Data extracted comprised of characteristics of study population, study design and details of outcome measurements (descriptive system, tariff used, method of valuation, time of measurement, mean utility data and other relevant measures).

2.7 Selection of utility data for use in the PLEASANT economic analysis

Selection of utility data to use in the PLEASANT economic analysis was based on i) quality of the study, ii) the relevance of utility data to the population and health states in PLEASANT, (iii) the extent to which the measurement method was in accordance with the NICE reference case.

3.0 Results

A total of 927 studies were retrieved from the database search and reference tracking. After removal of duplicates, 683 studies were screened at titles and abstract. A total of 659 studies were excluded at this stage. The most common reasons for exclusion were that the population was aged over 18 years, that utility values were not reported or that the values reported were not preference-based utility values (Appendix 3). Subsequently, 24 papers were screened at full-text and 10 papers were excluded with reasons given for each paper in Appendix 4. Finally, 14 papers were included in this review. Figure summarises the search process of this review.

Study characteristics for the included studies are summarised in Table . The study populations are summarised in Table 2 and methods used to measure health-related quality of life (HRQoL) are summarised in Table 3. Details regarding study quality are provided in

Table 4. Details regarding the suitability of the studies for use in the economic model, based on the criteria described above, are provided in Table 5.

Figure 1: Flow diagram of search process

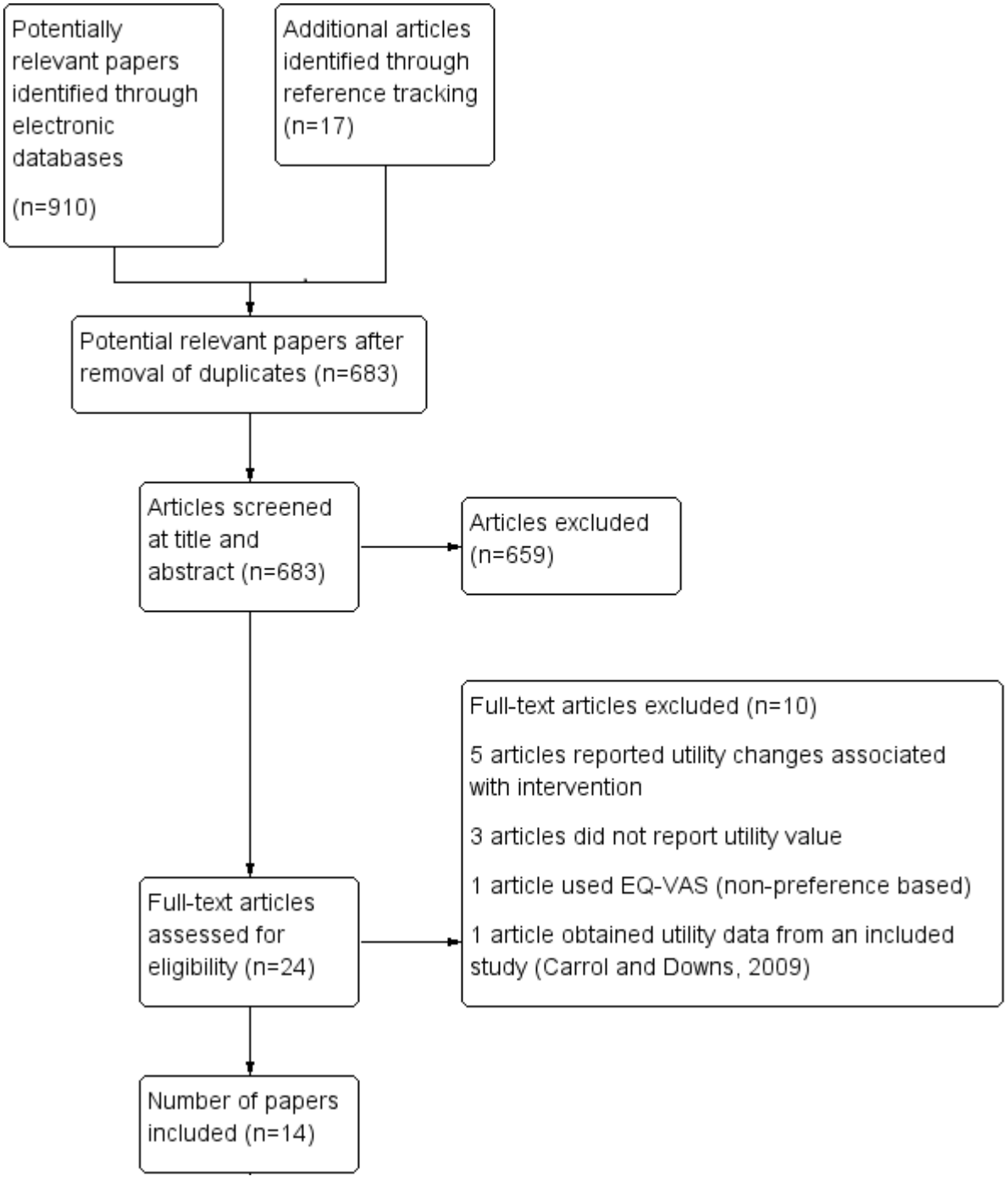

Table 2: Characteristics of included studies

No	Authors, (year)	Country	Study Design	Total participants	Duration	Intervention	Control	Primary outcome(s)
1	Willems et al. (5)	Netherlands	Economic evaluation alongside an RCT	109 (56 aged under 18)	1 year	Nurse-led telemonitoring	Usual care	Cost per QALY
2	Powell et al. (6)	UK	Multi-centre, double blind, RCT	508 children	1 month	Nebulised magnesium sulphate	Usual care	Asthma severity score 1 hour after treatment
3	Price et al. (7)	UK	Single blind, RCT, pragmatic	687 (mixed age group, 12-80 years)	2 years	Leukotriene receptor antagonist (step 2) As above plus ICS (step 3)	ICS (step 2), ICS+ LABA (step 3)	Changes in Mini AQLQ
4	Brusselle et al. (8)	Belgium	Cohort	158 (mixed age group)	52 weeks	Omalizumab	N/A [single arm study]	Clinical effectiveness (asthma symptoms, lung function, HRQoL) and safety of omalizumab
5	Chiou et al. (9)	USA	Outcome measure was used in the baseline assessment of an RCT	Utility measurement was performed on a sample of 72 children from the RCT	Baseline utility measurement	Environmental intervention	Placebo	HRQoL

No	Authors, (year)	Country	Study Design	Total participants	Duration	Intervention	Control	Primary outcome(s)
6	Mittmann et al. (10)	Canada	Cross-sectional survey	17,626 household residents of which 229 had asthma	Cross-sectional	None	None	HRQoL
7	Juniper et al. (11)	Canada	Cohort	52 children	9 weeks	None	None	Validity of outcome measures in children
8	Norman et al. (12)	UK	Decision model, EQ-5D data from EXALT study used for day-to-day symptoms Literature based estimate used for exacerbation	EXALT: 404 (mixed age group)	EXALT: 36 weeks	Omalizumab and usual care	Usual care	Cost per QALY
9	Briggs et al. (13)	Multinational	Economic evaluation of GOAL (multi-national, double blind, RCT), CSM data from GOAL were mapped onto EQ-5D	GOAL:3,416 (mixed age group)	GOAL: 52 weeks, model as weekly event	Salmeterol/fluticasone	Fluticasone	Cost per QALY

No	Authors, (year)	Country	Study Design	Total participants	Duration	Intervention	Control	Primary outcome(s)
10	Doull et al. (14)	Multinational	Decision model, CSM data from GOAL (multi-national, double blind, RCT) were mapped onto EQ-5D	GOAL:3,416 (mixed age group)	GOAL: 52 weeks, model as weekly event	Salmeterol/fluticasone	Fluticasone	Cost per QALY
11	Rodriguez et al. (15)	Colombia	Decision model (Markov), utility values were derived from a utility valuation survey	76 parents were involved in the survey	Utility measured at one time point	Budesonide, fluticasone, ciclesonide	Beclomethasone dipropionate	Cost per QALY
12	Carroll et al. (16)	USA	Cross-sectional	4,016 parents, each valued 3 of 29 health states (~415 valuations per health state)	Duration of recruitment : 2 years HRQoL measurement was performed at a time point	None	None	Utility values
13	Brown et al. (17)	Multinational	Decision model(Markov), CSM data from ETOPA (open-label trial)	ETOPA: 312 (mixed age group)	1 year	Omalizumab and BSC	BSC	Cost per QALY

No	Authors, (year)	Country	Study Design	Total participants	Duration	Intervention	Control	Primary outcome(s)
			were mapped onto EQ-5D					
14	Gerald et al. (18)	USA	Decision model (decision tree and Markov)	Utility data based on study by Chiou et al. (2005)	Time horizon: 1 year, cycle length: 1 day	Four school based asthma screening strategies	Status quo	Cost per QALY

CSM: Condition specific measure, RCT: randomised controlled trial, HRQoL: health-related quality of life, BSC: best supportive care, MgSO4: magnesium sulphate, ICS: inhaled corticosteroids, LABA: long acting beta2-agonist, AQLQ: Asthma Quality of Life Questionnaire

Table 2: Population of included studies

Authors, (year)	Disease type	Severity/stage	Age, Mean(sd)	Male Gender (%)	Ethnicity
Willems et al. (5)	Mild to moderate asthma managed in outpatient care	GINA stage I to III, mean FEV1% predicted for children: 96.5 (sd 8.4) for intervention and 99.4 (sd 11.3) for control	7-18 years strata, intervention: 10.57 (sd 2.1) control: 10.85 (sd 2.3)	Intervention: 72.4% control: 55.6%	Not reported
Powell et al. (6)	Acute asthma	Severe acute asthma (BTS/SIGN definition)	Median 4.0 (IQR 3.0–7.0), range: 2–16 years	58%	Not reported
Price et al. (7)	Poorly controlled asthma at BTS/SIGN Step 2or 3	ACQ≥1 or MiniAQL ≤ 6	Step 2: 44.74 (16.49), Step 3: 50.02 (15.93), range 12-80 years	Step 2: 162 (49.7%), Step 3: 136 (37.7%)	98% Caucasian
Brusselle et al. (8)	Poorly controlled severe persistent allergic asthma on ICS/LABA (GINA definition)	Mean FEV1%<80% predicted, day and night symptoms, ≥2 exacerbations (requiring systematic steroid , ED or hospitalizations) in past 2 years	Mean 48.17 (17.18), range 12-83 years	73 (46.2%)	94.9% Caucasian
Chiou et al. (9)	Diagnosed asthma	Mild to severe	7-8 years (37.5%), 9-10 years (34.7%), 11-12 years (27.8%)	Not reported	White (15.3%), Asian (40.3%), African American (29.2%)

Authors, (year)	Disease type	Severity/stage	Age, Mean(sd)	Male Gender (%)	Ethnicity
Mittmann et al. (10)	Asthma generally	Not reported	Not reported. 10.5% (N=1,847) of total respondents were under 19 years	8,058 (45.7%) but data was not stratified to age	Caucasian
Juniper et al. (11)	Symptomatic asthma	Mean FEV1% predicted: 85±16.6 no previous exacerbation in past 2 weeks	12.(3.1),range:7-17 years	30 (57.7%)	Majority Caucasian
Norman et al. (12)	Poorly controlled severe persistent allergic asthma on high dose ICS and LABA with >1 severe exacerbations in previous year and FEV <80% predicted	BTS/SIGN ≥Step 4 EXALT: FEV 40-80% predicted >1 severe exacerbations within previous year	EXALT: Mean across both arms: 44.7 range: 12-75 years [only 5 patients under 18 years]	EXALT: 141 (35.2%)	Not reported
Briggs et al. (13)	Diagnosed asthma (≥ 6 months), no use of LABA or oral $beta_2$-agonists in previous 2 weeks	Uncontrolled asthma, mean FEV1 % predicted: ranged from 76 to 79	SFC: stratum 1; 36.1 (15.6), stratum 2; 40.4 (16.4), stratum 3; 44.1 (15.9); FC: stratum 1; 36.4 (15.6), stratum 2; 40.3 (16.6), stratum 3; 42.7 (15.7)	42%	Not reported

Authors, (year)	Disease type	Severity/stage	Age, Mean(sd)	Male Gender (%)	Ethnicity
Doull et al. (14)	Diagnosed asthma (≥ 6 months), no use of LABA or oral beta$_2$-agonists in previous 2 weeks	Uncontrolled asthma, mean FEV1 % predicted: ranged from 76 to 79	SFC: stratum 1; 36.1 (15.6), stratum 2; 40.4 (16.4), stratum 3; 44.1 (15.9); FC: stratum ;1 36.4 (15.6), stratum 2; 40.3 (16.6), stratum 3; 42.7 (15.7)	42%	Not reported
Rodriguez et al. (15)	Persistent asthma	Mild to moderate asthma	Not reported	Not reported	Caucasian
Carroll et al. (16)	Persistent asthma	Mild to severe	Not reported	1,982(49%) [gender of parent's child]	African American (48%) Caucasian (47%)
Brown et al. (17)	Poorly controlled severe persistent allergic asthma despite high-dose ICS and LABA	Subgroup of severe patients from ETOPA included	For whole ETOPA trial: Omalizumab 37.5 (range: 12–73), best supportive care: 39.3 (range: 12–71)	For whole ETOPA trial: Omalizumab and best supportive care: 58 (28.2%), best supportive care: 34 (32.1%)	Caucasian
Gerald et al. (18)	Asthma symptom-free day (ASFD), symptom days, exacerbation recovery days, emergency department visits, and hospitalization days	Intermittent, mild, moderate, severe	Utility data based on study by Chiou et al (2005)	Utility data based on study by Chiou et al (2005)	Utility data based on study by Chiou et al (2005)

Table 3: Outcome measurement and utility values in each study

Authors, (year)	Descriptive system	Type	Descriptive measure filled by	Population in valuation	Valuation method	When HRQoL data were obtained	Mean, (sd)	Other HRQoL measures
Willems et al. (5)	EQ-5D (child version)	Generic	Carer(age<12), ≥ 12 by patient	Adult UK tariff (19)	TTO	Baseline, 4 month, 8 month, 12 month	7-18 years strata at baseline: usual care, 0.96 (0.07), telemonitoring, 0.92 (0.20)	PAQLQ
Powell et al. (6)	EQ-5D	Generic	Carer of children age between 5 -16 years	Adult UK tariff (19)	TTO	1 month post exacerbation	Exacerbation: 0.52 (based on mean ASS score of 5.8 mapped to EQ-5D 22222) 1 month: magnesium group, 0.86 (0.04), standard care, 0.88 (0.04)	PedsQL
Price et al. (7)	EQ-5D	Generic	Patient	Adult UK tariff (19)	TTO	2 months and 2 years	Step 2 at baseline: Intervention 0.795 (0.245), Control 0.830 (0.195), Step 3 baseline: Intervention 0.780 (0.237), Control 0.772 (0.234)	Mini AQLQ, asthma control questionnaire
Brusselle et al. (8)	EQ-5D	Generic	Patient	Belgian tariff	VAS	Baseline, 52 weeks	At baseline:0.54 (0.24)	AQLQ

Authors, (year)	Descriptive system	Type	Descriptive measure filled by	Population in valuation	Valuation method	When HRQoL data were obtained	Mean, (sd)	Other HRQoL measures
Chiou et al. (9)	PAHOM	Population -specific measure	Patient	Adults valuing for children	VAS, SG	Single time point	General asthma (VAS:0.7 converted SG:0.83)	None
Mittmann et al. (10)	HUI3	Generic	Participant was interviewed by phone or in person	HUI2 (Canada algorithm) 293 parents of school children	VAS, SG	Single time point	12-19 years: 0.90 (0.12)	None
Juniper et al. (11)	HUI2 (interviewer version)	Generic	Children	HUI2 (Canada algorithm) 293 parents of school children	VAS, SG	Baseline, week 5 and week 9	At baseline: 0.89 (0.09) (0.67–1.00)	PAQLQ, Feeling thermometer, direct valuation via SG
Norman et al. (12)	EQ-5D	Generic	Patients	Not stated	Not stated	31 weeks	31 weeks: standard care 0.719 (0.026), omalizumab 0.767 (0.02)	AQLQ
Briggs et al. (13)	Mapped EQ-5D from AQLQ	Mapping of CSM to EQ-5D	Patient	Valuation population not reported	Valuation method not reported	Baseline, 12, 24, 36, and 52 weeks	Totally Controlled: 0.946 (SE 0.011), well-controlled: 0.900 (SE 0.011), not well controlled: 0.842 (SE 0.011), exacerbation:	AQLQ

Authors, (year)	Descriptive system	Type	Descriptive measure filled by	Population in valuation	Valuation method	When HRQoL data were obtained	Mean, (sd)	Other HRQoL measures
							0.729 (SE 0.013)	
Doull et al. (14)	Mapped EQ-5D from AQLQ	Mapping of CSM to EQ-5D	Patient	Valuation population not reported	Valuation method not reported	Baseline, 12, 24, 36, and 52 weeks	Symptom free: 0.97 (0.014), with symptoms: 0.85 (0.015)	AQLQ
Rodriguez et al. (15)	Direct valuation using vignettes	Direct valuation	N/A	Parents	SG	Single time point	No symptoms (0.989), symptom no exacerbation (0.705) and asthma exacerbation (0.275)	None
Carroll et al. (16)	Direct valuation using vignettes	Direct valuation	N/A	Parents	TTO, SG	Single time point	SG: mild intermittent 0.91 (0.18), mild persistent 0.90 (0.18), moderate persistent 0.88 (0.18), severe persistent asthma 0.83 (0.21), 10 day hospitalization 0.94 (0.14) TTO: mild intermittent 0.91 (0.17), mild persistent 0.91 (0.18), moderate persistent 0.91 (0.15), severe persistent asthma 0.85 (0.20), 10 day hospitalization: 0.95 (0.15)	None

Authors, (year)	Descriptive system	Type	Descriptive measure filled by	Population in valuation	Valuation method	When HRQoL data were obtained	Mean, (sd)	Other HRQoL measures
Brown et al. (17)	Mapped EQ-5D from mini AQLQ	Mapping of CSM to EQ-5D	Patient	Adult UK tariff for EQ-5D (19)	TTO	Baseline and 52 weeks	Daily symptoms, baseline: best supportive care 0.62, omalizumab 0.58, Daily symptoms, week 52: best supportive care 0.65, omalizumab 0.82	Mini AQLQ
Gerald et al. (18)	PAHOM	Population specific measure	N/A (utility data for modelled states were estimated by averaging utility values of PAHOM states)	PAHOM: adults valuing for children	VAS, SG	N/A	ASFD 1.0 (0.98-1.0) Symptomatic 0.90 (0.84-0.96) Recovery 0.70 (0.64-0.76) ED 0.43 (0.37-0.49) Hospitalization 0.06 (0.01-0.11)	None

AQLQ: Asthma Quality of Life Questionnaire, EQ-5D: EuroQol-5 Dimension Questionnaire, CSM: Condition specific measure, FEV1: Forced Expiratory Volume in the first second, HUI2: Health Utilities Index Mark 2, HUI3: Health Utilities Index Mark 3, ICS: inhaled corticosteroid, LABA: long acting beta2-agonist, LTRA: Leukotriene receptor antagonist, PAHOM: Pediatric Asthma Health Outcome Measure, PAQLQ: Paediatric Asthma Quality of Life Questionnaire , PEDSQL™: Pediatric Quality of Life, SF6D: Short Form 6D

Table 4: Quality assessments of included papers

Authors, (year)	Sample size	Number loss at follow up	Methods of handling missing data
Willems et al. (5)	109 (mixed age group)	7/109 (4 children)	Data imputation by using mean for baseline score, interpolation between scores and last value carried forward
Powell et al. (6)	508 children	Postal survey response rate: 45%. 228 completed PedsQL. 89 patients aged over 5 completed EQ-5D questionnaires (46 in magnesium arm, 43 in placebo)	Multiple imputation by chained equations was used to impute missing data. In under 5s the EQ-5D scores were estimated by mapping from the PEDSQOL scores. EQ-5D scores at time of exacerbation were mapped subjectively from ASS scores.
Price et al. (7)	687 (mixed age group)	Step 2: 20/326 excluded post randomisation, 13/306 loss to follow-up but 300/306 had some data post-randomisation step 3: 9/361 excluded post randomisation, 12/352 were lost to follow up but 350/352 had some data post randomisation	Complete data in: 218/683 patients (32%), less than 4 missing data out of 13 data: 514/683 (75%). 19% missing visit 2 EQ-5D data. Complete case analysis presented. In addition imputed case presented using Rubin's multiple imputation
Brusselle et al. (8)	158 (mixed age group)	Only 126 of 158 patients had baseline EQ-5D values and only 67 had EQ-5D data at 1 year.	Not reported

Authors, (year)	Sample size	Number loss at follow up	Methods of handling missing data
Chiou et al. (9)	72 children	Not applicable	Not reported
Mittmann et al. (10)	17,626 household residents of which 229 had asthma	Not relevant as cross-sectional data	Not reported
Juniper et al. (11)	52 children	None	Complete datasets provided for all patients
Norman et al. (12)	EXALT: 404 (mixed age group)	EQ-5D scores available for 318 (79%) at 31 weeks	Not reported
Briggs et al. (13)	GOAL: 3,416 (mixed age group)	526 withdrawals including 111 lost of follow up. Reasons were adverse events, withdrawal of consent, protocol violation, ineligible for study, data that could not be analysed (n=117)	Not reported
Doull et al. (14)	GOAL: 3,416 (mixed age group)	526 withdrawals including 111 lost of follow up. Reasons were adverse events, withdrawal of consent, protocol violation, ineligible for study, data that were not able to be analysed (n=117)	Not reported
Rodriguez et al. (15)	76 parents	Not reported	Not reported

Authors, (year)	Sample size	Number loss at follow up	Methods of handling missing data
Carroll et al. (16)	4,016 parents, 29 diseases	Not reported	Not reported
Brown et al. (17)	ETOPA: 312 (mixed age group)	Not reported	Imputation method for patient prematurely withdrawn. Event with zero duration was assigned if patient did not experience any event after 7 days of discontinuation
Gerald et al. (18)	Utility data based on study by Chiou et al (2005)	Utility data based on study by Chiou et al (2005)	Utility data based on study by Chiou et al (2005)

Table 5: Relevance of studies to the PLEASANT analysis and the NICE reference case

Authors, (year)	Relevance of population	Relevance of health states	Instrument	Measured from	Tariff	Valuation method	Applicability issues
Willems et al. (5)	Stratified into adults and children	Baseline utility for mild-moderate asthma patients	EQ-5D	Carer or children (≥12 years)	Adult UK tariff (19)	TTO	EQ-5D from non-UK population
Powell et al. (6)	Young children	Utility of severe acute asthma and post exacerbation	EQ-5D for post exacerbation. For acute exacerbation, EQ-5D states were mapped to ASS scores	Carer as proxy for children ≥5 years	Adult UK tariff (19)	TTO	EQ-5D are preferred but subjective mapping was used to estimate EQ-5D from ASS during exacerbation
Price et al. (7)	Mixed age (above 12 years, mean age of 44.7 years in Step 2, 50 years in Step 3	Baseline utility (uncontrolled asthma) by intervention arm, utility changes due to intervention	EQ-5D	Patient	Adult UK tariff (19)	TTO	Utility decrement for exacerbations not reported
Brusselle et al. (8)	Population is constrained to severe asthma with long duration of asthma, older population (mean age 48 years), allergic and on maintenance steroids	Baseline utility of population with uncontrolled severe allergic asthma	EQ-5D	Patient	Belgian tariff	VAS	Utility decrement for exacerbations not reported None UK Tariff VAS not TTO

Authors, (year)	Relevance of population	Relevance of health states	Instrument	Measured from	Tariff	Valuation method	Applicability issues
Chiou et al. (9)	Children with diagnosed asthma of at least mild persistent severity	Utility of asthma generally, score stratified by severity	PAHOM	Children	Adult preference	VAS, SG (converted from VAS)	Utility decrement for exacerbations not reported
Mittmann et al. (10)	Stratified by age 12-19 years	Utility of asthma generally	HUI3	Patient	HUI2 (Canadian algorithm)	VAS, SG	Utility decrement for exacerbations not reported
Juniper et al. (11)	Children population, symptomatic asthma, with no exacerbation in past 2 weeks, FEV1 >80% predicted	Baseline utility in general asthma	HUI2	Children	HUI2 (Canadian algorithm)	VAS, SG	Utility decrement for exacerbations not reported
Norman et al. (12)	Poorly controlled severe persistent allergic asthma	Utility of day to day symptoms (not exacerbation)	EQ-5D	Patients	Not stated	Not stated	Utility decrement for exacerbations not derived from this study (literature based estimates used)

Authors, (year)	Relevance of population	Relevance of health states	Instrument	Measured from	Tariff	Valuation method	Applicability issues
Briggs et al. (13)	Mean age >30, mean FEV1 <80% predicted, utility adjusted in regression to UK population, population treated with inhaled fluticasone or salmeterol/fluticasone	Relevant health states: totally controlled (TWC), well-controlled (WC), not well controlled without exacerbation (NWC) and exacerbation (X)	Mapped EQ-5D from AQLQ	Patient	Not reported	Not reported	Used an unpublished mapping algorithm and insufficient details reported to assess validity mapping method
Doull et al. (14)	Mean age >30, mean FEV1 <80% predicted, utility adjusted in regression to UK population, population treated with inhaled fluticasone or salmeterol/fluticasone	Health states were less relevant than those used by Briggs et al (2006) as the exacerbation state was combined with other symptomatic states	Mapped EQ-5D from AQLQ	Patient	Not reported	Not reported	Used an unpublished mapping algorithm and insufficient details reported to assess validity mapping method
Rodriguez et al. (15)	Parents answering for children	Health states were no symptoms, suboptimal control, no exacerbation and asthma exacerbation	Direct valuation	Parents	No	SG	Direct valuation of clinical vignettes does not meet the NICE reference case
Carroll et al. (16)	Carer valuing for children age between 0-18 years	Utility data for different asthma severity	Direct valuation	Parents	No	TTO, SG	Direct valuation of clinical vignettes does not meet the NICE reference case

Authors, (year)	Relevance of population	Relevance of health states	Instrument	Measured from	Tariff	Valuation method	Applicability issues
Brown et al. (17)	Poorly controlled allergic, severe asthma with mean age of 37.5-39.3 years	Utility for day to day symptoms at baseline and 1 year	Mapped EQ-5D from mini AQLQ	Patient	Adult UK tariff (19) for EQ-5D	TTO	Utility decrement for exacerbations not derived from this study (literature based estimates used)
Gerald et al. (18)	Cohort of school children with asthma	Reported health states related to asthma exacerbations	PAHOM	Estimated based on children's characteristics	PAHOM derived from adult preferences	VAS, SG (SG converted from VAS)	Health states were subjectively mapped to PAHOM state

Six studies included UK patients, three of which were multinational studies. Three papers were from the USA, two were Canada-based and one each was from the Netherlands, Belgium and Colombia. Only studies by Juniper et al. (11), Chiou et al. (9), and Powell et al. (6) directly measured HRQoL in populations confined to children. Chiou et al. (9) recruited children aged between 7 and 12 years with diagnosed asthma of at least mild persistent severity, while Juniper et al. (11) studied children with symptomatic asthma with mean age of 12 years (range 7 to 17 years) and Powell et al. (6) included children aged between 2 and 16 years with acute severe asthma. Two studies, Rodriguez et al. (15) and Carroll et al. (16) elicited preferences from parents regarding health states in children. The other studies comprised of populations with mixed age groups. Among these studies, Mittmann et al. (10) and Willems et al. (5) presented HRQoL data stratified by age.

The populations in the included studies differed in asthma severity and characteristics. Five (35.7%) studies measured HRQoL using EQ-5D. Other studies used outcome measurements, such as the Paediatric Asthma Health Outcome Measurement (PAHOM) (n=2, 14.3%) and the Health Utilities Index (n=2, 14.3%) [Mark 2 (HUI2) (n=1) and Mark 3 (HUI3) (n=1)]. Direct valuation using vignettes was used in two studies (14.3%). This review also included three (21.4%) modelling studies which estimated EQ-5D data from mapping exercises.

EQ-5D is a generic preference-based measure in which the descriptive systems consist of five dimensions: mobility, depression/anxiety, self-care, usual activities, pain and discomfort. Each dimension has three levels of severity and this gives rise to 243 possible health states described by EQ-5D. In the UK, scoring of EQ-5D was based on time-trade off (TTO) in a representative sample of 2,997 adults administered using the York Measurement and Valuation of Health TTO protocol. Public preferences were obtained for 43 health states and regression was used to model data for the remaining health states. Utility score from the algorithm was anchored at “1” for perfect health and “0” for a state equivalent to death (20).

Willems et al. (5), Price et al. (7) and Powell et al. (6) were randomised controlled trials (RCTs) which elicited an EQ-5D index score using UK preferences, whereas the EQ-5D score in a cohort study by Brusselle et al. (8) was based on a Belgian tariff. Norman et al. (12) was a modelling study which used EQ-5D collected from the EXALT trial. The tariff used in the EXALT study is not described by Norman et al. (12), but the data is described as being consistent with the NICE reference case suggesting that the UK TTO valuation set was

used. In the MAGNETIC trial, Powell et al. (6) included a population of children (n=508) with severe acute exacerbations, as defined by BTS/SIGN. The MAGNETIC trial was a prospective, double-blind, multicentre RCT in the UK, designed to compare efficacy of nebulised magnesium sulphate with usual care. EQ-5D and Paediatric Quality of Life (PedsQL™) postal questionnaires were collected at one month post-exacerbation. EQ-5D data were obtained for children aged ≥ 5 years and were filled by parents as proxy, while PedsQL™ were obtained for all children and were self-completed if children were aged over five years. Respondents were asked to recall events in the previous four weeks while filling out the outcome measures. Adult UK tariff by Dolan (19) was applied to EQ-5D to obtain utility values for each child. Utility values for patients under five years were estimated through mapping between the EQ-5D and PedsQL™. In this study, baseline EQ-5D during exacerbation was not collected for ethical reasons. Therefore, asthma symptom scores (ASS) at exacerbation were mapped to EQ-5D based on experts' opinions. The expert team comprised of a paediatric consultant and two respiratory nurses who routinely treated asthmatic paediatric patients. An EQ-5D health state of 11111 was assigned to ASS scores of 1-3 in the base case, while ASS scores of 4-6 and 7-9 were mapped to EQ-5D health states of 22222 and 33333, respectively. In our opinion, the subjective nature of this mapping between ASS and EQ-5D was considered to make the EQ-5D scores estimated at the time of exacerbation very uncertain. Furthermore, these data would only be relevant to the subgroup of patients who have severe acute exacerbations requiring treatment in secondary care as this was the population recruited into the MAGNETIC study. This study was blinded to patients, healthcare providers and outcome analysts. Therefore, it had low risk of performance and detection bias. However, the study was subjected to risk of attrition bias due to the low response rate of EQ-5D questionnaires. The authors addressed this limitation by using a mapping function to estimate EQ-5D data for those who had PedsQL™ data. The mapping function was based on the subset of patients for whom both PedQL and EQ-5D data were available. Following mapping estimations, a total of 218 EQ-5D data were available for analysis for the outcome 1 month after exacerbation.

Price et al. (7) included patients in the UK aged between 12 and 80 years with poorly controlled asthma at BTS/SIGN treatment Step 2 or 3. Mean age of patients was 44.74 (sd 16.49) at Step 2 and 50.02 (sd 15.93) at Step 3. In Step 2 patients, Leukotriene receptor antagonist (LTRA) was compared with inhaled corticosteroid (ICS). In step 3 patients who were already receiving ICS, LTRA was compared with long acting β2-agonist (LABA). EQ-

5D data were directly measured from patients and were presented by treatment steps and interventions at baseline, two months and two years. Utility values were estimated using UK preferences. This RCT had a high retention rate, with 5-10% loss to follow-up. A large proportion (75%) of patients presented with less than four missing data and missing data were handled using multiple imputation. This single blinded RCT (n=687) was robust, with large sample size, low risk of attrition bias and measured outcomes with EQ-5D. However, utility data presented were not stratified by age nor related to asthma exacerbations. Therefore, these data lack applicability to the PLEASANT trial and the health states modelled.

Norman et al. (12) evaluated the cost-effectiveness of omalizumab in addition to standard care by using a Markov model. Norman et al. (12) used EQ-5D scores measured in the EXALT study for day-to-day asthma symptoms. The EXALT study was an open-label RCT, which comprised of 404 patients in the UK (age range from 12-75 years) with poorly controlled severe allergic asthma (FEV_1 <80% predicted). Utility for day-to-day symptoms (by treatment arm) was estimated from EQ-5D scores recorded in the EXALT study.

Norman et al. (12) also conducted a systematic review of HRQoL literature to identify HRQoL data of relevance to both adult and paediatric populations. In their base case analysis they used data from Lloyd et al. (21), a study conducted in an adult population which provides estimates of the health utility decrement (loss) associated with exacerbations requiring oral steroid treatment and exacerbations requiring hospitalisation. The decrement was measured by comparing baseline EQ-5D values to those reported at 4 weeks for patients who did and did not experience exacerbations during that 4 week period. They cited another study by Steuten et al. (22), which also provided utility values for exacerbations in an adult population. However, this study collected data at 3 to 6 month intervals which could make it harder to detect the relationship between short term exacerbations and health utility than the 4 week interval used by Lloyd et al. (21).

Willems et al. (5) used UK preferences to estimate utility scores for asthmatic patients in the Netherlands. Populations comprised of adults (n=53) and children (n=56) with mild to moderate asthma (GINA state I to III). EQ-5D questionnaires were completed by carers for children under 12 years and self-completed for those aged 12 years and over. There were only four children with loss of follow up, and various imputation techniques were applied. Missing baseline scores were imputed with mean scores. Quality of life at baseline (usual care, 0.96,

nurse monitoring, 0.92) were consistent with the good lung function of the study's population (mean FEV_1 above 90% predicted). However, these results were elicited from a non-UK population although they did use a UK valuation set. Willems et al. (5) did not examine the utility decrement in exacerbation.

Brusselle et al. (8) conducted a one-year cohort study (n=158) to determine the efficacy and safety of omalizumab by looking at changes from baseline in a single arm study. The mean age of the population studied was 48.17 (sd 17.18) and age ranged from 12 to 83 years. Included patients had poorly controlled severe allergic asthma (FEV_1 <80% predicted) and a past history of exacerbations. The Belgian tariff was applied to the collected EQ-5D data at baseline and one year. Only 126 of 158 patients had baseline EQ-5D values and only 67 had EQ-5D data at 1 year. Handling of missing data, however, was not reported. This tariff was obtained from public preferences in Belgium using visual analogue scale (VAS) valuation method (56). However, valuation using VAS is not a choice-based method. In the UK, NICE has expressed a preference for using a choice-based method such as TTO over VAS (23). Therefore, utility data estimated from this study do not meet the NICE requirement of using a choice-based valuation method.

Chiou et al. (9) and Gerald et al. (18) were two USA-based studies that used Paediatric Asthma Health Outcome Measure (PAHOM). PAHOM is an asthma-specific preference-based measure designed for children. It consists of a descriptive system with three dimensions: symptoms, emotions and activity. The symptoms dimension is classified to three levels of severity while emotions and activity are dichotomous choices to indicate presence or absence of problems. Unlike EQ-5D with a recall period of one day, respondents are asked to describe health states for the past seven days using PAHOM. The utility value in children is calculated as the average utility values over seven days. Preference weights for PAHOM were elicited from 114 adults in Seattle, USA, who responded for children. VAS was used to value all health states and SG was used to value subset of health states to reduce the cognitive burden on respondents. VAS values were transformed into SG values using relative risk attitude equation (9).

Chiou et al. (9) used PAHOM to measure utility value in 72 children (aged 7-12 years) with diagnosed asthma of at least mild persistent severity. The utility value was measured as 0.83 (converted SG value). Chiou et al. (9) also reported mean VAS and SG values for patients

according to asthma severity with SG values of 0.79 for mild or no symptoms, 0.70 for moderate and 0.28 for severe. A limitation of this study was the small sample size, which may have affected the accuracy and validity of results, particularly for the estimates stratified by severity. Values stratified by presence or absence of exacerbation were not reported.

Gerald et al. (18) performed a modelling study on different screening strategies for asthma. Decision tree and Markov models for a cohort of children were constructed. The Markov model consists of five health states: asthma symptom-free day (ASFD), symptom days, exacerbation recovery days, emergency department visits and hospitalisation days. The utility value for each health state was derived using PAHOM. PAHOM states were allocated to the modelled health states. When several PAHOM states could describe a modelled health state, utility values of the relevant states were averaged to estimate a single utility value. For example, three to four PAHOM states were thought to characterise "symptom days" in the model. The utility values of these states were averaged to derive utility value for "symptom days". The authors highlighted that this approach may fail to capture valuation of "symptom days" accurately. In our opinion, the subjective nature of this mapping from modelled health states to PAHOM states reduces the robustness of these utility estimates. In addition, a general concern regarding PAHOM was that this measure was not validated for its psychometric properties. Furthermore, validation of the relative risk attitude equation used to derive SG values was not performed (9).

Two Canada-based observational studies used HUI as an outcome measure. Juniper et al. (11) studied the minimum skills required by children to complete outcome measurements unassisted. Paediatric Asthma Quality of Life Questionnaire, Feeling Thermometer, HUI2 and direct valuation were administered to 52 children aged 7 to 17 years (mean: 12 years) with symptomatic asthma (mean FEV_1: 85% predicted). The HUI2 Canadian tariff was applied to obtain utility values. The mean HUI baseline value for asthma was reported as 0.89 (sd 0.09).

The six-dimensional version of HUI2 is a common generic outcome measure in children. Each dimension has three to five levels allowing 8,000 unique health states to be defined. The HUI2 tariff was estimated from a sample of 293 parents of school children in Ontario, Canada. Valuations were performed using VAS and three health states were valued with VAS

and SG. A power function was then derived to map VAS values to SG values and multi-attribute utility theory was used to derive the valuation functions (20).

Mittmann et al. (10) conducted a cross-sectional study to measure HRQoL of 20 chronic diseases. The HUI3 was administered through interview to 17,626 household residents (≥12 years) in Canada. HUI3 is an adapted version of HUI2 with additional dimensions and levels. HUI3 weights were elicited from a random sample of adults (n=504) in Ontario, Canada. In this study, however, the HUI2 scoring algorithm was used for HUI3 data. The mean HUI score reported for children (age 12-19 years) with asthma was similar to those reported by Juniper et al. (11).

In measuring and valuing children's health, NICE is less clear on the preferred instrument, but advises use of a standardised and validated preference-based measure designed for children. Although HUI is an example of an instrument that meets the mentioned criteria, the HUI data from these studies may not be valid, as the study designs lack rigour. Firstly, the small sample size (n=52) recruited by Juniper et al. (11) may introduce inaccuracy to the results. Secondly, HUI3 data was inappropriately scored using HUI2 scoring algorithm in the study by Mittmann et al. (10) and utility scores estimated were deemed by the authors as provisional. Furthermore, neither of these studies reported the utility decrement attributable to asthma exacerbation.

Three modelling studies performed mapping to estimate EQ-5D values. Brown et al. (17) constructed Markov models to evaluate cost-effectiveness of omalizumab in addition to standard care. The utility values for day to day symptoms at baseline and 52 week were estimated by mapping mini-AQLQ scores from the ETOPA trial onto EQ-5D, using a published algorithm by Tsuchiya et al. (24). The ETOPA trial was a multinational open-label trial which recruited 312 patients aged between 12 and 73 years (mean: above 35 years) with poorly controlled allergic asthma (mean FEV_1 <73% predicted) (25). (NB: Brown et al. (17) used data from the subgroup of ETOPA patients with severe disease but baseline characteristics are not described for this subgroup so Table 2 provides characteristics for the ETOPA trial as a whole). The AQLQ scores were mapped to EQ-5D for patients separated by disease state and responder status. The mapping algorithm used by Brown et al. (17) was derived from an RCT of 3,000 adults in the UK with a wide range of asthma severity (24). In the RCT used to generate the mapping algorithm, both EQ-5D and AQLQ were collected

(26). Domains in EQ-5D were found to overlap with those in AQLQ, with correlations between 0.56 and 0.65. Six main mapping models and two supplementary models were derived using the regression method and were validated using an external dataset. However, these mapping functions were associated with large marginal errors and should only be considered as second best to direct elicitation of EQ-5D data (20, 24).

Brown et al. (17) used literature based estimates to model the decrement associated with exacerbations as the authors stated that the ETOPA trial collected insufficient patient quality of life data during exacerbations. The literature based estimates cited by Brown et al. (17) appear to be from an earlier publication of the study by Lloyd et al. (21).

The modelling studies by Briggs et al. (13) and Doull et al. (14) mapped AQLQ scores from the 52-week GOAL trial onto EQ-5D values. GOAL was a multinational double-blind RCT designed to evaluate efficacy of a combination of fluticasone/salmeterol compared to fluticasone in terms of asthma control. The GOAL study comprised of 3,416 patients (mean age: >35 years; range: 12-80 years) with uncontrolled asthma (mean FEV_1 <80% predicted) from 44 countries (27). Asthma control in GOAL was classified by Briggs et al. (13) using the GINA definitions. The classifications were totally controlled (TC), well-controlled (WC), not well controlled (NWC) and exacerbation requiring oral steroid or secondary care (X). As GOAL only collected AQLQ data, a mapping function obtained through personal communication with Macran and Kind was used to transform AQLQ scores to EQ-5D values. Subsequently, the utility value for each asthma control health state was derived using regression. In the regression model, a UK indicator was added as a dummy variable to adjust for UK specific-population. The dependent variable was the utility value while asthma control and the UK indicator were the independent variables. All independent variables were found to be significant predictors of quality of life. The quality of life data from this study is of relevance to the PLEASANT trial. However, the mapping function used in the analysis by Briggs et al. (13) was inadequately described by the authors and a published article providing more details could not be identified from searches. Therefore, an assessment of mapping performance was not possible.

Doull et al. (14) adapted the analysis by Briggs et al. (13) and reclassified asthma control to “symptom free” and “with symptoms”. Totally controlled asthma was classified as “symptom free”, while other states were classified as “with symptoms”. The weekly utility in the “with

symptom" state was equivalent to the weighted average of the weekly utility in WC, NWC and X health states from Briggs et al. (13). Regression was used to estimate the relationship between asthma control and quality of life, where quality of life was obtained from mapping AQLQ scores to EQ-5D. Asthma control and the UK indicator were entered into the model as the independent variables, while weekly utility was entered as the dependent variable. Subsequently, utility for the "with symptoms" and the "symptoms free" health states were estimated from the regression coefficients. As utility data in this study were adapted from Briggs et al. (13) which mapped AQLQ scores to EQ-5D using the mapping function by Macran and Kind, the validity of mapped data was likewise not assessable.

The method used in Carroll et al. (16) and Rodriguez et al. (15) involved valuation of hypothetical health states by parents. Parents were asked to value health states described in vignettes by imagining their children affected by those states. Descriptions in vignettes, however, differed across studies. Rodriguez et al. (15) developed asthma-specific vignettes based on PAHOM (9) and these were validated by expert opinions, whereas Carroll et al. (16) developed general descriptions of 29 health states with the inclusion of time as a factor. Rodriguez et al. (15) requested parents (n=76) to value vignettes using SG, while Carroll et al. (16) used SG and time-trade off (TTO) methods in a sample of 4,016 parents (NB: each parent only valued 3 of a potential 29 states providing around 415 values per state). Neither studies constructed vignettes based on rigorous methods such as a focus group. The lack of standardised descriptive systems of vignettes and different valuation methods also resulted in a lack of comparability of results between studies. In addition, vignettes are limited to specific descriptions of a condition and may not fully reflect all experiences of a patient. Therefore, vignettes do not meet the NICE reference case and are considered of little function in economic evaluations (23). In view of the various limitations associated with vignettes, utility values from Carroll et al. (16) and Rodriguez et al. (15) were not considered suitable for use in the PLEASANT economic analysis.

3.1 Health state utility values selected for use in the PLEASANT economic analysis

The systematic review did not identify any studies that directly measured exacerbation-related utility decrements in children using preference-based measures. Some studies estimated utility decrement via mapping, either subjectively (6, 18), or using an unpublished mapping algorithm with insufficient details (13).

The utility values used in the economic evaluation by Briggs et al. (13) appear to be most relevant to our proposed model structure as they are reported for relevant health states, including an exacerbation state, and have been estimated from a trial population which included some children. However, the mapping algorithm used to convert from the condition specific HRQoL measure (AQLQ) to the EQ-5D utility score is not from a published source and is not described in detail making it difficult to assess its validity. However, if the values reported by Briggs et al. (13) are taken at face value, they provide an estimate of the utility loss for exacerbation versus total asthma control of -0.216 (SE 0.007). It is possible that some patients do not have total asthma control in the absence of an exacerbation and the difference between the utility values for the exacerbation state and the not well controlled states is smaller at -0.112. The data from Briggs et al. (13) suggest that the utility decrement for exacerbation in the average patient is likely to fall in the range of -0.112 to -0.216.

There is a reasonable agreement between the values reported by Briggs et al. (13) and Lloyd et al. (21). The utility decrements provided by Lloyd et al. (21) from an adult population are -0.1 and -0.2 for exacerbations requiring oral steroids and exacerbations requiring hospitalisation respectively.

Given the uncertainty regarding the mapping algorithm used by Briggs et al. (13) compared to the direct collection of EQ-5D data in Lloyd et al. (21), and the use of data from Lloyd et al. (21) in a number of published economic evaluations, we decided to use data from Lloyd et al. (21) as the best estimate for utility decrement associated with an exacerbation in children. However, utility decrement from the adult population in Lloyd et al. (21) may not reflect the actual decrement in children due to the differences in asthma experience and perception of quality of life between children and adults.

Therefore, data from Briggs et al. (13) have been explored in a sensitivity analysis using the difference between the total control state and the exacerbation state (-0.216) to estimate the quality of life decrement from exacerbations. This sensitivity analysis is considered to provide an upper limit on the utility decrement attributable to exacerbation.

We accept that the estimates provided by Briggs et al. (13) and Lloyd et al. (21) probably underestimate the degree of utility loss in children with a severe or life-threatening acute exacerbation during the period of hospitalisation. This is because the utility values were not measured during the acute exacerbation period itself. In the MAGNETIC study, which estimated utility scores in children attending EDs with severe acute asthma, the utility was estimated to be reduced from a baseline of 0.88 to 0.516 during the initial acute period giving a utility decrement of 0.364. However, in the MAGNETIC trial, this more severe utility decrement was only applied until hospital discharge with the average length of hospital stay being 1 day. If we apply a decrement of 0.364 for 1 day and assume a loss of 0.2 in the remaining 6 days, the average utility loss over the whole week of exacerbation (-0.22) would be similar to that reported by Briggs et al. (13).

For patients without an exacerbation we have taken the baseline utility score for the control arm of the study by Willems et al. (5) as this provides an estimate based on the child version of the EQ-5D valued using the adult UK TTO valuation set. The population was Dutch children aged 7 to 18 with GINA severity stage I to III receiving standard outpatient care. The value applied to patients without an exacerbation will affect the calculation of absolute QALYs in each trial arm of the PLEASANT trial but does not affect the estimation of incremental QALY gain which goes into the cost-effectiveness ratio, as the PLEASANT study assumes that there is no impact of the letter intervention on survival. Therefore the selection of this data source is less critical than that used to determine the decrement attributable to exacerbations. The data that have been identified for the PLEASANT economic analysis are summarized in Table 7.

Table 7: Health state utility values to be applied in PLEASANT

Health state	**Health utility value**	**Description of state from source study**	**Measurement**	**Source**
Base case scenario				
No exacerbation	0.96 (sd 0.07)	Average baseline utility across children (n=27) aged 7 to 18 with GINA severity stage I to III receiving standard outpatient care in the Netherlands as part of the control arm of an RCT.	EQ-5D child version (filled out by parent for age<12). UK adult TTO valuation set	(5)
Exacerbation not requiring hospitalisation (including those managed in ED)	-0.10 relative to no exacerbation	Adult patients enrolled in a prospective observational study who have moderate or severe asthma (BTS 4 /5) at baseline and who have experienced one exacerbation requiring oral steroid treatment (without hospitalisation) in the previous 4 weeks (n=22)	EQ-5D UK adult valuation set	(21)
Exacerbation requiring hospitalisation	-0.20 relative to no exacerbation	Adult patients enrolled in a prospective observational study who have moderate or severe asthma (BTS 4 /5) at baseline who have experienced one exacerbation requiring hospitalisation in the previous 4 weeks (n=5)	EQ-5D UK adult valuation set	(21)
Sensitivity analysis				
No exacerbation	As per base case	As per base case	As per base case	As per base case
Any exacerbation	-0.216 relative to no exacerbation	Patients aged over 12 years (including adults) enrolled in the GOAL study who experienced an exacerbation (defined as deterioration in asthma requiring treatment with an oral corticosteroid, or an emergency department visit or hospitalisation)	AQLQ values mapped to EQ-5D (valuation set not stated)	(13)

3.0 Discussion

The review identified studies which differed in their objectives, study designs, population and outcome measurements which led to variations in the characteristics of the utility data provided. Only three studies were confined to children while most recruited mixed-aged populations comprised mainly of adults. Of these, only a few studies stratified HRQoL by age. Generalising utility from mixed-aged populations to children would disregard the fact that children have different perspective on HRQoL than adults (28). Among children and adolescents, utility values may also vary due to differences in cognitive development (29, 30). Therefore, future studies should stratify HRQoL in children by age groups.

The review focused on utility data which would meet the NICE reference case requirements. There were challenges in identifying preference-based utility data in children with asthma, particularly EQ-5D. Younger children do not have adequate cognitive ability to comprehend EQ-5D which was designed for adults. Thus, studies measuring HRQoL in young children relied on carer as proxy in the measurement (5, 6). However, proxy reported values were found to differ from those of children especially in chronic diseases such as asthma, since parents tend to underestimate the impact of asthma on physical activity of children (30). Additionally, valuations of EQ-5D were based on adults' tariff which may not represent children's perspective of health state values. Furthermore, EQ-5D was associated with lack of sensitivity in children due to ceiling effects (28). In view of these limitations and the lack of EQ-5D data in children with asthma, the systematic review was not constrained to utility values derived from EQ-5D, but included values estimated from other preference-based measures.

From the review, EQ-5D was used in 5 studies (35.7%), while children specific measurement such as HUI and PAHOM which were completed by children were reported at a lesser extent (14.3% each). Other validated instrument in children such as CHU-9D and EQ-5D-Y were not used in the reviewed studies. Self-reports from a child specific instrument is expected to provide a better representation of children's quality-of-life than proxy reports, but preference weights were usually elicited from adults or parents which still may not accurately represent children's perspective (28). Further research into the measurement of HRQoL in children is required particularly in the development of child-based tariffs. In addition, there is a need to

standardise outcome measurement in children for the purpose of cross-programme comparisons.

None of the studies directly measured the utility decrement due to asthma exacerbation using EQ-5D or other preference-based measures. In the absence of a robust estimate on the impact of exacerbation on HRQoL for children, utility data from adults identified from the review were selected as the best estimates to inform the PLEASANT economic analysis.

This systematic review was performed in accordance to methodological guidance from Papaioannou et al. (4). The scope of the review was kept broad to identify preference based utility values derived from other instruments than the EQ-5D. A comprehensive search strategy with no limitations of publication dates, language or study design was used. Nonetheless, non-English language full-texts were excluded during the study selection stage. A quality of life filter was adapted to include newly-developed preference-based measures for children to increase search sensitivity. In addition, full texts were referred to whenever abstracts were unclear as quality of life is seldom mentioned in abstracts. Studies were critically appraised for quality, relevance to the PLEASANT economic analysis and NICE reference case. This review also serves as a case study on how health state utilities are identified, critically reviewed and assessed for relevance to an economic model and the preferences of a decision-making body.

A synthesis of health state utility values to improve the precision of estimates was not performed because the populations of the included studies were not homogenous and varied in outcome measurements. Searching for unpublished studies, citation searches and authors-based searching was not conducted. However, an extensive search was performed by using several electronic databases and screening of reference lists to identify all relevant studies.

Given that published utility data derived using preference-based measure in children with asthma were lacking, future studies may consider incorporating utility measurement into the study design following recommendations from the ISPOR Task Force on Good Research Practices for Collecting Health-State Utility Estimates for Economic Models in Clinical Studies. The report is currently under development and will serve as a framework on planning collection of high quality data for economic models (31). Researchers should consider the ethical aspect of health utility assessment during asthma exacerbation as well as

the timing of assessment in order to capture the transient effect of the acute event on quality of life (31).

4.0 Conclusion

Various outcome measurements were used to measure health utilities in children with asthma. However, there is a lack of robust estimates on utility decrement in children with exacerbation which met the NICE reference case. Future studies should incorporate collection of health state utilities in children with asthma, taking into account the ethical and methodological considerations of HRQoL assessment during asthma exacerbation.

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Appendices

Appendix 1: Full search strategy

Search database	Search terms
MEDLINE / EMBASE	1. exp child/ 2. exp adolescent/ 3. (adolescen$ or teenager$ or teen$ or preteen$ or pre-teen$ or young$ or youth or young one$ or paediat$ or pediat$ or child$ or "young people").ti,ab. 4. 1 or 2 or 3 5. exp asthma/ 6. (asthma$ or (asthma$ adj exacerbate$) or "asthma exacerbation").ti,ab. 7. 5 or 6 8. 4 and 7 9. quality adjusted life year/ 10. quality adjusted life.tw. 11. (qaly$ or qald$ or qale$ or qtime$).tw. 12. disability adjusted life.tw. 13. daly$.tw. 14. health status indicators/ 15. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. 16. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. 17. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. 18. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. 19. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.

	20. (euroqol or euro qol or eq5d or eq 5d).tw. 21. (eq5d child$ or eq 5d child$ or eq5d-youth or eq-5d-y or EuroQol 5D-Youth or EQ-5D Youth or eq 5d youth).ti,ab. 22. (chu-9d or chu9d or Child Health Utility Index 9D).tw. 23. (asui or Asthma Symptom Utility Index).tw. 24. (hql or hqol or h qol or HRQoL or hr qol).tw. 25. (hye or hyes).tw. 26. health$ year$ equivalent$.tw. 27. health utilit$.tw. 28. (hui or hui1 or hui2 or hui3).tw. 29. disutili$.tw. 30. rosser.tw. 31. quality of wellbeing.tw. 32. qwb.tw. 33. willingness to pay.tw. 34. standard gamble$.tw. 35. time trade off.tw. 36. time tradeoff.tw. 37. tto.tw. 38. (preference-based or preference based).tw. 39. or/9-39 40. 8 and 40
COCHRANE LIBRARY (CDSR, HTA, NHS EED)	Search Name: pop(Children asthma) Utility(adapted) filter10 Last Saved: 04/07/2014 19:06:48.699 Description: revised 4/7/14 (eq-5d youth) - nhs eed, SR, HTA

	ID Search #1 MeSH descriptor: [Child] explode all trees #2 MeSH descriptor: [Adolescent] explode all trees #3 (adolescen* or teenager* or teen* or preteen* or pre-teen* or young* or youth or young one* or paediat* or pediat* or child* or "young people"):ti,ab #4 #1 or #2 or #3 #5 MeSH descriptor: [Asthma] explode all trees #6 (asthma* or (asthma*adj exacerbate*) or "asthma exacerbation"):ti,ab #7 #5 or #6 #8 #4 and #7 #9 MeSH descriptor: [Quality-Adjusted Life Years] explode all trees #10 quality adjusted life:ti,ab #11 (qaly* or qald* or qale* or qtime*):ti,ab #12 "disability adjusted life":ti,ab #13 daly*:ti,ab #14 MeSH descriptor: [Health Status Indicators] explode all trees #15 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six):ti,ab #16 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six):ti,ab #17 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve):ti,ab #18 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen):ti,ab #19 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty):ti,ab

	#20 (euroqol or euro qol or eq5d or eq 5d):ti,ab #21 (eq5d child* or eq 5d child* or eq5d-youth or eq-5d-y or EuroQol 5D- Youth or EQ-5D Youth or eq 5d youth):ti,ab #22 (chu-9d or chu9d or Child Health Utility Index 9D) #23 ("aql-5d" or "Asthma Quality of Life Utility Index- 5d" or "Asthma Quality of Life Utility Index- 5 dimension"):ti,ab #24 (asui or "Asthma Symptom Utility Index"):ti,ab #25 (hql or hqol or h qol or HRQoL or hr qol):ti,ab #26 (hye or hyes):ti,ab #27 health* year* equivalent*:ti,ab #28 health utilit*:ti,ab #29 (hui or hui1 or hui2 or hui3):ti,ab #30 disutili*:ti,ab #31 rosser:ti,ab #32 quality of wellbeing:ti,ab #33 qwb:ti,ab #34 willingness to pay:ti,ab #35 standard gamble*:ti,ab #36 time trade off:ti,ab #37 time tradeoff:ti,ab #38 tto:ti,ab #39 ("preference-based" or "preference based"):ti,ab #40 or/9-39 #41 #8 and #40 in Cochrane Reviews (Reviews and Protocols), Other Reviews, Technology Assessments and Economic Evaluations
SCHARRHUD	1. asthma* or (asthma*adj exacerbate*) or "asthma exacerbation"/ Any field
Econlit	1. (adolescen$ or teenager$ or teen$ or preteen$ or pre-teen$ or young$ or youth or young one$ or paediat$ or pediat$ or child$ or

	"young people").ti,ab. 2. (asthma$ or (asthma$ adj exacerbate$) or "asthma exacerbation").ti,ab. 3. 1 and 2 4. quality adjusted life.tw. 5. (qaly$ or qald$ or qale$ or qtime$).tw. 6. disability adjusted life.tw. 7. daly$.tw. 8. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. 9. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. 10. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. 11. (euroqol or euro qol or eq5d or eq 5d).tw. 12. (eq5d child$ version or eq 5d child$ version or eq5d-youth or eq-5d-y).tw. 13. (chu-9d or chu9d or Child Health Utility Index 9D).tw. 14. (aql-5d or Asthma Quality of Life Utility Index- 5d or Asthma Quality of Life Utility Index- 5 dimension).tw. 15. (hql or hqol or h qol or HRQoL or hr qol).tw. 16. (hye or hyes).tw. 17. health$ year$ equivalent$.tw. 18. health utilit$.tw. 19. (hui or hui1 or hui2 or hui3).tw. 20. disutili$.tw. 21. rosser.tw. 22. quality of wellbeing.tw.

	23. qwb.tw. 24. willingness to pay.tw. 25. standard gamble$.tw. 26. time trade off.tw. 27. time tradeoff.tw. 28. tto.tw. 29. (preference-based or preference based).tw. 30. or/4-29 31. 3 and 30

Appendix 2: Quality of life filter

Source / database	Filter
Original Quality of life (ISSG) MEDLINE/EMBASE	1. value of life/ 2. quality adjusted life year/ 3. quality adjusted life.tw 4. (qaly$ or qald$ or qale$ or qtime$).tw 5. disability adjusted life.tw 6. daly$.tw 7. health status indicators/ 8. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw 9. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw 10. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw 11. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw 12. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw 13. (euroqol or euro qol or eq5d or eq 5d).tw 14. (hql or hqol or h qol or HRQoL or hr qol).tw 15. (hye or hyes).tw 16. health$ year$ equivalent$.tw 17. health utilit$.tw

	18. (hui or hui1 or hui2 or hui3).tw 19. disutili$.tw 20. rosser.tw 21. quality of wellbeing.tw 22. quality of wellbeing.tw 23. qwb.tw 24. willingness to pay.tw 25. standard gamble$.tw 26. time trade off.tw 27. time tradeoff.tw 28. tto.tw 29. or/1-28
A) Adapted Quality of life (ISSG): MEDLINE/EMBASE	1. quality adjusted life year/ 2. quality adjusted life.tw. 3. (qaly$ or qald$ or qale$ or qtime$).tw. 4. disability adjusted life.tw. 5. daly$.tw. 6. health status indicators/ 7. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. 8. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. 9. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. 10. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. 11. (sf20 or sf 20 or short form 20 or shortform 20 or

	sf twenty or sftwenty or shortform twenty or short form twenty).tw. 12. (euroqol or euro qol or eq5d or eq 5d).tw. 13. (eq5d child* or eq 5d child* or eq5d-youth or eq-5d-y or EuroQol 5D- Youth or EQ-5D Youth or eq 5d youth).ti,ab. 14. (chu-9d or chu9d or Child Health Utility Index 9D).tw. 15. (aql-5d or Asthma Quality of Life Utility Index-5d or Asthma Quality of Life Utility Index- 5 dimension).tw. 16. (asui or Asthma Symptom Utility Index).tw. 17. (hql or hqol or h qol or HRQoL or hr qol).tw. 18. (hye or hyes).tw. 19. health$ year$ equivalent$.tw. 20. health utilit$.tw. 21. (hui or hui1 or hui2 or hui3).tw. 22. disutili$.tw. 23. rosser.tw. 24. quality of wellbeing.tw. 25. qwb.tw. 26. willingness to pay.tw. 27. standard gamble$.tw. 28. time trade off.tw. 29. time tradeoff.tw. 30. tto.tw. 31. (preference-based or preference based).tw. 32. or/1-31
B) Adapted Quality of Life (ISSG) Cochrane **QOL FILTER**	Search Name: QOL FILTER - 4/7/14 Last Saved: 04/07/2014 19:54:10.631 Description:

	ID Search #1 MeSH descriptor: [Quality-Adjusted Life Years] explode all trees #2 quality adjusted life:ti,ab #3 (qaly* or qald* or qale* or qtime*):ti,ab #4 "disability adjusted life":ti,ab #5 daly*:ti,ab #6 MeSH descriptor: [Health Status Indicators] explode all trees #7 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six):ti,ab #8 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six):ti,ab #9 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve):ti,ab #10 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen):ti,ab #11 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty):ti,ab #12 (euroqol or euro qol or eq5d or eq 5d):ti,ab #13 (eq5d child* or eq 5d child* or eq5d-youth or eq-5d-y or EuroQol 5D- Youth or EQ-5D Youth or eq 5d youth):ti,ab #14 (chu-9d or chu9d or Child Health Utility Index 9D) #15 ("aql-5d" or "Asthma Quality of Life Utility Index- 5d" or "Asthma Quality of Life Utility Index-

	5 dimension"):ti,ab #16 (asui or "Asthma Symptom Utility Index"):ti,ab #17 (hql or hqol or h qol or HRQoL or hr qol):ti,ab #18 (hye or hyes):ti,ab #19 health* year* equivalent*:ti,ab #20 health utilit*:ti,ab #21 (hui or hui1 or hui2 or hui3):ti,ab #22 disutili*:ti,ab #23 rosser:ti,ab #24 quality of wellbeing:ti,ab #25 qwb:ti,ab #26 willingness to pay:ti,ab #27 standard gamble*:ti,ab #28 time trade off:ti,ab #29 time tradeoff:ti,ab #30 tto:ti,ab #31 ("preference-based" or "preference based"):ti,ab #32 or/1-31

Appendix 3: Reasons for exclusion at titles and abstracts

Reasons	Number of studies excluded
Aged 18 years and above	175
Did not publish utility data	197
Non-asthma population	87
Non-English papers	8
Non preference based/ non-utility measure	158
Publication types	34
Total	659

Appendix 4: Reasons for exclusion at full-texts

Study	Reasons for exclusion
Janse et al., 2005	Used HUI3 but did not report utility data. Results were presented as percentage similarity in outcome measurements between physician and parents
Mo et al., 2004	Used HUI3 but did not report utility data. Results were presented as graphical differences of quality of life between diseases
Willems et al., 2009	Used EQ-5D but did not report utility data. Results were presented as EQ-5D interclass coefficients and Spearman coefficients between outcome measures
Burstrom et al., 2011	Used direct valuation using EQ-VAS as outcome measure (non–preference based) in Swedish children
Finnell et al., 2012	Utility data was obtained from an included study by Caroll and Downs (2009)
Brodtkorb et al., 2010	Utility data was presented as utility changes associated with intervention
Meadows et al., 2013	
Smith et al., 2004	
Wilson et al., 2010a	
Wilson et al., 2010b	