Economic evaluation of interventions for the treatment of asthma in children

Economic evaluation of interventions for the treatment of asthma in children: a systematic review

Luca Adél Halmai[1],

Aileen Rae Neilson [2],

Mary Kilonzo[3]

[1] The review was undertaken as part of an academic MSc dissertation research project at the University of Aberdeen, Present institutional affiliation: MediConcept Ltd., Health Economics Department (Budapest, Hungary)

[2] Edinburgh University, Usher Institute of Population Health Sciences and Informatics (School of Molecular Genetic and Population Health Sciences) (Edinburgh, United Kingdom)

[3] University of Aberdeen, Health Economics Research Unit (Aberdeen, United Kingdom)

Running title: Economic evaluation of paediatric asthma

Correspondence: Luca Adél Halmai, MediConcept Ltd., Health Economics Department (Budapest, Hungary), Email: l.a.halmai.16@aberdeen.ac.uk

Word count: 3,500 words

Number of tables and figures: 2

Number of supplementary appendix: 3

i Conflict of interests

There are no competing interests.

ii Funding information

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sector.

iii Abstract

Objectives: This systematic review aims to identify and critique full economic evaluations (EEs) of childhood asthma treatments with the intention to guide researchers and commissioners of paediatric asthma services towards potentially cost-effective strategies.

Methods: 'MEDLINE', 'Embase', 'Econlit', 'NHS EED', and 'CEA' databases were searched to identify relevant EEs published between 2005 and May 2017. Quality of included studies was assessed with a published checklist.

Results: Eighteen studies were identified and comprised one cost-benefit analysis, 11 cost-effectiveness analyses, one cost-minimisation analysis, and six cost-utility analyses. Treatments included pharmaceutical (n=11) and non-pharmaceutical (n=7) interventions. Fourteen studies identified cost-effective strategies. The quality of the studies varied and there were uncertainties due to the methods and relevance of data used.

Conclusion: Good quality economic evaluation studies of paediatric asthma treatments are lacking. EE of new technologies adapted to local settings is recommended and can result in cost-savings.

Key words: adverse childhood experience, asthma, child, cost-effectiveness, costs and cost analysis, economic evaluation, respiratory tract diseases, systematic review

iv Main text

Introduction

Asthma is a chronic inflammatory disease which narrows the airways[1] and leads to reduced airflow during inhalation and exhalation[2]. Asthma often manifests in childhood[3] and can lead to severe or life-threatening consequences. The disease cannot be cured[1]; however, it can be effectively treated by symptoms control and risk reduction against future adverse outcomes[3-6]. Treatment is substantial for all ages while the burden of symptoms impairs the patients' everyday life and has a considerable negative impact on its quality[7,8].

The management of asthma encompasses pharmaceutical[9,10] and non-pharmaceutical strategies (e.g. education techniques, self-management, and environmental controls[9]). In children, the disease control and management differ from those of the adult population. Until children fully possess emotional, cognitive and physical development to understand and manage the disease entirely on their own, their parents and caregivers have a considerable influence on their medical decisions[11].

Worldwide, the prevalence of asthma is roughly around 235 million as reported by the World Health Organisation (WHO). In the United Kingdom (UK) asthma affects approximately 5.4 million people (including about 1.1 million children), and the estimated cost of illness is around £1.1 billion, and it is likely to increase[9,12-14].

Systematic reviews (SRs) assessing the cost-effectiveness of treatments are essential to guide policy decisions about those interventions which offer 'good value for money' versus those which are of 'poor' value. Economic evaluations (EEs) are used to provide a rational and transparent decision-making framework to make well-informed decisions. In health care, EEs help to identify new alternatives and evaluate the evidence on the cost-effectiveness of different programs, by comparing the alternatives regarding both their costs and consequences/benefits[15].

Full EEs address both the costs and consequences. They have a similar method of assessing the costs. However, the method used to measure the benefits of the interventions is different[15].

- Cost-benefit analysis (CBA) - measures both the outcomes and costs in monetary units, e.g. willingness to pay (WTP);

- Cost-consequences analysis (CCA) - considers all the costs and benefits of the interventions and reports them without aggregation;
- Cost-effectiveness analysis (CEA) – uses natural units (e.g. life years gained, asthma attacks prevented) to assess the benefits. It involves the calculation of the incremental cost-effectiveness ratio (ICER), which shows the additional cost per unit of achieving an outcome while comparing it to an alternative treatment[16]. To measure the value for money, the ICER needs to be compared with a predefined cost-effectiveness threshold[15] that is applied to distinguish interventions which are cost-effective with ones which are not cost-effective;
- Cost-minimisation analysis (CMA) - focuses just on costs and assumes equal benefits;
- Cost-utility analysis (CUA) - expresses the outcome as a utility which incorporates the consumers' preferences into the valuation, typically measured as quality-adjusted life years (QALYs)[15].

A few SRs conducted of EE studies for the treatment of childhood asthma were identified. Ungar 2009[17] only assess paediatric population, while further reviews assessed both adult and paediatric population EEs[18-22]. This current review aimed to systematically review and critically appraise the literature of EEs that focusses specifically on paediatric asthma and takes a broader view of eligible treatments (both pharmaceutical and non-pharmaceutical interventions).

Methods

The search process, screening, data extraction and quality assessment was done by one reviewer (LH) based on pre-defined criteria. A second reviewer (AN) was involved when there was uncertainty.

Search strategy

A systematic search was performed to identify full EEs of paediatric asthma interventions published between 2005 and May 2017. English language articles were searched in multiple databases:

- 'CEA Registry',
- 'ECONLIT'
- 'EMBASE'
- 'National Health Service (NHS) Economic Evaluation Database (EED)',
- 'Ovid MEDLINE'.

An additional hand search was carried out for conference abstracts and study protocols identified in the online databases. The search strategy drew from recommended filters such as Kua et al.[23], NHS EED[24] and Cochrane Library[25]. The mixture of the following terms was employed to identify the study population: 'Adolescent', 'Teenager', 'Teen', 'Preteen', 'Pre-teen', 'Young', 'Youth', 'Young one', 'Paediatric', 'Children', 'Child' and 'Young people' and 'Child' and 'Adolescent' (MeSH). To identify the condition, 'Asthma' (MeSH) and 'Asthma,' 'Asthma exacerbation'. To recognise Randomized Control Trials (RCTs) and economic evaluations, terms from the research filters were used[24,25]. The search began in 2005 and included a two-year overlap with the formerly conducted SR[17]. This overlap reduces the possibility of missing relevant studies due to the methodological differences of the reviews (e.g. Ungar 2009[17] searched only two databases). Studies conducted in the joint period and covered in Ungar 2009[17] were excluded from the current review.

Study selection and Data extraction

Inclusion criteria:

- paediatric populations (<18 years)
- mixed-population (both adults and children) studies if separate analysis for children available
- no restriction on the interventions or comparators
- full EEs conducted alongside RCTs together with model-based EEs

Exclusion criteria:

- no population age reported
- no separate analysis for children in mixed-population studies
- RCTs with a small sample size (<20 children in each group)
- illnesses, diagnostic tests or those not directly assessing asthma treatment
- costing studies only
- qualitative studies, letters, editorials, case reports, SRs and reviews

Search results were summarised, and duplicates were filtered out both by hand and using RefWorks software. Initial screening was carried out at the title-abstract level, then the full-text article was assessed for the selected, potentially relevant or ambiguous studies.

Data extraction was based on Kua et al.[23] and Campbell et al.[18]. Information on the characteristics of the included studies (author, year, country, study design, setting, type of EE, population studied, comparators), details on their methods (perspective, time horizon, discount rate, costs, outcomes), results and conclusion were extracted.

The SR aimed to conduct a qualitative data synthesis and a narrative summary of the review findings.

Quality assessment of EEs

For appraising the quality of the selected studies, the ISPOR Consolidated Economic Evaluation Reporting Standards (CHEERS) statement[26] was used. CHEERS is a validated, 24-item checklist for judging the reporting quality of studies. Answers to the checklist include ‘yes’, ‘no’, ‘unclear’ or ‘not applicable’. When conducting the quality assessment of studies, the percentage of ‘yes’ answers given to the questions in the checklist were considered.

A narrative summary of the characteristics of the included studies, sources of unit costs and measures of benefits/outcomes was conducted to gain further potential information on their methodological quality.

Results

Following the removal of study duplicates, 200 titles and abstracts were screened from which 165 studies were excluded. Eighteen of the 35 studies selected to assess the full text met the inclusion criteria and were included in this review. Figure 1 contains details of the literature search process.

Main study characteristics

Most of the 18 studies[27-44] included originated from the United States of America (USA) [27,28,32,34,35,38,43], followed by the UK[29,31,36], Colombia[40,41], the Netherlands[42,44], Canada[30], Germany[37], Hong Kong[33] and Venezuela[39] (see Appendices).

The **population** in the studies represented a broad age range (0-18 years). Two studies[31,44] assessed a mixed-population, although only the results restricted to paediatric patients were considered. The **asthma type and severity** of the included studies differed, including allergic[37], persistent[35,40,41], acute[36,39] and chronic[31] asthma.

The **settings** of the studies varied: nine hospital-based[27,30,32,33,35,36,39,42,44] , three school-based[28,34,40], a hospital- and school-based[38], a study centre-based[43] intervention and four studies[29, 31, 37, 41] did not report the study setting.

The **type of EEs included,** ten CEAs[27,28,30,32-35,37,42,43], five CUAs[29,31,40,41,44], a CMA[39], a CBA[38], and one study[36] included both a CEA and CUA. According to study design, twelve studies were trials[28,32-39,42-44], and six were models[27,29-31,40,41].

To inform the estimates of treatment effectiveness, three models reported synthesising data from RCTs[29,40,41], one from an SR[30], one[31] from a meta-analysis and one model[27] did not state the source of data.

Eight studies[29,31-33,35,37-39] did not *explicitly* report the **perspective** of the study. Other studies used: societal[28], hospitals' [30], health care system[40,41] and both societal and health care system[27,42-44] perspectives.

The **time horizon** in modelling studies ranged from approx. four days[30] to ten years[29], while in trial based EEs was between a month[36] and three years[37].

Eleven studies[27,28,32-35,38,39,42-44] did not report whether they used **discounting** – which is a method for adjusting all future costs and benefits to their present day values[15], although discounting would not be appropriate in ten of these studies[27,28,32-35,38,42-44] as they used time horizons of less than one year. Five studies[30,31,36,40,41] reported that discounting was not required and two further studies used a discount rate of 3%[37], 3.5%[29].

Comparators/interventions

Eleven pharmaceutical[27,29-31,35-37,39-41,43] and seven non-pharmaceutical interventions[28,32-34,38,42,44] were identified. Two[28,33] of the **non-pharmaceutical interventions** included educational interventions:

- intensive asthma education program vs. standard program[33]
- "Power Breathing" program, which focuses on asthma education, control strategies, and their psychosocial effects vs. no intervention[28].

The further five studies[32,34,38,42,44] were management programs:

- Peer-led asthma self-management program vs. an adult-led one[38]
- School-Based Asthma Therapy (SBAT) program vs. no treatment[34]
- nurse-led tele-monitoring program vs. usual care (UC)[44]
- Real-Time Medication Monitoring (RTMM) with Tailored short message service (SMS) reminders vs. a control group without SMS reminders[42]
- parent mentor (PM) program which provided help and advice to families to enhance the children's asthma management vs. UC[32].

The eleven studies that included **pharmaceutical interventions**[27,29-31,35-37,39-41,43] examined the following treatments and comparators:

- prescribed and dispensed inhaled corticosteroids vs. UC[27]
- daily inhaled corticosteroids vs. Intermittent inhaled corticosteroids[40]
- omalizumab+ standard therapy vs. standard therapy[29]
- fluticasone propionate (FP) vs. montelukast (MON)[35,43]
- salmeterol/fluticasone propionate combination (SFC) corticosteroid vs. FP versus beclomethasone dipropriate (BDP)[31]
- budesonide (BUD) vs. FP vs. BDP[41]
- nebulised magnesium sulphate (MgSO4) vs. placebo[36]
- one dose of nebulised formoterol fumarate (FF) vs. three doses of nebulised Albuterol ampoules[39]
- Subcutaneous Specific Immunotherapy (SCIT) plus asthma medication vs. medication only[37]
- metered-dose inhaler (MDI) vs. wet nebulizer[30]

Outcomes

All CEAs assessed asthma-related outcomes such as: symptom-free days (SFD)[28,34], asthma control days[42,43]. The CBA study[38] calculated net cost savings and the CMA[39] contrasted the cost of two treatments after comparing the patient's vital parameters to confirm the two treatments were equal in terms of their effectiveness presumably. The primary outcome of CUAs[29,31,36,40,41,44] was QALYs.

Findings of the studies

The findings of the included studies are reported narratively because of the heterogenous nature of the data and the use of a meta-analysis was inappropriate. The use of a network meta-analysis was outside of the scope of this present study.

From the eleven CEAs (including Petrou et al.[36], which incorporated both a CEA and CUA), eight[27,28,32-34,36,37,42] compared the intervention to placebo, UC, control group or standard therapy and three[30,35,43] involved different active treatments. Within the group that compared the intervention to placebo, seven articles[27,28,32-34,36,37] stated that the new intervention was more cost-effective than the comparator. From the seven studies, only three[32,34,36] reported the ICER, which found that the cost-effectiveness of the SBAT program cost on average $10/an additional SFD gained. Petrou et al.[36] demonstrated that the MgSO4 along with the standard therapy could show 75.1% cost-effectiveness at the £1,000/unit decrement in Asthma Severity Score (ASS) (ICER=£189). The PM program[32] was associated with cost savings, attaining an ICER of -$597.10/asthma exacerbation-free day gained. Vasbinder et al.[42] concluded that there was no evidence on better asthma control in the intervention group except adherence and no difference in costs were identified, apart from the price of the SMS intervention.

Studies not reporting ICER showed positive results, for example, toward the "Power Breathing" program. This program was more cost-effective than the control group with the cost of $3.90/participant/SFD gained[28].. Reinhold et al.[37] estimated the probability of SCIT being cost-effective at around 90%. Ng et al.[33] reported that the intensive asthma programs could be less costly, as it was associated with HK$969 net saving per patient. Andrews et al.[27] found that switching to an alternative delivery method could be beneficial both clinically and financially. The medication "dispensing" arm was linked with $7,000 total cost savings compared to UC.

The three trial-based CEAs[30,35,43] that compared active treatments revealed cost-effective therapies. The MDI was associated with an ICER of CA$2,499/admission averted compared to the wet nebulization technique[30]. The treatment with FP was cost saving[43]. Ostrom et al.[35] found that asthma-related costs were not only lower for FP, but it was also more effective than MON (no ICER reported).

Three CUAs[29,36,44] included the use of UC as the comparator but none of the studies showed positive results in favour of the new intervention. Willems et al.[44] found that the nurse-led tele-monitoring program had only 22% probability of being cost-effective at the €40,000/QALY threshold. Petrou et al.[36] found that the probability of the nebulized MgSO4 being cost-effective at the accepted threshold level was only 68.6%. Burch et at[29] revealed that the use of omalizumab for children age six-eleven is not cost-effective at the £20,000-30,000/QALY threshold (ICER=£91,169).

Three further CUAs[31,40,41] that compared active treatments found that as stated in Rodriguez-Martinez et al. 2013[41] BDP was the most cost-effective method when the WTP was below £21,129.22/QALY. Doull et al.[31] found a particular type of SFC (Evohaler) to be the most cost-effective with the ICER £15,739/QALY gained. In Rodriguez-Martinez et al. 2015[40] daily therapy with ICS was considered dominant.

Rhee et al.[38], (CBA), found that the peer-led program yields more healthcare cost savings than the adult-led one. Rodriguez et al.[39], (CMA), revealed that using a single dose of nebulised FF powder could not only be simpler but also cheaper than three doses of nebulised Albuterol ampoules.

Quality assessment of the included EEs and evidence

The average reporting quality score of the studies based on the CHEERS checklist was 70.61%, standard deviation: 13.88% (see Table 1). Summarising the results of the checklist shortcomings in describing uncertainty, price date and conversion details, discounting were identified. However, the included studies seem to be strong in reporting general information when conducting an EE (e.g. time horizon, health outcomes, model assumptions for models, settings or location), and at describing limitations and study findings (see Appendices).

Discussion

Main findings

This SR provides a summary of recent treatments available to treat childhood asthma. The SR focussed specifically on the paediatric population which allowed us to include a broad scope of asthma treatments that is slightly different than in other recent reviews.

A total of the 18 studies[27-44] were included in this review which incorporated various asthma therapies with differing degree of cost-effectiveness. The studies were heterogeneous as they originated from different countries, the year of publication varied, and they included different types of EEs and various outcomes. The reporting quality of the studies varied greatly. Key aspects of the methodology of the included studies were further examined, and the investigation suggests uncertainties around the results due to the methods and the relevance of the data used. The age range of the study population differed in the studies, and some of them accepted 17-18 years old patients[30,38,39,41], who might not appropriately represent children; moreover, the detailed information on the distribution of age and gender in the groups were incomplete. Information on allocation concealment, blinding, and loss to follow-up were not available in each trial.

The time horizon of the studies was relatively short even in the models. The lack of examination of long-term consequences begs the question of whether the results of the studies would still be robust when extrapolated to a longer period or a lifetime. Also, sensitivity analyses were not contained in all studies to explore any uncertainty (surrounding model assumptions, data sources etc.) and their potential impact on the study results.

The interpretation and comparability of results were restricted since the asthma treatment protocol, and clinical guidelines differed in the countries, meaning that some essential asthma medications were not available in low and middle-income countries[40], or the dose of medicines was not licensed for specific age groups[31].

Some studies remarked at the lack of research available on their topic. Studies[31,37] experienced restrictions in comparing their results with the findings of previous research because those were not available or they[32,36,39,43] outlined that their research was the first in examining the cost-effectiveness of the particular treatment. The generalisability of the results to other similar settings and populations with the same characteristics should be confirmed by future research[28,32,36] with, for example, a larger sample size for trial-based EEs.

Two studies[27,41] hinted that the unit costs they used, might not be representative of the whole asthma paediatric population of the country. Furthermore, studies[30,31,38] acknowledged that the preferences they used might be misleading. Preferences are patient-reported values that are converted to an index score to measure the health-related quality of life[45]. Four studies[29,31,36,44] reported the use of EuroQol five-dimensions questionnaire (EQ-5D) or Short-Form Six-Dimension questionnaire (SF-6D) to obtain the preferences. Rodriguez-Martinez et al. 2013[41] and 2015[40] reported the use of a health state utility valuation survey. However, the National Institute for Health and Care Excellence (NICE) recommends the use of the EQ-5D to obtain utility scores, it is not validated in children[46]. That is, a value set for children does not yet exist and so most EE studies apply the adult value set instead to obtain health state utility values for children. Both Noyes et al.[47] and Willems et al.[48] used EQ-5D in their research and they recommend its use.

Generalisability was limited due to the diverse cost sources, differing perspectives which means that different types of costs were considered in each perspective.

The current review faces similar difficulties in cross-study comparison as Kim et al.[20] does and it supports the need for standardised data sources and methods. Similar to the general findings of Rodriguez-Martinez at al. 2018[22] the results of our review also found the quality of the reporting of the study methods to be variable, so introducing the potential for some uncertainties in several important aspects relating to the methods and relevance of data used.

The strengths and limitations reported by the study authors' themselves suggest that the current quality of the economic evidence base appears to be moderate and there is some uncertainty around the long-term cost-effectiveness and generalisability of the study's findings.

However, the review can further guide the design of future EEs by highlighting key parts that should be considered when conducting a study or publishing it. To improve the current landscape of EEs of paediatric asthma interventions research with high quality of evidence, relevant and robust methods is needed.

Context with other reviews

SRs have been identified that contain EE studies concerning the treatment of childhood asthma. While Ungar[17] is limited to paediatric population, the others assess both adult and

paediatric population. Though the full search strategy of the study[17] was not available to the researcher to make comparisons, it showed similarities with the current research.

Ungar 2009[17] was based on primary data from 2002 to 2007 and included economic models or RCTs. As a result of the overlap in the search period of the two reviews, four studies[49-52] of Ungar 2009[17] were captured by the searches of the current review and were excluded.

Four further studies[31,33,35,44] were identified from the common time period of the two reviews and were identified from a database used in both reviews but were not included in Ungar 2009[17]. Therefore, differences in the search strategies of the studies can be assumed.

Ungar 2009[17] identified ten studies over the five-year period and included both pharmaceutical and non-pharmaceutical interventions, though the number of pharmaceutical interventions was lower (30%, vs. 61% in the present review). The non-pharmaceutical care interventions were the same as the current review. Similar limitations were detected in the two reviews.

The current review did not show an increasing trend in the total number of EE studies in the field of paediatric asthma treatments, however, the proportion of studies examining pharmaceutical treatments increased since the previous review[17].

Both reviews emphasised that explicit statements about the perspective of the studies and WTP threshold were necessary to interpret the results of EEs. Furthermore, the current review confirmed the lack of enough, high-quality research on the matter of childhood asthma.

Strengths and Limitations

This SR searched five databases and followed formerly tested search protocols. An additional hand search was carried out. Study selection followed the PRISMA recommendations. The search was not limited by the type of EE, intervention or outcome measure. However, some limitations need to be noted. Only English language publications were considered meaning that potential articles published in other languages were left out. Including the use of the CHEERS, the methodology of the studies was not examined by a formerly tested checklist. The screening and data extraction were done by one reviewer. However, pre-defined criteria for both processes stated in the protocol was applied. One additional study[53] was identified through the publishing process that was not captured by our search strategy but is potentially eligible for inclusion. We acknowledge that this might be a limitation of our SR.

Conclusion

There remains a lack of good quality EE studies in the field of paediatric asthma treatments and further research is needed for allocation decisions. Research with high quality of evidence, relevant and robust methods, which includes studying the long-term effects of the treatments is essential. Furthermore, the use of a utility measure validated in children is necessary. The use of non-pharmaceutical programs, such as management techniques, along with medicines is encouraged as they can improve disease management. Besides, the simplification of medication dosing seems to be effective. EE of new technologies adapted to local settings is recommended as new treatments can be more cost-effective than the UC or standard therapy.

Contributors

LH: Conducted the systematic review as part of her MSc research project and drafted the manuscript.

AN & MK: Contributed to the search strategy, supervised the review process and commented on the manuscript.

v Acknowledgement

Not applicable

vi References

1. Mayo Clinic. Mayo Clinic - Diseases and Conditions. Diseases and Conditions Asthma. 1988-2017. Available at: http://www.mayoclinic.org/diseases-conditions/asthma/basics/definition/con-20026992. Accessed May 14, 2017.
2. WHO. World Health Organisation. Chronic respiratory diseases. 2017. Available at: http://www.who.int/respiratory/asthma/definition/en/. Accessed May 14, 2017.
3. Global Initiative for Asthma. www.ginasthma.org - Global Strategy for Asthma Management and Prevention. Global Strategy for Asthma Management and Prevention. 2016. http://ginasthma.org/wp-content/uploads/2016/04/GINA-2016-main-report_tracked.pdf. Accessed May 11, 2017.
4. Moorman JE, Rudd RA, Johnson CA, et al. National surveillance for asthma—United States, 1980–2004. MMWR Surveill Summ. 2007;56(8):1-54.
5. Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. European Respiratory Journal. 2008;31:143-178.
6. Global Initiative for Asthma. www.ginasthma.org - Global Strategy for Asthma Management and Prevention. 2014. http://ginasthma.org/wp-content/uploads/2016/01/GINA_AtAGlance_2014.pdf. Accessed May 11, 2017.
7. Barnes PJ, Casale TB, Dahl R, Pavord ID, Wechsler ME. The Asthma Control Questionnaire as a clinical trial endpoint: past experience and recommendations for future use. Allergy. 2014;69(9):1119-1140.
8. Dean BB, Calimlim BC, Sacco P, Aguilar D, Maykut R, Tinkelman D. Uncontrolled asthma: assessing quality of life and productivity of children and their caregivers using a cross-sectional Internet-based survey. Health and quality of life outcomes. Health and quality of life outcomes. 2010;8(1):96.
9. Yong YV, Shafie AA. Economic evaluation of enhanced asthma management: a systematic review. Pharmacy Practice. Oct-Dec 2014;12(4):493.
10. Shanmugam S, Varughese J, Nair ,MAS, et al. Pharmaceutical care for asthma patients: A Developing Country's Experience. Journal of Research in Pharmacy Practice. 2012;1(2):66–71.

11. Ungar WJ, Economic Evaluation in Child Health, New York: Oxford University Press DOI:10.1093/acprof:oso/9780199547494.001.0001, 2009, pp. 3-32, 197-209, 289-302.

12. Asthma UK. Annual Asthma Survey 2016 report. Available at: https://www.asthma.org.uk/globalassets/get-involved/external-affairs-campaigns/publications/annual-asthma-care-survey/annualasthmasurvey2016final.pdf. Accessed May 27, 2017.

13. Asthma UK. Asthma deaths in UK at highest level in over a decade. Asthma UK. Aug 31, 2016. Available at: https://www.asthma.org.uk/about/media/news/asthma-deaths-uk-highest-level-in-over-a-decade/. Accessed July 24, 2017.

14. WHO. World Health Organisation - Asthma. April 2017. Available at: http://www.who.int/mediacentre/factsheets/fs307/en/. Accessed May 29, 2017.

15. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for Economic Evaluation of Health Care Programmes, 3rd ed., New York: Oxford University Press, 2005, pp. 1-240, 277-359.

16. Donaldson C, Mugford M, Vale L. Evidence-based Health Economics - From eddectiveness to efficiency in systematic review. London: BMJ Books; 2002.

17. Ungar WJ, Economic evaluation in child health, Sullivan JD and Campbell SD, Eds., New York: Oxford University Press DOI:10.1093/acprof:oso/9780199547494.001.0001, 2009, pp. 197-209.

18. Campbell JD, Spackman DE, Sullivan SD. Health economics of asthma: assessing the value of asthma interventions. Allergy. 2008:63: 1581-1592.

19. McQueen RB, Sheenan D, Whittington M, van Boven J, Campbell J. Cost-Effectiveness of Biological Asthma Treatments: A Systematic Review and Recommendations for Future Economic Evaluations. PharmacoEconomics. 2018;36(8):957–971.

20. Kim C, Dilokthornsakul P, Campbell J, van Boven J. Asthma Cost-Effectiveness Analyses: Are We Using the Recommended Outcomes in Estimating Value? J Allergy Clin Immunol Pract. 2018;6(2):619-632.

21. Dominguez-Ortega J, Phillips-Angles E, Barranco P, Quirce S. Cost-effectiveness of asthma therapy: a comprehensive review. J Asthma. 2015;526:529-537

22. Rodriguez-Martinez C, Sossa-Briceño M, Castro-Rodriguez J. Cost Effectiveness of Pharmacological Treatments for Asthma: A Systematic Review. Pharmacoeconomics. 2018;36(10):1165-1200.

23. Kua WS, Davis S. Systematic review of health state utilities in children with asthma. The University Of Sheffield - Health Economics & Decision Science (HEDS) Discussion Paper Series. 2016.

24. Centre for Reviews and Dissemaination. Centre for Reviews and Dissemaination - Search strategies. 2017. Available at: http://www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedmedline. Accessed June 2, 2017.

25. The Cochrane Collaboration, Cochrane Handbook for Systematic Reviews of Interventions, Higgins JPT and Green S, Eds., England: John Wiley & Sons Ltd., 2008, pp. 3-383, 449-554.

26. Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. Value in Health. 2013;16(2):231-250.

27. Andrews AL, Teufel RJ, Basco WT, Simpson KN. A cost-effectiveness analysis of inhaled corticosteroid delivery for children with asthma in the emergency department. The Journal of pediatrics. 2012;161(5):903-907.

28. Atherly A, Nurmagambetov T, Williams S, Griffith M. An economic evaluation of the school-based “power breathing” asthma program. Journal of Asthma. 2009;46(6):596-599.

29. Burch J, Griffin S, McKenna C, et al. Omalizumab for the treatment of severe persistent allergic asthma in children aged 6-11 years: a NICE single technology appraisal. Pharmacoeconomics. 2012;30(11):991-1004.

30. Doan Q, Shefrin A, Johnson D. Cost-effectiveness of metered-dose inhalers for asthma exacerbations in the pediatric emergency department. Pediatrics. 2011;127(5):e1105-e1111.

31. Doull I, Prince D, Thomas M, et al. Cost-effectiveness of salmeterol xinafoate/fluticasone propionate combination inhaler in chronic asthma. Current medical research and opinion. 2007;23(5):1147-1159.

32. Flores G, Bridon C, Torres S, et al. Improving asthma outcomes in minority children: a randomized, controlled trial of parent mentors. Pediatrics. 2009;124(6):1522-1532.

33. Ng DK, Chow PY, Lai WP, Chan KC, Tsang BL, So HY. Effect of a structured asthma education program on hospitalized asthmatic children: a randomized controlled study. Pediatrics international. 2006;48(2):158-162.

34. Noyes K, Bajorska A, Fisher S, Sauer J, Fagnano M, Halterman JS. Cost-effectiveness of the school-based asthma therapy (SBAT) program. Pediatrics. 2013;131(3):e709-e717.

35. Ostrom NK, Decotiis BA, Lincourt WR, et al. Comparative efficacy and safety of low-dose fluticasone propionate and montelukast in children with persistent asthma. The Journal of pediatrics. 2005;147(2):213-220.

36. Petrou S, Boland A, Khan K, et al. Economic evaluation of nebulized magnesium sulphate in acute severe asthma in children. International journal of technology assessment in health care. 2014;30(04):354-360.

37. Reinhold T, Ostermann J, Thum-Oltmer S, Brüggenjürgen B. Influence of subcutaneous specific immunotherapy on drug costs in children sufferingfrom allergic asthma. Clinical and translational allergy. 2013;3(1):30.

38. Rhee H, Pesis-Katz I, Xing J. Cost benefits of a peer-led asthma self-management program for adolescents. Journal of Asthma. 2012;49(6):606-613.

39. Rodriguez E, Vera V, Perez-Piugbo A, et al. Equivalence of a single saline nebulised dose of formoterol powder vs three doses of nebulised Albuterol every twenty minutes in acute asthma in children: a suitable cost effective approach for developing nations. Allergologia et immunopathologia. 2008;36(4):196-200.

40. Rodriguez-Martinez CE, Nino G, Castro-Rodriguez JA. Cost-utility analysis of daily versus intermittent inhaled corticosteroids in mild-persistent asthma. Pediatric pulmonology. 2015;50(8):735-746.

41. Rodríguez-Martínez CE, Sossa-Briceno MP, Castro-Rodriguez JA. Cost-utility analysis of the inhaled steroids available in a developing country for the management of pediatric patients with persistent asthma. Journal of Asthma. 2013;50(4):410-418.

42. Vasbinder EC, Goossens LMA, Rutten-van Molken MPMH. e-Monitoring of Asthma Therapy to Improve Compliance in children (e-MATIC): a randomised controlled trial. European Respiratory Journal. 2016;48:758-767.

43. Wang L, Hollenbeak CS, Mauger DT, et al. Cost-effectiveness analysis of fluticasone versus montelukast in children with mild-to-moderate persistent asthma in the Pediatric Asthma Controller Trial. Journal of Allergy and Clinical Immunology. 2011;127(1):161-166.

44. Willems DC, Joore MA, Hendriks JJ, Wouters EF, Severens JL. Cost-effectiveness of a nurse-led telemonitoring intervention based on peak expiratory flow measurements in asthmatics: results of a randomised controlled trial. Cost Effectiveness and Resource Allocation. 2007;5(1):10.

45. (York) YHEC. Preference-Based Measures [online]. 2016. Available at: http://www.yhec.co.uk/glossary/preference-based-measures/. Accessed August 06, 2018.

46. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. 2017. Available at: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case#measuring-and-valuing-health-effects. Accessed July 20, 2017.

47. Noyes J, Edwards R. EQ-5D for the assessment of health-related quality of life and resource allocation in children: a systematic methodological review. Value in Health. 2011;14(8):1117-1129.

48. Willems D, Joore M, Nieman F, Severens J, Wouters E, Hendriks J. Using EQ-5D in children with asthma, rheumatic disorders, diabetes, and speech/language and/or hearing disorders. International journal of technology assessment in health care. International Journal of Technology Assessment in Health Care. 2009;25(3):391-399.

49. Kattan M, Stearns S, Crain Eea. Cost-effectiveness of a home-based environmental intervention for inner-city children with asthma. J Allergy Clin Immunol. 2005;116(5):1058–63.

50. Polisena J, Tam S, Lodha A, Laporte A, Coyte P, Ungar W. An economic evaluation of asthma action plans for children with asthma. J Asthma. 2007;44(7):501-8.

51. Sullivan S, Lee T, Blough D ea. A multisite randomized trial of the effects of physician education and organizational change in chronic asthma care: cost-effectiveness analysis of the Pediatric Asthma Care Patient Outcomes Research Team. Arch Pediatr Adolesc Med. 2005;159(5):428-34.

52. Karnick P, Margellos-Anast H, Seals G, Whitman S, Aljadeff G, Johnson D. The pediatric asthma intervention: a comprehensive cost-effective approach to asthma management in a disadvantaged inner-city community. J Asthma. 2007;44(1):39-44.

53. Rodriguez-Martinez CE, Sossa-Briceño MP, Castro-Rodriguez JA. Cost–utility analysis of once-daily versus. Journal of Asthma. 2016: DOI: 10.3109/02770903.2015.1116087

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow diagram of the search process

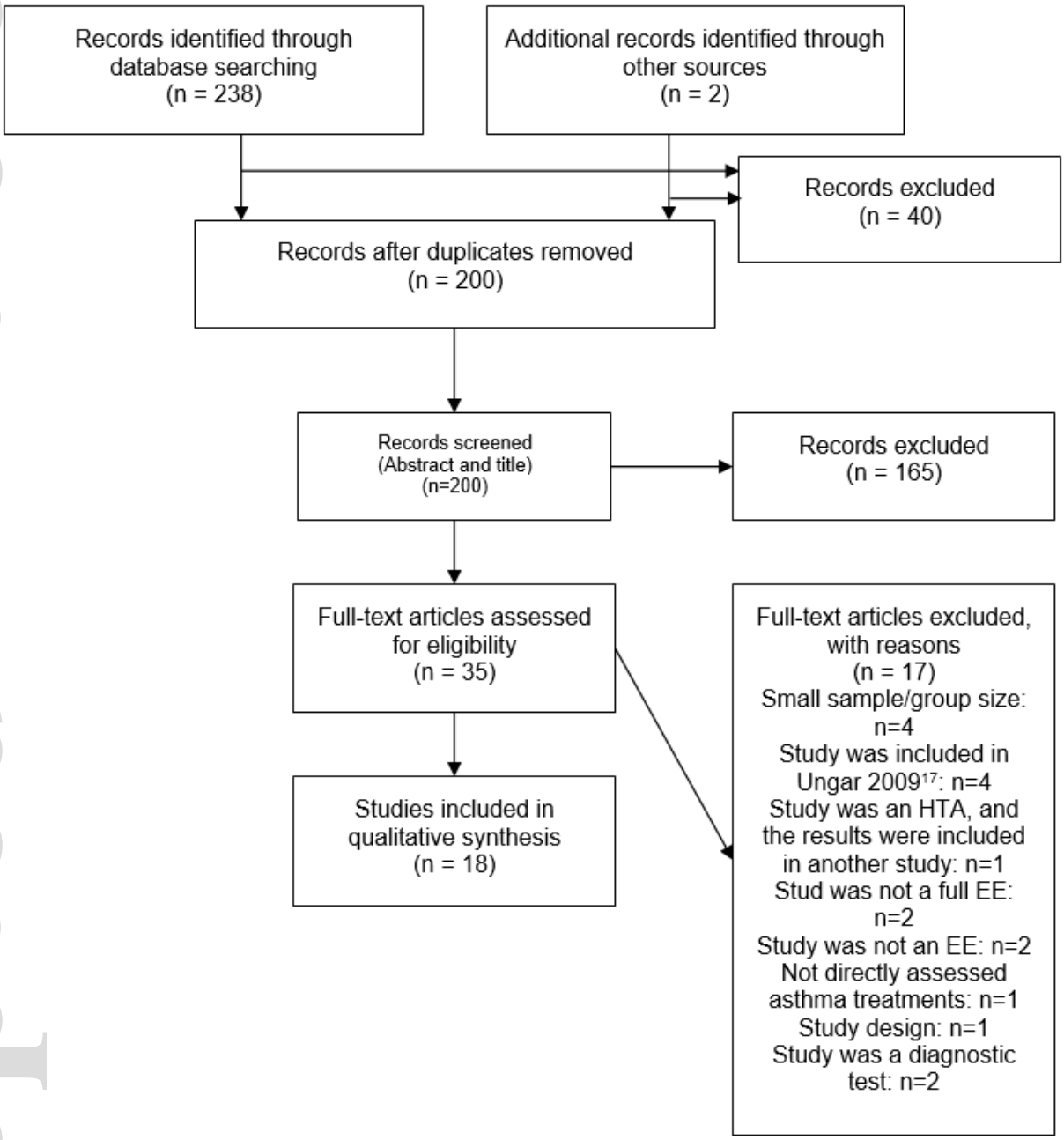

Table 1 Results of the CHEERS checklist

Author	CHEERS score†
Wang, 2011[43]	91%
Rodriguez-Martinez, 2015[40]	88%
Petrou, 2014[36]	87%
Willems, 2007[44]	87%
Rodriguez-Martinez, 2013[41]	80%
Noyes, 2012[34]	78%
Rhee, 2012[38]	78%
Doull, 2007[31]	76%
Doan, 2011[30]	72%
Below average‡	
Flores, 2009[32]	70%
Vasbinder, 2016[42]	70%
Andrews, 2012[27]	68%
Ostrom, 2005[35]	61%
Ng, 2006[33]	57%
Reinhold, 2013[37]	57%
Burch, 2012[29]	56%
Atherly, 2009[28]	52%
Rodriguez, 2008[39]	43%

† CHEERS score represents the percentage of 'yes' answers

‡ Average score: 70.61%; standard deviation: 13.88%

Appendices

Appendix Table 1: Models (Data extraction table)

Author, year	Country	Study design /Type of economic evaluation	Comparators	Setting	Study perspective	Time horizon	Discount rate	Costs	Outcomes	Results/ICER (if applicable)	Main conclusion	CHEERS (%)
Andrews, 2012[27]	USA	Model *(Decision tree)* CEA	1. prescribed ICS 2. dispensed ICS 3.UC	Hospital-based	1. Health system (USA) 2. Societal perspective	1 months	Not reported	Direct + indirect costs: UC = $27100, Uniform prescribing = $22000 and Uniform dispensing = $20100	1. Return to ED/100 patients within a month	ICER not reported Total cost saving per 100 patients comparing the UC with medication dispensing arm is $7000	Both prescribing and dispensing of ICS is an alternative approach clinically and financially	68
Burch, 2012[29]	UK	Model *(Markov model)* CUA	1. omalizumab + standard therapy 2. standard therapy	Not explicitly reporter (the study suggests NHS England and Wales)	1. Not explicitly reported (the study suggests an NHS perspective)	10 years	3.5%	actual cost of omalizumab at the time of the analysis was used	1. QALYs	Base-case ICER £91169/QALY in a subgroup analysis ICER £65911/QALY ICER threshold: £20000-30000 per QALY	NICE does not recommend the routine use of omalizumab for children age 6-11	56
Doan, 2011[30]	Canada	Model CEA	1. MDI 2. wet nebulization	Hospital-based	1. Hospital	Time of the ED admission to 2 days post-ED admission (average admission is 48-hours) ≈4 days	Not require	Treat a patient in the ED with : - MDI = CAN$262.73 - wet nebulizer= CAN$417.68	1. Disposition from ED	ICER -CA$2499.16 /admission averted Using MDI may result in Can$154.95 net saving per patient	MDI yield significant cost savings for hospitals, HC systems and families	72
Doull, 2007[31]	UK	Model CUA	1. SFC 2. FP (current and increased dose) 3. (estimates for BDP)	Not reported	1. Not reported	1 year	Not required	Price of FP = £178.97 Price of SFC (Accuhaler/ Evohaler) = £379.86/ £230.11	1. QALYs	SFC Evohaler vs increased dose FP ICER £15739/QALY and Accuhaler ICER £63736/QALY SFC compared to FP resulted in annual cost saving $47-77	Switch to SFC is a cost-effective approach	76
Rodriguez-Martinez, 2013[41]	Colombia	Model *(Markov model)* CUA	1. FP 2. BUD 3. ciclesonide 4. BDP	Not reported	1. National HC system (Colombia)	12-months	Not required	BDP average cost/unit= £106.16 FP average cost/patient = £231.19	1. QALYs	ICUR (FP vs BDP) £19,835.28/QALY BDP was associated with the lowest cost, FP resulted in greatest QALYs	BDP is the most cost-effective method to threat paediatric patients, when WTP is less than £21,129.22/QALY, otherwise FP, which has 18% probability for being cost-effective at WTP £9803.96/QALY	80

Rodriguez-Martinez, 2015[40]	Colombia	Model *(Markov model)* CUA	1. daily ICS therapy 2. intermittent ICS therapy	School-based	1. National HC system (Colombia)	12-months	Not required	School patients: Daily ICS=$437.02 Intermittent=$585.03 Prechool patients: Daily ICS=$704.02 intermittent=$749.81	1. QALYs	ICER was not calculated as the daily therapy was dominant School children: daily therapy had lower costs and greater gain in QALYs (0.9629 vs 0.9392) on average /patient over the 12 months. Pre-schoolers: daily therapy also had lower costs and greater gain in QALYs (0.9238 vs 0.9130 QALY on average /patient over the 12 months.	Daily therapy is more cost-effective with greater gain in QALYs and lower total treatment costs	88

ICS- Inhaled corticosteroids; UC- Usual care ; MDI- Metered-dose inhaler ; FP- Fluticasone propionate; BUD- Budesonide; BDP- Beclomethasone dipropriate; SFC- Salmeterol; ED- emergency-related; QALY- Quality-adjusted life year; ICER- Incremental cost-effectiveness ratio; ICUR- Incremental cost-utility ratio; HC – Health Care

Appendix Table 2: Trials (Data extraction table)

Author/year	Country	Study design/Type of economic evaluation	Comparators	Setting	Study perspective	Time horizon	Discount rate (%)	Costs	Outcomes	Results/ ICER (if applicable)	Main conclusion	CHEERS (%)
Atherly, 2009[28]	USA	Quasi-experimental CEA	1. "Power Breathing" educational intervention 2. control group	School-based	1. Societal	3-months follow-up	Not reported	Annualized cost to respondent was estimated to be $6,500, $30.37 per student	1. SFD	Not reported The program showed a statistically significant impact with greater decline in symptoms in the intervention group. The program costs approx. $3.9/symptom free day gained. Other interventions (BUD) cost approx. $11/SFD gained.	Power Breathing interventions is cost-effective.	52
Flores, 2009[32]	USA	RCT CEA	1. PM 2. traditional asthma care	Hospital-based	1. Not reported	1 year	Not reported	- Average monthly cost for PM per patient = $60.42, - Intervention cost = $120.84/child	1. Reduction of asthma exacerbation days	ICER -$597.10 /asthma exacerbation-free days gained, For high-participation group (attended ≥25% of meetings and completed ≥50% of telephone contacts) ICER -$46.16/ asthma exacerbation-free days gained	PMs are associated with reasonable costs and net savings	70
Ng, 2006[33]	Hong Kong	Prospective randomised single blinded controlled trial CEA	1. Intensive asthma education program (B) 2. standard asthma education program (A)	Hospital-based	1. Not reported	3 months	Not reported	Average cost of public ward services is HK$1702/day Hospitalisation in standard program/child HK$6213 and HK$5003 in the intensified program. Extra cost in group B is nursing fee/hour HK$241/ patient.	1. Number of visits to the ED 2. Number of hospitalisations	Not reported Improved health outcomes and the net saving is HK$969/ patient.	Intensive asthma education program might be more cost-effective	57
Noyes, 2012[34]	USA	Based on SBAT Trial CEA	1. School-Based Asthma Therapy 2. UC	School- based	1. Medicaid	One school year (approximately 7-9 months)	Not reported	SBAT program costs= $4822 /100 children/ month, Total costs: SBAT=$12463 UC=$10880	1. SFD	Total direct costs: $28 per SFD 95%CI(418 to 75) Total costs: $10 per SFD gained (-4 to 46) The net saving due to the intervention was $3,240. SBAT schools could save on average $1,146 in lost revenue compared to UC schools.	SBAT was cost-effective in reducing symptoms in urban children with asthma compared to existing programs	78

Ostrom, 2005[35]	USA	Randomised double-blind, double-dummy, parallel-group study CEA	1. FP 2. MON	Hospital-based	1. Not reported	12 weeks	Not reported	Daily cost for FP was $1.08, for MON $3.05 and $0.11/puff for albuterol; costs for asthma related outpatient/clinic visits($286.85) and hospitalisation ($3,796)	1. Percent change in morning pre-dose FEV1	Not reported Main daily total asthma-related cost/patient in the FP group was approx. one third of the costs in MON ($1.25 SD=0.41 vs $3.49 SD=0.5); the total asthma-related costs/ successfully treated patient (achieved ≥15%FEV1) was lower in FP group compared to MON group ($4.03 vs $17.45).	Asthma-related costs are lower in FP and it is also more effective	61
Petrou, 2014[36]	UK	Prospective RCT CEA, CUA	1. MgSO4 2. isotonic saline (placebo)	Hospital-based	1. NHS 2. personal social services	The time horizon extended to discharge and to 1 month post-randomization for the purposes of the CUA	Not required	Mean total health and social service (societal) cost were GBP1,067 (GBP 1,157) in MgSO4 GBP 1,119 (GBP1,202) in the placebo group	1. unit change in ASS (CEA) 2. QALYs (CUA)	CEA: ICER £189/unit decrement in ASS and it had 75.1% probability of being cost-effective at £1000 unit per decrement in ASS threshold and 36.6% probability of being less costly CUA: MgSO4 had a 67.6% probability of being cost-effective at a £20000/ QALY gained threshold and 69.1$ probability of being less costly	The probability of CE of nebulized MGSO4, given as an adjuvant to standard treatment is less than 70% across accepted CE threshold for an additional QALY	87
Reinhold, 2013[37]	Germany	Piggy back analysis – randomized control multi-center study CEA, cost-analysis, break even analysis	1. SCIT with asthma medication 2. asthma medication only	Not reported	1. Not reported	3-years	3%	SCIT in 2012 were assumed to be about €1597 over the 3-years intervention period Total mean costs per patient for SCIT 770€ 95%CI [701 to 839] and for controls €383 95%CI [317 to 449]	1. Mean annual morning peak flow	Not reported SCIT (with Acraoid) is associated with superior effectiveness, the mean adjusted morning peak flow over the 3 years of SCIT intervention shows higher values. The probability that SCIT leads to superior effectiveness compared to controls is about 90%	Intervention reduces asthma medication intake and has cost-saving effects	57
Rhee, 2012[38]	USA	Prospective study design, data collected from a randomised controlled study CBA	1. Peer-led asthma self-management program 2. adult led asthma self-management progam	School- and hospital-based	1. Not reported	9-months	Not reported	Total costs: - Peer-led program= $7955 - Adult-led program =$7305. Individual costs: - Peer-led program = $64/capita - Adult-led program= $99/capita	1. Net cost savings	Not applicable The peer-led group one had fewer acute office visits than the adult-led group. At 3-months follow-up, compared to adult-led program, the net cost saving from the peer-led program was $5.8 /person, which reflected $11 more/person for the cost of the peer-led program offset by $16.8 less/person associated with acute office visits, assuming the average costs for an office visit to be $80 in 2008 USD. The net cost savings in non-research setting was estimated to be$51.8/person for a 3-months period.	Peer leaders can potentially yield health care cost savings through the reduction in acute office visits in comparison to a traditional program led by healthcare professionals. Note: In an additional subgroup analysis the sample size was smaller than 20, though the base-case analysis was appropriate for the criteria of this SR.	78
Rodriguez, 2008[39]	Venezuela	Prospective double-blinded RCT CMA	1. Nebulised Formoterol Fumarate powder single dose (FF) 2. 3 dose of nebulised Albuterol ampoules	Hospital-based	1. Not reported	Not reported	Not reported	Nebulised FF single dose = US$1.35 and 3 dose of Albuterol= US$6.73	1. Cost of treatment 2. Health outcomes	Not applicable 1 dose of Nebulised FF seems to be equivalent to 3 doses of nebulised Albterol. FF is a simpler and more cost-effective approach.	FF is a simpler and a more cost-effective approach.	43

Vasbinder, 2016[42]	The Netherlands	Multicentre RCT CEA	1. Real-Time medication monitoring (RTMM)+ tailored SMS (intervention group) 2. RTMM alone (control group)	Hospital-based	1. Healthcare (the Netherlands2. societal	12 months	Not reported	Total costs in intervention group from health care perspective: €731 and from societal perspective: €1,043 Total costs in control group from health care perspective: €636 and from societal perspective: €764	1. Adherence to ICS 2. Asthma control 3. QoL 4. Frequency of asthma exacerbation	No reported No difference in asthma control, QoL, exacerbation and adherence improved. Higher cost in intervention group.	Apart from the cost of SMS intervention there was no difference in costs and there was no evidence on better asthma control, improved asthma-specific QoL or fewer asthma exacerbation.	70
Wang, 2011[43]	USA	Randomized, controlled, double-blind trial CEA	1. FP 2. MON	Study centres - based	1. Health-care (USA) 2. third party payer 3. societal	48-weeks	Not reported	Direct costs: $759 for FP and $1,189 for MON. Societal costs: $1075 for fluticasone, $1,673 for montelukast.	1. Asthma-control days (ACD) 2. Improvement in FEV1 3. Number of exacerbations avoided	ICER -$11 / 1 more ACD gained The probability of FP being cost-effective is at least 95% considering sampling uncertainty	FP had lower costs and higher effectiveness	91
Willems, 2007[44]	The Netherlands	Single-centre Prospective RCT CUA	1. Nurse-led tele-monitoring program 2. UC	Hospital-based	1. health-care (the Netherlands) 2. societal	12 months	Not reported	Total costs (mean/SD/)=intervention group €1206/601/ and control group €597/863/	1. QALYs	Health care perspective: ICER €58,726/QALY, Societal perspective: ICER €59,071/QALY gained Probability 68% at a ceiling ration €80000/QALY and 22% at a ceiling ratio of € 40000/QALY gained from societal perspective. When monitor cost were left out the effectiveness ratio changed from 68% to 93% and all the costs decreased	The nurse led tele-monitoring program is not cost saving in children	87

SFD-Symptom-free day; PM- Parent mentor; UC- Usual care; SBAT- School-Based Asthma Therapy; FP- Fluticasone propionate; MON- Montelukast; MgSO4- Magnesium sulfate; SCIT- Subcutaneous Specific Immunotherapy; FF- Formoterol Fumarate ; RTMM- Real-time medication monitoring ; ACD- Asthma-control day; QALY- Quality-adjusted life year; ICER- Incremental cost-effectiveness ratio; BU

Appendix Table 3: Results of CHEERS checklist

CHEERS			Trials												Models						Summary			
	Title and abstract		Athey, 2009[36]	Flores, 2009[37]	Ng, 2006[38]	Noyes, 2012[34]	Ostrom, 2005[35]	Petrou, 2014[40]	Reinhold, 2013[27]	Rhee, 2012[39]	Rodriguez, 2008[33]	Vasbinder, 2016[41]	Wang, 2011[33]	Williams, 2007[42]	Andrews, 2012[27]	Burch, 2012[29]	Dean, 2011[30]	Doull, 2007[31]	Rodriguez-Martinez, 2013[41]	Rodriguez-Martinez, 2015[42]	% of 'Yes'	% of 'No'	% of 'Unknown'	% of 'N/A'
	Title	1	Y	N	N	Y	N	Y	N	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	66.67%	33.33%	-	-
	Abstract	2	N	Y	Y	Y	Y	Y	Y	Y	U	N	Y	Y	Y	N	Y	Y	Y	Y	77.78%	16.67%	5.56%	-
Introduction	Background and objectives	3	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.00%	-	-	-
			Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.00%	-	-	-
Methods	Target population and subgroups	4	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	88.89%	5.56%	5.56%	-
	Setting and location	5	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	U	Y	N	N	Y	77.78%	16.67%	5.56%	-
	Study perspective	6	Y	N	N	Y	N	Y	N	N	N	Y	Y	Y	Y	U	Y	N	Y	Y	55.56%	38.89%	5.56%	-
	Comparators	7	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	U	88.89%	-	11.11%	-
	Time horizon	8	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	94.44%	5.56%	-	-
	Discount rate	9	N	N	N	N	N	Y	Y	N	N	N	N	N	Y	Y	Y	Y	Y	Y	44.44%	55.56%	-	-
	Choice of health outcomes	10	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.00%	-	-	-
	Measurement of effectiveness	11a†	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	-	-	-	-	-	-	91.67%	8.33%	-	-
		11b‡	-	-	-	-	-	-	-	-	-	-	-	-	U	U	N	Y	Y	Y	50.00%	16.67%	33.33%	-
	Measurement and valuation of preference-based outcomes	12	N/A	N/A	N/A	N/A	N/A	Y	N/A	N/A	N/A	N/A	N/A	Y	N/A	Y	N/A	Y	Y	Y	33.33%	-	-	66.67%
	Estimating resources and costs	13a*	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	Y	-	-	-	-	-	-	66.67%	33.33%	-	-
		13b‡	-	-	-	-	-	-	-	-	-	-	-	-	Y	U	Y	Y	Y	Y	83.33%	-	16.67%	-
	Currency, price date, and conversion	14	N	N	N	Y	N	Y	N	Y	N	Y	Y	Y	Y	N	U	Y	Y	Y	55.56%	38.89%	5.56%	-
	Choice of model	15‡	-	-	-	-	-	-	-	-	-	-	-	-	Y	Y	U	U	Y	Y	66.67%	-	33.33%	-
	Assumptions	16‡	-	-	-	-	-	-	-	-	-	-	-	-	Y	Y	Y	Y	Y	Y	100.00%	-	-	-
	Analytical methods	17	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	N	72.22%	27.78%	-	-
Results	Study parameters	18	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N	N	Y	N	N	66.67%	33.33%	-	-
	Incremental costs and outcomes	19	N	Y	Y	Y	Y	Y	N	Y	N	U	Y	Y	N	Y	Y	Y	Y	Y	72.22%	22.22%	5.56%	-
	Characterising uncertainty	20a†	N	N	N	N	N	Y	N	N	N	Y	Y	Y	-	-	-	-	-	-	33.33%	66.67%	-	-
		20b‡	-	-	-	-	-	-	-	-	-	-	-	-	N	Y	Y	N	Y	Y	66.67%	33.33%	-	-
	Characterising heterogeneity	21	N/A	Y	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Y	N/A	N/A	U	N/A	N/A	Y	Y	22.22%	-	5.56%	72.22%
Discussion	Study findings, limitations, generalisability, and current knowledge	22	U	Y	Y	Y	N	U	Y	Y	Y	U	Y	Y	Y	U	Y	Y	Y	Y	72.22%	5.56%	22.22%	-
Other	Source of funding	23	N	Y	N	Y	N	N	Y	Y	N	Y	Y	N	Y	Y	N	Y	N	Y	55.56%	44.44%	-	-
	Conflicts of interest	24	Y	Y	N	Y	Y	Y	U	Y	N	Y	Y	Y	Y	Y	Y	U	Y	Y	77.78%	11.11%	11.11%	-
	Summary§	Y N U N/A	12 8 1 2	16 6 0 1	13 8 0 2	18 3 0 2	14 7 0 2	20 1 1 1	13 6 2 2	18 3 0 2	10 10 1 2	16 3 2 2	21 1 0 1	20 2 0 1	17 5 1 2	14 5 6 0	18 3 2 2	19 3 2 1	20 4 1 0	22 2 1 0	301	80	20	25
			52%	70%	57%	78%	61%	87%	57%	78%	43%	70%	91%	87%	68%	56%	72%	76%	80%	88%				

†only applicable in trials; ‡only applicable in models; §Total score for trials: 23; Total score for models: 25