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Developing Core Economic Outcome Sets for Asthma Studies: A Protocol for a Systematic Review

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Developing Core Economic Outcome Sets for Asthma Studies: A Protocol for a Systematic Review

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ABSTRACT

Introduction

Core outcome sets are standardised lists of outcomes, which should be measured and reported in all clinical studies of a specific condition. This study aims to develop core outcome sets for economic evaluations in asthma studies. Economic outcomes include items such as costs, resource use or quality-adjusted life years. The starting point in developing core outcome sets will be conducting a systematic literature review to establish a preliminary list of reporting items to be considered for inclusion in the core outcome set.

Methods and analysis

We will conduct literature searchers of peer-reviewed studies published from January 1990 until January 2017. These will include any comparative or observational studies (including economic models) and systematic reviews reporting economic outcomes. All identified economic outcomes will be tabulated together with the major study characteristics, such as population, study design, the nature and intensity of the intervention, mode of data collection and instrument(s) used to derive an outcome. We will undertake a “realist synthesis review” to analyse the identified economic outcomes. The outcomes will be summarized in the context of evaluation perspectives, types of economic evaluation and methodological approaches. Parallel to undertaking a systematic review we will conduct semi-structured interviews with stakeholders (including people with personal experience of asthma, health professionals, researchers and decision makers) in order to explore additional outcomes which have not been considered, or used, in published studies. The list of outcomes generated from the systematic review and interviews with stakeholders will form the basis of a Delphi survey to refine the identified outcomes into a core outcome set.

Ethics and dissemination

The review will not involve access to individual-level data. Findings from our systematic review will be communicated to a broad range of stakeholders including clinical guideline developers, research funders, trial registries, ethics committees and other regulators.

Keywords: asthma trials, economic evaluation, core outcome set

Strengths and limitations of this study

This study represents a key step in standardising economic outcomes in asthma trials. Introducing economic outcome sets will:

- reduce heterogeneity between economic outcomes in future studies;
- facilitate evidence synthesis;
- minimise the risk of outcome reporting bias;
- help decision making about resource allocation in healthcare.

INTRODUCTION

Core outcome measures are standardised sets of outcomes, which represent the minimum set of parameters that should be measured and reported in all clinical studies of a specific condition.[1] The purpose of developing core outcome sets is to enable the results of these studies to be compared, contrasted and combined as appropriate. Including core outcome sets in future studies will help to reduce heterogeneity between reported outcomes, facilitate evidence synthesis and minimise the risk of outcome reporting bias. Core outcomes should be relevant to health service users, people making decisions about health care, research funders, clinical guideline developers and other regulators.

In 2010 the Core Outcome Measures in Effectiveness Trials (COMET) Initiative was launched by the MRC North West Hub for Trials Methodology (NWHTMR).[1] The COMET Initiative brings together academics, clinical researchers, research funders, health service users, policy makers and trial regulators interested in developing and using standardised sets of outcome measures. Currently, there is no such set for asthma in the UK and a range of reviews have identified a large variety of outcomes used to evaluate the clinical effectiveness and cost effectiveness of healthcare interventions for people with asthma.[2-6]

While there has been a more general move towards the standardisation of measures for economic evaluation,[7-9] within the asthma field, the focus has tended to be in the context of effectiveness (rather than costs) since the purpose of many new treatment strategies is better control and avoidance of unscheduled health care use resulting from poor control. We therefore wanted to turn attention in this area specifically to economic outcomes. Aside from resource use and cost measures (e.g. use of primary care services, hospital admissions, emergency department and outpatient visits, tests, investigations, medication, absence from work and school), another type of outcome that could be considered 'economic' is preference-based measures of health-related quality of life, such as quality-adjusted life years (QALYs), which are usually measured specifically to inform cost-effectiveness decisions at the health system level.

The starting point in developing core outcome sets is to conduct a systematic review to determine what outcomes are already in use, and to establish a preliminary list of reporting items to be considered for inclusion in the core outcome set.[10,11] We therefore present here a protocol for a systematic review of studies of asthma that report economic outcomes.

METHODS AND ANALYSIS

The systematic review will be conducted using methodology described in the Cochrane Handbook for Systematic Reviews of Interventions,[12] and reported in accordance with the PRISMA-P (The Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) guidelines.[13]

Aims and Objectives

The aim of this systematic review is to identify, evaluate and explain economic outcomes reported in studies of healthcare interventions for people with asthma.

The objectives of this systematic review are:

- To identify, obtain and review relevant studies;
- To identify economic outcomes used in asthma studies;
- To develop lists of economic outcome measures used for adults, children and adolescents.

Definitions

For the purpose of this review, we will use the following definitions:

Economic outcomes are economic results or consequences of an intervention. These can be associated with resources (e.g. number of prescriptions or days in hospital), costs, preference-based measurements of health-related quality of life, such as quality-adjusted life years (QALYs), combined metrics of costs and outcomes (e.g. incremental cost-effectiveness ratio, net benefit, or probability of intervention being cost-effective), or compliance.

Economic outcome measures are tools (both validated and non-validated) through which economic outcomes are assessed e.g. resource use questionnaires, outcome measures, proformas.

Inclusion criteria

Types of studies:

Any comparative or observational studies (including economic models) and systematic reviews reporting economic outcomes.

Types of interventions:

1. Interventions designed to improve diagnosis, investigation, treatment, monitoring or management of asthma.
2. Interventions to improve services and their delivery for people with asthma;
3. Public heath interventions for asthma prevention.

Participants:

Adults, children and adolescents. We will include studies with children aged five and older due to the challenge of objective confirmation of asthma diagnosis in children under five.[14-16]

Settings:

We will place no restrictions regarding setting of care.

Types of economic evaluations:

We will place no restrictions upon types of health economics analyses.

Literature search

A literature search will be conducted in two stages. The first step will be conducted using the following sources: COMET database for core outcomes in clinical trials, Cochrane Library, HTA library, NHS Economic Evaluation Database (NHS EED), PubMed, EMBASE, PsycINFO, Web of Science, EconLit and CINAHL. In the second step we will use a "snowballing approach", whereby reference lists and bibliographies of relevant papers will be searched for additional studies. Database searches will include studies published from January 1990 until December 2017. Abstracts of articles will be searched using terms related to asthma, economic(s), and outcomes/measures/instruments. The exact search terms are included in Appendix 1.

Selecting studies

To minimize the possibility of selection bias, two reviewers will be involved in the selection process. Initial screening will include titles and abstracts. The title/abstract screening checklist is shown in Appendix 2. In the second step each reviewer will independently read each of the studies that can potentially be included in the review. Any discrepancies regarding whether a study is relevant for inclusion in the review will be resolved by open discussion to reach a consensus. A PRISMA diagram will be drawn to describe the selection process.[17]

Data extraction

All identified economic outcomes will be tabulated together with the major study characteristics, such as population, study design, mode of data collection, the nature and intensity of the intervention and other outcome measures. The design of the table will be developed in due course. An example of an extraction table is shown in Appendix 3.

Data synthesis

Data will be synthesised according to the guidelines for synthesising qualitative research for health technology assessments and systematic reviews.[18] Due to the scope of the review, neither a qualitative or quantitative data synthesis will produce meaningful results so, for the purpose of this study, we will undertake a realist synthesis approach.[19,20] This method is increasingly used in evidence-based research since it applies to the real world of policy formation. Realist synthesis goes beyond creating a list of economic outcomes used in asthma studies. It accounts for context, questions outcome integrity and compares expectations (what was intended to be measured) with practice (what was actually measured). We will be answering the following key questions: What type of outcome? In what studies? How measured? Does it answer the economic research question? Is it useful for decision makers? The process of realist synthesis is described in Appendix 4. We will summarise economic outcomes included in asthma studies in the context of evaluation perspectives (e.g. societal, healthcare provider, personal social services etc.), types of economic evaluation (e.g. cost-effectiveness, cost-utility, cost-consequences and cost-benefit analysis) and methodological approaches (e.g. retrospective or prospective, data sources).

ETHICS AND DISSEMINATION

We did not seek ethical approval for conducting the systematic review since it will not involve access to individual-level data. Formal ethics approval will be sought to conduct interviews and Delphi studies with stakeholders.

Findings from our systematic review will be communicated to a broad range of stakeholders. We will work in close conjunction with the Asthma UK Centre for Applied Research (AUKCAR; http://www.aukcar.ac.uk/), which brings together the leading asthma researchers from 13 universities across the UK, Asthma UK, people affected by asthma, NHS partners and other organisations. We will disseminate our findings at international workshops and conferences, including Core Outcome Measures in Clinical Trials initiative (COMET) meetings.

The next step, of developing an economic core outcome set for studies focusing on people with asthma, will involve Delphi methodology to determine which economic outcomes should be included in effectiveness studies.[10,11] Findings from this systematic review will inform protocol development for the Delphi consensus process. A national expert panel will be convened for round-table discussions to a group of experts from the Asthma UK Centre for Applied Research. The panel will include representatives from the AUKCAR Patient Advisory Group, consisting of people with mild to severe and brittle asthma, as well as parents, relatives and carers of people with asthma, to identify important economic outcomes. Once a consensus on an outcome set is reached, an international workshop will be convened to discuss the applicability of the Delphi-generated core outcome set across international settings and relevant disciplines. Subsequent developments of the core outcome set will be validated internally (via a further expert panel) and externally (by including in national/international asthma studies). To ensure uptake of the core outcome set we will engage with clinical guideline developers, research funders, trial registries, ethics committees and other regulators.

Acknowledgements

This work is funded by Asthma UK as part of the Asthma UK Centre for Applied Research (AUK-AC-2012-01)

Contributors

NH led the development of the protocol, wrote the first draft and integrated comments from coauthors. AP, DF and CH critically revised the manuscript and provided methodological input. AP provided intellectual leadership to the project.

Competing interests

None declared

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Appendix 1. Search terms

Condition	Key term	Secondary Term
asthma	economic	
	cost	
	resource	
	service	
	expen*	
	burden	
	productivity	
	income	
	financial	
	absent*	
	out of pocket	
	consultation	
	hospitalisation	
	appointment	
	attendance	
	check	
	inpatient	
	outpatient	
	A&E	
	clinic	
	prescription	
	test	
	investigation	
	diagnostic	
	self-management	
	NHS direct	
	NHS 24	
	GP	
	general practitioner	
	consultant	
	nurse	
	health visitor	
	councilor	
	social worker	
	carer	
	caregiver	
	medication	use
	inhaler	use
	travel	time
	caring	time
	childcare	time
	work*	time
	school	time

travel	time
lost	time
primary	care
secondary	care
tertiary	care
social	care
home	care
emergency	care
intensive	care
informal	care
community	care
ambulatory	care
private	care
social	support
family	support
care	support

Appendix 2. The title/abstract screening checklist

Question Number	Question	Answer	Action
Q1	Is the study an economic evaluation?	Yes or unsure No	Go to Q2 Exclude
Q2	Does it report economic outcomes (e.g. resource use, costs, cost-effectiveness ratios, QALYs)?	Yes or unsure No	Go to Q3 Exclude
Q3	Are the population adults, adolescents or children aged five years and older with confirmed asthma diagnosis?	Yes or unsure No	Go to Q4 Exclude
Q4	Does the study include primary data on economic outcomes?	Yes or unsure No	Go to Q5 Exclude
Q5	Is the paper written in English?	Yes No	Proceed to the full text selection Exclude

Appendix 3. Data extraction template (with illustrative example)

Title, authors and year	Population and age	Setting	Type of study	Asthma severity	Intervention	Type of economic evaluation	Perspective	List of economic outcomes	Instruments used to collect economic outcomes	Outcomes address research question?	Comments
Enhancing ventilation in homes of children with asthma: cost-effectiveness study alongside randomised controlled trial *Edwards et al. 2011*	Children 5-14 years old	Council houses in Wrexham County Borough, Wales, UK.	RCT	Moderate to severe	Housing modifications: installing ventilation systems or central heating	Cost-effectiveness analysis using PedsQL	Public sector (NHS and Social Services)	**Service use** (GP, out-of hours, practice nurse, A&E, inpatient, outpatient) and prescriptions (bronchodilators short-term and long-term; single drug corticosteroids; combination corticosteroids; respiratory drugs; antibacterial drugs; gluocosteroids; drugs acting on the nose; emollient, barriers, topical corticosteroids, eczema preparations; peak flow meters and other devices); **Costs** of resourse use; Local authority costs; **ICER**	Parent-completed service use questionnaire; general practice records	Yes	ICER (cost per change in PedsQL) is difficult to interpret. Parent-reported service use questionnaires were not used in analysis due to large number of missing items.

Appendix 4. Realist synthesis (adapted from Pawson et al. 2004)*

Define the scope	Identify the question	What is the nature and content of the intervention? What are the circumstances or context for its use? What are the policy intentions or objectives? What are the nature and form of its outcomes or impacts? Conduct exploratory searches to inform discussion with stakeholders.
Search for and appraise the evidence	Search for the evidence	Outline literature searching procedures; Define search sources, time frame, methods, inclusion and exclusion criteria, types of outcomes.
	Appraise the evidence	Test relevance of study: does it include economic outcomes? Does it include relevant populations? Test rigor: do outcomes support the conclusions drawn from it by the researchers or the reviewers?
Extract and synthesise findings	Extract the results	Develop data extraction forms or templates; Extract data to populate the evaluative framework with evidence.
	Synthesise findings	Compare and contrast outcomes used in studies with different evaluation perspectives, types of economic evaluation and methodological approaches. Use findings from studies to address objectives of systematic review.
Draw conclusions and make recommendations		Involve stakeholders in review of findings; Draft and test out recommendations and conclusions based on findings with key stakeholders; Disseminate review with findings, conclusions and recommendations.

* Pawson R, Greenhalgh T, Harvey G, Walshe K: Realist Synthesis: an introduction. ESRC Research Methods Programme: University of Manchester RMP: Methods Paper 2/2004. Available at http://www.ccsr.ac.uk/methods/publications/documents/RMPmethods2.pdf Accessed 17 March 2017.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	N/A
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 1
Sponsor	5b	Provide name for the review funder and/or sponsor	Page 1
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Pages5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 6

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 6 Appendix 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 6 Appendix 2
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 7 Appendix 3
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 7 Appendix 3
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	N/A (all outcomes and outcome measures will be included)
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	N/A
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	N/A
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Appendix 4

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Ethics and dissemination

The review will not involve access to individual-level data. Findings from our systematic review will be communicated to a broad range of stakeholders including clinical guideline developers, research funders, trial registries, ethics committees and other regulators.

Keywords: asthma trials, economic evaluation, core outcome set

Strengths and limitations of this study

This systematic review represents a key step in standardising economic outcomes in asthma trials.

Strengths of this review are:

- We will produce a list of economic outcomes for use in future studies;
- We will involve stakeholders in review of findings.

Limitations of this review are:

- Quality of studies included in the systematic review will be not assessed given the scope of this study;
- Economic outcomes identified in this review (e.g. resource use) may be not comparable to other countries and settings due to differences in healthcare organisation.

INTRODUCTION

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In 2010 the Core Outcome Measures in Effectiveness Trials (COMET) Initiative was launched by the MRC North West Hub for Trials Methodology (NWHTMR).[1] The COMET Initiative brings together academics, clinical researchers, research funders, health service users, policy makers and trial regulators interested in developing and using standardised sets of outcome measures. Currently, there is no such set for asthma in the UK and a range of reviews have identified a large variety of outcomes used to evaluate the clinical effectiveness and cost effectiveness of healthcare interventions for people with asthma.[2-6]

While there has been a more general move towards the standardisation of measures for economic evaluation,[7-9] within the asthma field, the focus has tended to be in the context of effectiveness (rather than costs) since the purpose of many new treatment strategies is better control and avoidance of unscheduled health care use resulting from poor control. We therefore wanted to turn attention in this area specifically to economic outcomes. Aside from resource use and cost measures (e.g. use of primary care services, hospital admissions, emergency department and outpatient visits, tests, investigations, medication, absence from work and school), another type of outcome that could be considered 'economic' is preference-based measures of health-related quality of life, such as quality-adjusted life years (QALYs), which are usually measured specifically to inform cost-effectiveness decisions at the health system level.

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Economic outcome measures are tools (both validated and non-validated) through which economic outcomes are assessed e.g. resource use questionnaires, outcome measures, proformas.

Inclusion criteria

Types of studies:

Any controlled and uncontrolled experimental and observational studies and reviews of economic outcomes published in English language.

Types of interventions:

1. Interventions designed to improve diagnosis, investigation, treatment, monitoring or management of asthma.
2. Interventions to improve services and their delivery for people with asthma;
3. Public heath interventions for asthma prevention.

Participants:

Adults, children and adolescents with confirmed asthma diagnosis. We will include studies with children aged five and older due to the challenge of objective confirmation of asthma diagnosis in children under five.[14-16] We will also exclude studies including patients with late asthma diagnosis (>50 years), since these are more likely to have a COPD-asthma overlap syndrome.[17]

Settings:

We will place no restrictions regarding setting of care.

Types of economic evaluations:

We will place no restrictions upon types of health economics analyses.

Literature search

A literature search will be conducted in two stages. The first step will be conducted using the following sources: COMET database for core outcomes in clinical trials, Cochrane Library, HTA library, NHS EED, DARE, PubMed, EMBASE, PsycINFO, Web of Science, EconLit and CINAHL. In the second step we will use a "snowballing approach", whereby reference lists and bibliographies of review articles will be searched for original studies which were not picked up by database searches. Database searches will include studies published from January 1990 until January 2017 due to the small number of economic evaluations published before 1990. Titles and abstracts of articles will be searched using terms related to asthma, economic(s), and outcomes. Examples of search strategies are included in Appendix 1. We will not search grey literature since this may lead to the double-counting of studies (e.g. in conference papers and journal articles).

Selecting studies

To minimize the possibility of selection bias, two reviewers will be involved in the selection process. Initial screening will include titles and abstracts. The title/abstract screening checklist is shown in Appendix 2. In the second step each reviewer will

independently read each of the studies that can potentially be included in the review. Any discrepancies regarding whether a study is relevant for inclusion in the review will be resolved by open discussion to reach a consensus. A PRISMA diagram will be drawn to describe the selection process.[18] Given the scope of this review we will not assess the quality of the included studies. However, we will exclude poorly reported studies which do not provide sufficient information about economic outcomes for our analyses.

Data extraction

All identified economic outcomes will be tabulated together with the major study characteristics, such as population, study design, mode of data collection, the nature and intensity of the intervention and other outcome measures. The design of the table will be developed in due course. An example of an extraction table is shown in Appendix 3.

Data synthesis

Data will be synthesised according to the guidelines for synthesising qualitative research for health technology assessments and systematic reviews.[19] Due to the scope of the review, neither a qualitative or quantitative data synthesis will produce meaningful results so, for the purpose of this study, we will undertake a realist synthesis approach.[20,21] This method is increasingly used in evidence-based research since it applies to the real world of policy formation. Realist synthesis goes beyond creating a list of economic outcomes used in asthma studies. It accounts for context, questions outcome integrity and compares expectations (what was intended to be measured) with practice (what was actually measured). We will be answering the following key questions: What type of outcome? In what studies? How measured? Does it answer the economic research question? Is it useful for decision makers? The process of realist synthesis is described in Appendix 4. We will summarise economic outcomes included in asthma studies in the context of population age (e.g. children 5-11 years, adults and adolescents 12+ years); evaluation perspectives (e.g. societal, healthcare provider, personal social services etc.); types of economic evaluation (e.g. cost-effectiveness, cost-utility, cost-consequences and cost-benefit analysis) and methodological approaches (e.g. retrospective or prospective, data sources).

ETHICS AND DISSEMINATION

We did not seek ethical approval for conducting the systematic review since it will not involve access to individual-level data. Formal ethics approval will be sought to conduct interviews and Delphi studies with stakeholders.

Findings from our systematic review will be communicated to a broad range of stakeholders. We will work in close conjunction with the Asthma UK Centre for Applied Research (AUKCAR; http://www.aukcar.ac.uk/), which brings together the leading asthma researchers from 13 universities across the UK, Asthma UK, people affected by asthma, NHS partners and other organisations. We will disseminate our findings at international workshops and conferences, including Core Outcome Measures in Clinical Trials initiative (COMET) meetings.

The next step, of developing an economic core outcome set for studies focusing on people with asthma, will involve Delphi methodology to determine which economic outcomes should be included in effectiveness studies.[10,11] Findings from this systematic review will inform protocol development for the Delphi consensus process. A national expert panel will be convened for round-table discussions to a group of experts from the Asthma UK Centre for Applied Research. The panel will include representatives from the AUKCAR Patient Advisory Group, consisting of people with mild to severe and brittle asthma, as well as parents, relatives and carers of people with asthma, to identify important economic outcomes. Once a consensus on an outcome set is reached, an international workshop will be convened to discuss the applicability of the Delphi-generated core outcome set across international settings and relevant disciplines. Subsequent developments of the core outcome set will be validated internally (via a further expert panel) and externally (by including in national/international asthma studies). To ensure uptake of the core outcome set we will engage with clinical guideline developers, research funders, trial registries, ethics committees and other regulators.

Acknowledgements

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Contributors

NH led the development of the protocol, wrote the first draft and integrated comments from coauthors. AP, DF and CH critically revised the manuscript and provided methodological input. AP provided intellectual leadership to the project.

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Appendix 1. Search strategy (PubMed)

#1 Search ((asthma[MeSH Terms]) AND (economic*[Title/Abstract] OR cost*[Title/Abstract] OR resource*[Title/Abstract] OR service*[Title/Abstract] OR burden[Title/Abstract] OR productivity[Title/Abstract] OR income[Title/Abstract] OR financial[Title/Abstract] OR QALY[Title/Abstract])) Filters: Clinical Trial; Full text; Publication date from 1990/01/01 to 2017/01/01; English

#2 Search ((asthma[MeSH Terms]) AND economic*[MeSH Terms]) AND (consultation[Title/Abstract] OR hospitalisation[Title/Abstract] OR hospitalization[Title/Abstract] OR appointment[Title/Abstract] OR attendance[Title/Abstract] OR check[Title/Abstract] OR inpatient[Title/Abstract] OR outpatient[Title/Abstract] OR emergency[Title/Abstract] OR clinic[Title/Abstract] OR prescription[Title/Abstract] OR test[Title/Abstract] OR investigation[Title/Abstract] OR diagnostic[Title/Abstract] OR GP[Title/Abstract] OR general practitioner[Title/Abstract] OR physician[Title/Abstract] OR clinician[Title/Abstract]OR consultant[Title/Abstract] OR nurse[Title/Abstract] OR counselor[Title/Abstract] OR counsellor[Title/Abstract] OR social worker[Title/Abstract] OR carer[Title/Abstract] OR caregiver[Title/Abstract]) Filters: Clinical Trial; Full text; Publication date from 1990/01/01 to 2017/01/01; English

#3 Search ((asthma[MeSH Terms]) AND economic*[MeSH Terms]) AND (medication [Title/Abstract] OR medicines[Title/Abstract] OR inhaler [Title/Abstract] OR nebuliser[Title/Abstract] OR nebulizer[Title/Abstract] OR caring[Title/Abstract] OR childcare[Title/Abstract] OR work*[Title/Abstract] OR school[Title/Abstract] OR absent*[Title/Abstract] OR travel[Title/Abstract] OR primary care[Title/Abstract] OR secondary care[Title/Abstract] OR tertiary care OR social care[Title/Abstract] OR home care[Title/Abstract] OR emergency care[Title/Abstract] OR intensive care[Title/Abstract] OR informal care[Title/Abstract] OR community care[Title/Abstract] OR ambulatory care[Title/Abstract] OR private care[Title/Abstract] OR social support[Title/Abstract] OR family support[Title/Abstract]) Filters: Clinical Trial; Full text; Publication date from 1990/01/01 to 2017/01/01; English

#4 Search ((asthma[MeSH Terms]) AND economic*[MeSH Terms]) AND outcome*[Title/Abstract] Filters: Review; Full text; Publication date from 1990/01/01 to 2017/01/01; English

Appendix 2. The title/abstract screening checklist

Question Number	Question	Answer	Action
Q1	Is the study an economic evaluation?	Yes or unsure No	Go to Q2 Exclude
Q2	Does it report economic outcomes (e.g. resource use, costs, cost-effectiveness ratios, QALYs)?	Yes or unsure No	Go to Q3 Exclude
Q3	Are the population adults <50 years, adolescents or children aged five years and older with confirmed asthma diagnosis?	Yes or unsure No	Go to Q4 Exclude
Q4	Does the study include primary data on economic outcomes?	Yes or unsure No	Go to Q5 Exclude
Q5	Is the paper written in English?	Yes No	Proceed to the full text selection Exclude

Appendix 3. Data extraction template (with illustrative example)

Title, authors and year	Population and age	Setting	Type of study	Asthma severity	Intervention	Type of economic evaluation	Perspective	List of economic outcomes	Instruments used to collect economic outcomes	Answers economics question?	Comments
Enhancing ventilation in homes of children with asthma: cost-effectiveness study alongside randomised controlled trial *Edwards et al. 2011*	Children 5-14 years old	Council houses in Wrexham County Borough, Wales, UK	RCT	Moderate to severe	Housing modifications: installing ventilation systems or central heating	Cost-effectiveness analysis using PedsQL	Public sector (NHS and Social Services)	**Service use** (GP, out of hours, practice nurse, A&E, inpatient, outpatient) and prescriptions (bronchodilators short-term and long-term; single drug corticosteroids; combination corticosteroids; respiratory drugs; antibacterial drugs; gluocosteroids; drugs acting on the nose; emollient barriers, topical corticosteroids, eczema preparations; peak flow meters and other devices); **Costs** of resourse use; Local authority costs; **ICER**	Parent-completed service use questionnaire; general practice records	Yes	ICER (cost per change in PedsQL) is difficult to interpret. Parent-reported service use questionnaires were not used in analysis due to large number of missing items.

Appendix 4. Realist synthesis (adapted from Pawson et al. 2004)*

Define the scope	Identify the question	What is the nature and content of the intervention? What are the circumstances or context for its use? What are the policy intentions or objectives? What are the nature and form of its outcomes or impacts? Conduct exploratory searches to inform discussion with stakeholders.
Search for and appraise the evidence	Search for the evidence	Outline literature searching procedures. Define search sources, time frame, methods, inclusion and exclusion criteria, types of outcomes.
	Appraise the evidence	Test relevance of study. Does it include economic outcomes? Does it include relevant populations? Test rigor. Do outcomes support the conclusions drawn from them by the researchers or the reviewers?
Extract and synthesise findings	Extract the results	Develop data extraction forms or templates. Extract data to populate the evaluative framework with evidence.
	Synthesise findings	Compare and contrast outcomes used in studies with different evaluation perspectives, types of economic evaluation and methodological approaches. Use findings from studies to address objectives of systematic review.
Draw conclusions and make recommendations		Involve stakeholders in review of findings; Draft and test out recommendations and conclusions based on findings with key stakeholders; Disseminate review with findings, conclusions and recommendations.

* Pawson R, Greenhalgh T, Harvey G, Walshe K: Realist Synthesis: an introduction. ESRC Research Methods Programme: University of Manchester RMP: Methods Paper 2/2004. Available at http://www.ccsr.ac.uk/methods/publications/documents/RMPmethods2.pdf Accessed 17 March 2017.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	PROSPERO registration number: CRD42017067867
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 8
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 1
Sponsor	5b	Provide name for the review funder and/or sponsor	Page 1
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Pages 5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Pages 6-7

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Appendix 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Pages 6-7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Pages 6-7 Appendix 2
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 7 Appendix 3
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 7 Appendix 3
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	N/A (all outcomes and outcome measures will be included)
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	N/A
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	N/A
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Appendix 4

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.