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Complete List of Authors:	Roukas, Chris; Queen Mary University of London Faculty of Medicine and Dentistry, Centre of Primary Care and Public Health Quayyum , Zahidul ; BRAC University James P Grant School of Public Health Patel, Anita; Anita Patel Health Economics Consulting Ltd Fitzsimmons, Deborah; Swansea University, Swansea Centre for Health Economics Phillips, Ceri; Swansea University, Swansea Centre for Health Economics Hounsome, Natalia; Brighton and Sussex Medical School, Global Health and Infection
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Developing core economic parameter sets for asthma studies: A systematic literature review and an analytical framework

Chris Roukas[1], Zahidul Quayyum[2], Anita Patel[3], Deborah Fitzsimmons[4], Ceri Phillips[4], Natalia Hounsome[5].

[1]Pragmatic Clinical Trials Unit, Centre of Primary Care and Public Health, Queen Mary University of London, London, UK
[2]BRAC James P Grant School of Public Health, BRAC University, Dhaka, Bangladesh
[3]Anita Patel Health Economics Consulting Ltd, London, UK
[4]Asthma UK Centre for Applied Research, Swansea Centre for Health Economics, Swansea University, Swansea, UK
[5]Brighton and Sussex Medical School, University of Sussex, Falmer, Brighton, UK

Correspondence to: Natalia Hounsome, Brighton and Sussex Medical School, University of Sussex, Falmer, Brighton, UK. Email: n.hounsome@bsms.ac.uk

Abstract

Objective: To develop a standardised set of economic parameters (core economic parameter set) for economic evaluations in asthma studies.

Design: Systematic literature review and an analytical framework.

Outcome measures: Economics parameters used to evaluate costs and cost-effectiveness of healthcare interventions for people with asthma.

Data sources: PubMed, the Cochrane Database of Systematic Reviews (CDSR), the NHS Economic Evaluation Database (EED), the Database of Abstracts of Reviews of Effects (DARE) and the HTA Library (January 1990 - January 2019).

Review methods: Research methods were based on the realist review methodology and included a number of non-sequential, iterative and overlapping components, such as: developing an analytical framework for the realist review; systematic literature review of economic parameters; identifying and categorising economic parameters; producing preliminary list of core economic parameters.

Results: Database searches found 2,531 publications of which 224 were included in the systematic review. We identified 65 economic parameters which were categorised into 11 groups to enable the realist synthesis. Parameters related to secondary care, primary care, medication use, emergency care and work productivity comprised 84% of all economic parameters. An analytical framework was used to investigate the rationale behind the choices of economic parameters in these studies. The main framework domains included: type of intervention, research population, study design, study setting, and a stakeholder perspective.

Conclusion: Past research thus suggests that parameters depicting the use of secondary care, primary care, medication, emergency care and work productivity can be considered as core economic parameters, since they apply to different types of studies. Parameters including diagnostics, healthcare delivery, school activity, informal care, medical devices and health utility apply to a particular type of study (or research question), and thus can be recommended as supplemental parameters.

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Keywords: asthma studies, health economics, core parameters

Strengths and limitations of this study

- This study reports the first step in developing a standartised set of economic parameters for use in asthma trials.
- Our systematic review identified 65 economic parameters used to evaluate costs and cost-effectiveness of healthcare interventions for people with asthma.
- We applied an analytical framework based on the realist review methodology to classify economic parameters which can be recommended for inclusion in future studies.
- The issue of public participation in this research will be addressed in the next phase (Delphi study), which will involve health care professionals, commissioners, people with asthma, and relatives/carers of people with asthma.

Background

Asthma is a common disease characterised by recurrent attacks of breathlessness and wheezing. It affects 5.4 million people in the UK: one in 11 children and one in 12 adults.[1,2] According to the International Clinical Trials Registry Platform [3] there are currently 4,391 registered trials for asthma. Many of these studies report different health outcomes, which has consequently made it difficult for researchers to compare the available evidence.[4,5] Selecting appropriate health outcomes at the study design stage is essential to ensure comparability between different studies, to reduce heterogeneity between reported outcomes, to facilitate evidence synthesis, and to minimise the risk of outcome reporting bias.[4-6]

In the last decade, there has been general move towards developing core outcome sets for use in clinical trials. The Core Outcome Measures in Effectiveness Trials (COMET) Initiative, launched in 2010, 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. The COMET initiative provides a methodological platform for developing core outcome sets for different diseases and medical conditions.[7]

In recent years, economic evaluation has become an essential part of clinical studies to assist decision makers with allocating resources in healthcare. Economic evaluation involves a "comparative analysis of alternative courses of action in terms of both their costs and consequences".[8] Therefore, economic evaluations necessarily need to collate information on both economic outcomes and health outcomes. Health outcomes represent health benefits (e.g. symptom relief, faster recovery or better quality of life) and may be either of a generic nature or specific to the condition being examined. Economic outcomes may include resource use (e.g. number of prescriptions, or days in hospital), costs (e.g. cost of medication and diagnostic equipment), or combined metrics of costs and outcomes (e.g. incremental cost-effectiveness ratio, probability of intervention being cost-effective). In the context of economic evaluations, preference-based health outcomes (e.g. quality-adjusted life years or disability-adjusted life years), can be also considered as economic outcomes. To differentiate between health outcomes and economic outcomes we will use the term "economic parameter".

While currently there are no core parameter sets available for economic evaluations in asthma trials, a number of studies have identified a range of parameters used to evaluate costs and cost-effectiveness of healthcare interventions for people with asthma.[4, 9-12] Standardising these parameters is essential to ensure consistency in data collection, analyses, reporting and thus to enable valid comparison and evidence synthesis to appropriately inform resource allocation decisions.

We thus set out to develop a core parameter set for economic evaluation of asthma interventions. This paper reports results from the first stage of this process – a systematic literature review and an analytical framework. The aim of this stage was to identify economic parameters which are already in use, and to establish a preliminary list of reported items to be considered for inclusion in the core parameter set. Due to the scope of the review, neither qualitative nor quantitative analyses would

produce meaningful results. Therefore, we applied a realist review methodology, which combines quantitative and qualitative approaches and focuses on contextual mechanisms that inform decisions and actions.[13-15] The protocol for this review was published elsewhere.[16]

Methods

Research strategy

The research strategy was based on the realist review methodology[13-15] and included a number of non-sequential, iterative and overlapping components, such as: developing an analytical framework for the realist review; systematic literature review of economic parameters; identifying and categorizing economic parameters; producing preliminary list of core economic parameters. The realist methodology uses a mixed methods approach (both quantitative and qualitative) to addressing relationships between context, mechanisms and outcomes. It asks the question "What works for whom, in what circumstances and why?"[13] The realist approach has been used to analyse the effectiveness of complex interventions in health care.[15] In this study we applied the realist framework to address the questions: What economic parameters are used in asthma studies? For what type interventions and populations? In what kind of settings? From what stakeholder perspectives? A systematic literature review was conducted according to the protocol described elsewhere.[16]

Literature searches

We conducted literature searches using PubMed, the Cochrane Database of Systematic Reviews (CDSR), the NHS Economic Evaluation Database (EED), the Database of Abstracts of Reviews of Effects (DARE) and the HTA Library for the period January 1990 - January 2019. Titles and abstracts were searched for inclusion of the MESH term "asthma" as well as health economics key terms such as "economic", "cost", "resource". More information about the search strategy is provided in the published protocol.[16] Records from different databases were merged and duplicate publications were removed.

Study selection

Study selection was conducted by three reviewers (including a researcher with experience of asthma) and comprised of two stages. In the first stage, the titles/abstracts were screened according to the pre-specified checklist to ensure that the selected studies reported economic parameters, included the relevant population, and were written in English. The second stage was full text screening of studies which fulfilled the above criteria, as well as studies classified as "unsure" in the first stage. Studies were excluded at this stage if they did not report economic parameters, or included people with co-morbidities, or if the full text of study was not available. We also excluded studies conducted with

children < 5 years (due to challenges of confirmation of asthma diagnosis) and adults >65 years (who are likely to have a COPD-asthma overlap syndrome), in accordance with the protocol for the systematic review.[16] Studies including children <5 years or adults >65 years among other age groups were marked as "unsure" for further scrutiny. Upon data extraction it was found that studies including children <5 years and adults >65 years along with other age groups comprised more than a half of identified publications. Consequently, a decision was made to include these studies in the systematic review, as this reflects the real-world research context in which a core economic parameter set would be required. Any discrepancies regarding whether a study was relevant for inclusion in the review were resolved via involving the third reviewer.

We did not conduct a formal assessment of the quality of publications in relation to study design or standardised reporting criteria, since, ideally, in the realist review no literature should be excluded.[15] However, we excluded poorly reported studies which did not provide necessary information concerning economic parameters. Figure 1 shows a diagram depicting the flow of papers through the selection process.

Data extraction

Data extraction was conducted by three researchers. All identified economic parameters were tabulated together with the major study characteristics: population; age; asthma severity; number of subjects; country; setting; type of study; type of intervention/comparators; type of economic evaluation; perspective of economic evaluation; costs; sources and instruments used to collect economic parameters. Although we did not formally assess the quality of publications selected for the systematic review, a control question was included asking whether the selected study addressed the health economics question(s).

Identifying economic parameters

Economic parameters were identified through term search in Microsoft Excel 2016 using wildcards and keywords (detailed in Appendix 1). Identified parameters were then aggregated into eleven resource groups according to their explicit and implicit meaning. For example, economic parameters such as "accident and emergency", "emergency department", "emergency room", "intensive care unit", "ambulance", and "out-of-hours visits" were thought to represent the same group "emergency care". Aggregating parameters into resource groups was necessary to reduce the number of parameters to enable the realist synthesis.

Ranking economic parameters

Economic parameters were allocated to one of 11 resource groups: “primary care”; “secondary care”, “emergency care”, “informal care”, “medication”, “medical devices”, ”diagnostics”, “work”; “school”, “health care delivery” and “health utility”. For example, if a study reported contacts with primary care doctors and nurses, these were counted as two outcomes, allocated to “primary care”. Results were presented as a frequency of using economic parameters for each resource group.

A ranking of resource groups was conducted to identify the most frequently used parameters which can be considered for inclusion in the core parameter set. The ranking was conducted in two ways: (i) ranking resource groups across all studies included in the systematic review (ii) ranking resource groups among studies with different types on interventions, study designs, population groups, settings and stakeholder perspectives (see below analytical framework).

Analytical framework

An analytical framework was developed using the conceptual framework analysis,[17] which included the following steps:

i) Initial scoping using group discussions with stakeholders and reviewing the literature;

ii) identifying and naming the concepts;

iii) deconstructing and integrating the concepts;

iv) synthesising concepts into a theoretical framework.

The initial scope for the analytical framework was identified from round table discussions within the research team. Initial discussions were carried out at the Asthma UK Centre for Applied Research (AUKCAR) Methodology Workshop “Maximising Information from Empirical Studies” (London, 23 January, 2017). Workshop discussions set out to understand the rationale behind the choices of economic parameters. Subsequent discussions were focused on identifying contexts in which different economic parameters were used (e.g. population age, asthma severity, study characteristics, type of economic analysis). The relationship between different contexts was analysed, and the contexts were integrated into framework domains. The hierarchy between framework domains was established and the domains were arranged into an analytical framework.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans at this stage.

Results

Selected studies

Literature searches identified a total of 3,011 entries before checking for duplicates (Figure 1). The PubMed searches were set deliberately broad and included, alongside specific terms such as "asthma" and "economic", a full range of general terms associated with healthcare resources, for example: "clinician", "nurse", "emergency", "attendance". These searches generated a large number of studies which did not include economic parameters. Therefore, our further searches of CDSR, NHS EED, DARE and the HTA Library included mainly economic terms such as "economic", "cost", "resource", "service", "productivity", etc. Removing duplicates generated 2,531 publications and abstracts were screened using the pre-defined checklist.[16] Approximately 81% of publications were excluded since these were not economic evaluations (e.g. clinical effectiveness studies, service delivery studies, editorials, protocols or methods papers). We also excluded papers which were not in English (n=43), included patients with co-morbidities (n=8), or non-confirmed asthma (n=3). The remaining 423 studies were selected for full-text screening. Out of these, the text was not available for 14 publications; 152 were not full-size papers or did not report economic parameters (e.g. abstracts, commentaries, editorials, reviews); 26 studies were excluded due to populations characteristics (included only children <5 years, adults >65 years old or people with co-morbidity); 4 publications were not in English; 3 reported parameters from the same study. Economic parameters were extracted for 224 studies (listed in Appendix 2).

Characteristics of selected studies

The summary characteristics of studies included in the systematic review are shown in Table 1. The majority (82%) were conducted in the USA, Europe (including the UK) and Canada. Studies undertaken in other countries (Australia, Brazil, Columbia, India, Japan, Thailand and Turkey) comprised 9% of identified studies. Approximately 8% of studies were multinational.

A quarter of selected studies (33%) involved both adult and child participants. Thirty percent of studies included only adults and 21% studies included only children. Population age was not specified in 16% of papers, including those based on economic models. The number of participants varied in wide range: 8% of studies included <100 individuals, 42% included 100-1,000 individuals, and 25 % included >1,000 individuals. Sample size was not specified in 25% of studies, half of which used hypothetical cohorts. With respect to asthma severity, the majority of studies included mixed populations. Participants with mild, moderate and severe asthma were presented in similar proportions (14%, 18% and 17%, respectively). However, a number of studies used different asthma severity classifications e.g. Global Initiative for Asthma (GINA) classification (intermittent, mild persistent, moderate persistent, and severe persistent), or British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS-SIGN) classification (mild, moderate, severe and life-

threatening). Approximately quarter of studies (33%) did not specify asthma severity. In terms of study design, 37% were cohort studies, 33% randomized controlled trials, 23% economic models and 7% were population-level surveys and literature reviews. Half were conducted from a healthcare provider perspective (included costs to healthcare system), 27% considered a societal perspective (e.g. included school absence or parental days off work); 15% pursued a third party payer perspective (e.g. included health insurance claims) and only 2% considered patient or employer perspectives (e.g. included costs to patients or employers). The most common type of economic evaluation was cost analysis (41%), followed by cost effectiveness analysis (36%) and cost utility analysis (18%). Other types of economic analyses (cost benefit, cost consequences etc.) were used in less than 7% of studies.

Economic parameters were measured using wide range of instruments: study records (e.g. preference-based and resource use questionnaires, diaries, case report forms) 38%; registries and databases (e.g. primary care records, hospital databases, medical insurance claims) 33%; published literature (e.g. research papers, systematic reviews, meta-analyses, guidelines, tariffs) 22%; population surveys (6%); expert panels (1%).

Characteristics of economic parameters

We identified 65 economic parameters which we aggregated into 11 groups, each containing from 3 to 10 items: medication, primary care, secondary care, emergency care, diagnostics, drug delivery devices, health care delivery, informal care, work productivity, school activity and health utility (Table 2)

Medication use was the largest group of economic parameters, capturing use of asthma medication (e.g. long-acting beta agonists, short-acting beta agonists, inhaled corticosteroids, allergen immunotherapy and monoclonal antibodies), combination therapies, concomitant medication, treatment of drug adverse events, and over-the-counter medication.

Primary care parameters included scheduled and unscheduled contacts with general practitioners and nurses (face-to-face appointments, telephone contacts and home visits), specialty consultations (e.g. chest physician, allergy/internal medicine specialist or ENT doctor), acupuncture and physiotherapy, and medical claims. Specialty consultations can be also provided as outpatient hospital appointments, depending on the health care system. Where outpatient/hospital appointments were not specifically mentioned, we allocated specialty consultations to primary care.

Secondary care parameters were used to measure hospital-based care, including outpatient appointments, hospital admissions and re-admissions, hospital supplies, room charges, and medical claims.

Emergency care parameters included ambulance calls and attendances, emergency department visits, intensive care costs, and out-of-hours contacts. While emergency services are mainly provided by the secondary care sector, these are usually analysed as a separate group.

Diagnostics parameters capture resources and costs associated with asthma diagnosis and monitoring, such as procedures (e.g. peak expiratory flow measurements), equipment (e.g. exhaled nitric oxide monitor) and laboratory tests (e.g. IgE test).

Drug delivery parameters apply to medical devices used to deliver drugs directly to the airways. These include inhalers (pressurised metered dose inhalers, breath-actuated aerosol inhalers and dry powder inhalers), nebulizers (which create mist breathed in through a mask or mouthpiece), spacers (extension devices that are placed at the interface between the patient and the inhaler) and valved holding chambers (extensions which allow inhalation and prevent exhalation into the chamber). Parameters related to drug delivery devices include cost and number of prescribed items and cost of respiratory therapy.

Health care delivery parameters include time and cost associated with attending health care appointments (e.g. travel and waiting), health care programme delivery costs (e.g. telemetry), and willingness to pay for services.

Informal care parameters capture burden and costs related to care (usually unpaid) provided by family or friends to people with asthma. These parameters include: caregivers' time off work, productivity losses, early retirement, housekeeping costs. We also allocated to this group household modifications (e.g. air filters or dehumidifiers), due to small number of such parameters.

Work productivity parameters capture the effect of asthma on work activity, for example, time off work due to illness, income loss, disability payments and premature retirement.

School activity parameters capture the effect of asthma on school attendance, presenteeism, contacts with school nurses, etc.

Health utility parameters are preference-based health-related quality of live values which people attach to the overall health status. We included in this group quality-adjusted life years and years lived with disability. It should be mentioned that health utilities are used as health outcomes as well as economic outcomes in asthma studies.

Figure 2 shows the proportional use of economic parameters in asthma studies. Secondary care parameters were the most frequently used group (24%), followed by primary care (20%) medication use (18%), emergency care (11%) and work (10%). Other parameter groups (informal care, school, diagnostics, healthcare delivery and health utilities) were found in 0.5% - 4% of studies.

Framework analysis

An analytical framework was developed to examine the use of economic parameters in different contexts of economic evaluation. The framework includes five domains (perspective of economic evaluation, intervention, population, study design and study setting; Figure 3) and is further described below alongside analysis of the identified economic parameters.

Perspective of economic evaluation reflects the stakeholders' viewpoint from which economic evaluation is conducted. Some studies adopt narrow perspectives such as that of patient, or health insurance provider. Wider perspectives include those of society, health care and social care. The following perspectives were identified: healthcare provider (n=122); societal (n=68); third-party payer (e.g. health insurance providers and government plans) (n=39); patient (n=5). Thirty-nine studies adopted multiple perspectives, such as healthcare provider and societal. In studies conducted from a healthcare provider perspective, the top three most frequently used parameters were: secondary care, primary care and medication use. In studies conducted from a societal perspective these were: primary care, secondary care and work. Studies which adopted a third-party payer perspective included secondary care, medication use and emergency care among the most frequently used parameters (Appendix 3).

Intervention is a health technology under investigation which may or may not be compared to an alternative technology. The types of interventions used in asthma studies included: medication (n=107), procedures (n=28), educational interventions (n=21) diagnostics (n=8) environmental interventions (n=2), adherence interventions (n=1) and non-interventional studies (e.g. surveys, cost of illness n=57). The most frequently used parameters for medication interventions were primary care, secondary care and medication use; for procedure interventions - secondary care, primary care and emergency care; for educational interventions – secondary care, emergency care and primary care; for diagnostics interventions – primary care, secondary care and diagnostics. The use of economic parameters in studies with different interventions is depicted in Figure 4. The full ranking of economic parameters is shown in Appendix 3.

Population refers to characteristics of study participants such as sample size, age, gender, severity of asthma, etc. We were able to isolate three age groups: children (<18 years) (n=46), adults (18+ years) (n=68), and a mixed population including both children and adults (n=75). More detailed breakdowns were not possible due to studies reporting aggregated age data. Secondary care, primary care, medication use and emergency care were the most frequently used parameters in all age groups. Studies with children also included parameters on school absence and informal care, while studies with adult population reported sick leave, productivity loss, work absenteeism and presenteeism. Secondary care, primary care, medication use and emergency care were also the most frequently reported parameters in patients with different asthma severity (mild, moderate and severe asthma, Appendix 3).

Study design refers to the methods and procedures of data gathering. The most frequently used research designs were cohort studies (n=83), randomized controlled trials (n=75) and economic modelling studies (n=51). Other designs such as surveys and literature reviews were used in 16 studies. Secondary care, primary care, medication use and emergency care were the most frequently used parameters across different study designs (Appendix 3).

Setting refers to different sites, facilities and providers of health and social care, such as GP practice, hospital, school, pharmacy, etc. The majority of experimental studies were conducted in primary care settings (n=100) and secondary care settings (n=80). Secondary care, primary care, medication use and emergency care were the most commonly used economic parameters in these settings. A small number of studies were conducted in schools (n=9), community (n=7), pharmacy (n=4) and A&E (n=2). These studies also included work- and school-related parameters (e.g. sick leave, productivity loss, school absence) among the most frequently used parameters.

Preliminary list of core economic parameters

To derive a preliminary list of core economic parameters used in past studies, we ranked 11 resource groups based on the frequency of usage of economic parameters. Parameters related to secondary care, primary care, medication use, emergency care and work (ranks 1-5, Table 3) comprised 84% of all economic parameters used in asthma studies. The less frequently used parameters were related to diagnostics (4.2%) health utility (3.5%), healthcare delivery (3.4%), informal care (2.5%), school (2.4%) and devices (0.5%). Additional ranking was performed using the analytical framework to categorize economic parameters with respect to different types of interventions, populations, study designs, settings and stakeholder perspectives (Table 4). The ranking shows that groups representing secondary care, primary care, medication use, emergency care and work productivity (ranks 1-5) were the most frequently used groups of economic outcomes across different studies. These followed by diagnostics (median rank 6), health utility and health care delivery (median ranks 8), school and informal care (median ranks 9) and drug delivery devices (median rank 11).

The above results suggest that economic parameters related to secondary care, primary care, medication use, emergency care and work productivity can be considered as the core parameters in asthma studies. Parameters related to asthma diagnostics, drug delivery devices, healthcare delivery, informal care, school and health utility can be considered as supplementary parameters, which apply to certain types of interventions, populations, study designs or stakeholder perspectives.

Discussion

We have described the first step in developing core parameters sets specifically for asthma-related economic evaluations. Our examination of past research suggests the core parameter set includes parameters related to secondary care, primary care, medication use, emergency care and work.

The methodology of developing core outcome sets is well developed and thoroughly described in literature.[4,6,18-21] It includes a range of qualitative techniques such as systematic literature reviews, interviews with stakeholders, group discussions, surveys, conceptual frameworks, Delphi studies, and combinations of these.[4,18,19,21]

The process of developing core outcome sets usually includes following steps:[6]

1. Defining a scope for developing core outcome set;
2. Identifying existing knowledge (e.g. using systematic literature reviews);
3. Involving key stakeholders (e.g. using surveys, interviews and focus groups);
4. Achieving consensus (e.g. using Delphi process);
5. Validating core outcome set (e.g. using reviews and feedback);
6. Implementing core outcome set.

While our work follows the approach set out by Willamson and co-authors [6], which specifically focuses on developing core outcome sets for defined clinical areas, we acknowledge alternative approaches to generalize the use of economic parameters in clinical studies.

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) initiative proposed a checklist of items to be reported in economic evaluations of healthcare interventions.[22] This included economic parameters such as incremental costs and effectiveness estimates, health utility, characteristics of uncertainty and heterogeneity. However, the checklist is necessarily general in nature because it aims to address all economic evaluations and it primarily focuses on improving *reporting* standards and thus provides limited guidance on the *choice* of parameters to be used.

The Database of Instruments for Resource Use Measurement (DIRUM) project aimed to develop a database of instruments for collecting economic parameters in clinical trials.[23.] The database currently contains 84 validated and non-validated instruments, including resource use questionnaires for asthma studies (http://www.dirum.org/instruments/all). Included questionnaires are unlikely to be used off the shelf, but they provide a good starting point in selecting and standardising parameters for new studies.

The Outcome Measures in Rheumatology (OMERACT) initiative focuses on developing effectiveness outcomes for rheumatology studies and its analytical framework incorporates economic outcomes

such as direct, indirect and intangible costs, and impacts on society, individuals and healthcare system.[24] It recommends including at least one domain describing resource use in clinical trials, but it does not specify the set of economic parameters to be collected.

Within the asthma area, the first attempt to standardise economic outcomes was undertaken at a National Institutes of Health workshop in March 2010.[12] The outcomes were classified as core (required in future studies), supplemental (used according to study aims and standardised), and emerging (requiring validation and standardisation). Core economic outcomes included asthma-specific hospital admissions, emergency department visits, outpatient visits and medication use. Supplemental parameters included primary care visits (scheduled and unscheduled), specialty and respiratory care; work and school absences. The emerging parameters were identified as patient-initiated remote care event (such as e-mail or telephone consultations), student achievements and test results. However, the above study[12] did not attempt to characterise the usage of economic parameters in asthma studies, as we have done here.

Our aim was to conduct a mixed-methods research which included a systematic literature review and an analytical framework. The methodology was based on a realist review approach to address the complexity of contexts and the heterogeneity of economic parameters.[13,14] Realist reviews have been previously used to analyse the effectiveness of complex policy interventions in health and social care, for example, providing school meals,[25] internet-based health education,[26] smoking cessation,[27] and managing diabetes in people with dementia.[28] We felt that the realist methodology can be equally applied to deriving core parameter sets, given that neither qualitative nor quantitative analyses alone would produce meaningful results.

We used an analytical framework analysis to identify contextual factors which inform the choice of economic parameters in asthma studies. These factors were: type of intervention, study design, target population, research setting and stakeholder perspective. The above framework was used to analyse economic parameters identified by the systematic literature review. The process of developing the framework was non-sequential and iterative in nature; the framework was changing as the new evidence was uncovered. The analytical framework was subsequently used to rank economic parameters identified by the systematic review. Sixty-five economic parameters were grouped into eleven economic categories to enable the analysis. This allowed identifying the most frequently used economic parameters across different intervention, study designs, target populations, research settings and stakeholder perspectives. These categories included parameters representing secondary care, primary care, medication use, emergency care and work, and can be identified as core economic parameters. Supplementary parameter categories such as health utility, healthcare delivery, school, informal care and devices could apply to a certain types of studies (e.g. community- and school-based interventions, uncontrolled asthma, organizational changes and drug delivery devices).

This study has following limitations:

1. The study would benefit from including wider literature sources (e.g. clinical guidelines) in the systematic review;

2. The study would benefit from involving stakeholders (e.g. patients and health care professionals) in identifying relevant economic outcomes.

These limitations will be addressed in the next stage of developing economic parameter sets –refining core economic outcomes using Delphi study. It will involve a national panel including health care professionals, people with asthma, parents, relatives and carers of people with asthma. Each participant will have an opportunity to rank each parameter as important or unimportant to them, as well as to nominate economic parameters of potential relevance that have not been identified from past studies. After the first round, any parameters that are universally considered to be unimportant will be removed. In the following round, participants will be given a feedback on how other stakeholders ranked the remaining parameters and have the opportunity to alter their ratings. Upon reaching consensus on parameters sets, an international workshop will be organised to discuss the applicability of proposed sets for asthma studies nationally and worldwide. To ensure uptake of the core parameters sets we will engage with clinical guideline developers, research funders, trial registries, ethics committees, patients and public representatives.

Abbreviations

AUKCAR: Asthma UK Centre for Applied Research; COMET: Core Outcome Measures in Effectiveness Trials; CHEERS: Consolidated Health Economic Evaluation Reporting Standards; DIRUM, Database of Instruments for Resource Use Measurement; OMERACT: Outcome Measures in Rheumatology; HR-QoL: Health-Related Quality of Life; QALY: Quality Adjusted Life Years, YLD: Years Lived with Disability.

Contributors

CR, ZQ and NH conducted database searches, literature selection and data extraction. AP conceived and provided intellectual leadership to the project and chaired group discussions at the Methodology Workshop “Maximising Information from Empirical Studies” (London, 23 January, 2017). NH conducted data analyses. NH and CR wrote the first draft of the manuscript and integrated comments from co-authors. AP, DF, CP and ZQ critically revised the manuscript and provided methodological input.

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Competing interests

The authors declare that they have no competing interests.

Patient consent

Not required

Ethics approval

Not required

Data sharing statement

No additional data are available

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Table 1. Summary characteristics of studies included in the systematic review (N=224)

Study characteristics	N	%
Country		
Europe (incl. Denmark, Finland, France, Germany, Ireland, Italy, Netherlands, Spain, Sweden, Switzerland)	83	37
UK	31	14
USA	82	37
Canada	20	9
Multinational	19	8
Other	20	9
Population		
adults only	68	30
children	46	21
adults and children	75	33
not specified *(incl. hypothetical cohorts)*	35	16
Sample size		
<100	19	8
100-1000	95	42
>1000	56	25
not specified *(incl. economic models)*	54	24
Asthma severity		
mild	41	18
moderate	53	24
severe	50	22
other classification (*incl. allergic, acute, persistent, uncontrolled*)	56	25
not specified	99	44
Type of study		
cohort study	83	37
RCT	75	33
economic model	51	23
survey	10	4
literature review	6	3
Type of intervention		
medication	107	48
procedures	28	13
educational interventions	21	9
tests	8	4
other interventions (*e.g. environmental, adherence*)	3	1
non-interventional studies *(e.g. surveys, cost-of-illness study)*	57	25
Perspective of economic analysis		
healthcare provider	122	54
societal	68	30
third-party payer *(e.g. insurance companies, managed care organisations)*	39	17
other perspectives *(e.g. patients, employer)*	6	3
not specified	21	9
Type of economic analysis		
cost analysis	94	42
cost effectiveness	84	38
cost utility	41	18
cost benefit	6	3
cost consequences	2	1
cost minimization	2	1
other analysis (*e.g. resource use, literature review of economic analysis*)	4	2
Sources of economic outcomes		
study records	89	40
registries and databases	77	34

published sources	51	23
population surveys	13	6
expert panels	3	1
not specified	2	1

*rounded to the nearest whole number. Some studies may belong to several groups, therefore percentages may not add to 100%

Table 2. Economic parameters identified by the systematic review

Resource group	Economic parameter
Secondary care	hospital admissions duration of stay in hospital use of hospital services/beds supplies and room charges outpatient visits/consultations re-admissions medical claims
Primary care	physician/GP visits contacts with nurse physiotherapy sessions specialist consultations home visits telephone consultations unscheduled consultations physiotherapy sessions acupuncture sessions medical claims
Medication use	drugs number/dose/frequency/cost number of items prescribed/number of prescriptions net ingredient cost combination therapies and concomitant medication treatment cost of drug-related adverse events pharmacy costs cost savings from medication averted pharmacy claims over-the-counter medication rescue/acute medication
Emergency care	emergency department visits and admissions intensive care ambulance calls and attendances out-of-hours services
Work	time off work due to illness number of sickness episodes productivity loss due to absenteeism and presenteeism lost income workers' compensations and disability payments inability to perform usual activities unpaid work premature retirement
Diagnostics	diagnostic procedures diagnostic equipment laboratory tests
Health utility	QALY YLD HR-QoL
Healthcare delivery	travel time/cost time spent by patient attending hospital/clinic time spent by accompanying person attending hospital/clinic waiting time/cost cost of care delivery programme willingness to pay for services
School	days off school number of sickness episodes school fees lost school clinic consultations

	cost of school nurse
Informal care	time off work for caregivers parents'/caregivers' work productivity losses loss of work/income for parents/caregivers early retirement of caregivers housekeeping costs household modifications (e.g. air filters, dehumidifiers)
Devices	type of inhaler device/cost number of items prescribed cost of respiratory therapy (nebuliser)

Table 3. Ranking of economic parameters according to frequency of their use in studies included in the systematic review

Parameter group	Count of use	% of total use	Rank
Secondary care	246	22.8	1
Primary care	215	19.9	2
Medication	185	17.1	3
Emergency care	153	14.2	4
Work	102	9.5	5
Diagnostics	45	4.2	6
Health utility	38	3.5	7
Healthcare delivery	37	3.4	8
Informal care	27	2.5	9
School	26	2.4	10
Devices	5	0.5	11

Table 4. Ranking of economic parameters (groups) in studies with different characteristics

Framework domain	Study characteristics	Secondary care	Primary care	Medication use	Emergency care	Work	Diagnostics	Health utility	Healthcare delivery	School	Informal care	Devices
Population	Adults	1	2	3	4	5	6	7	8	11	9	10
	Children	1	2	3	4	5	7	10	8	6	9	11
	Mild asthma	1	3	2	4	5	6	8	9	7	10	11
	Moderate asthma	1	2	3	4	5	6	7	8	9	10	11
	Severe asthma	1	3	2	4	5	6	7	8	10	9	11
Study design	RCT	2	1	3	4	5	6	8	10	7	9	11
	Cohort study	1	3	2	4	5	6	10	9	7	8	11
	Economic model	1	3	2	4	6	7	5	8	10	9	11
	Cost analysis	1	4	2	3	5	7	11	8	6	9	10
	Cost-effectiveness analysis	2	1	3	4	5	6	9	7	10	8	11
	Cost-utility analysis	2	1	3	5	6	7	4	8	10	9	11
Intervention	Medication	2	1	3	4	5	7	6	10	9	8	11
	Education	1	3	7	2	4	6	9	5	8	11	10
	Procedure	1	2	10	3	4	7	9	6	5	8	11
	Test	2	1	6	4	7	3	8	5	10	11	9
Setting	Primary care	1	2	3	4	5	6	8	7	9	10	11
	Secondary care	1	2	3	4	5	6	7	8	10	9	11
Perspective	Health care provider	1	2	3	4	5	7	6	8	10	9	11
	Societal	2	1	4	5	3	8	10	9	7	6	11
	Third party payer	1	4	2	3	5	6	7	9	11	8	10
Median rank		**1**	**2**	**3**	**4**	**5**	**6**	**8**	**8**	**9**	**9**	**11**

Figure 1. Flow diagram showing the process of identifying and selecting relevant studies

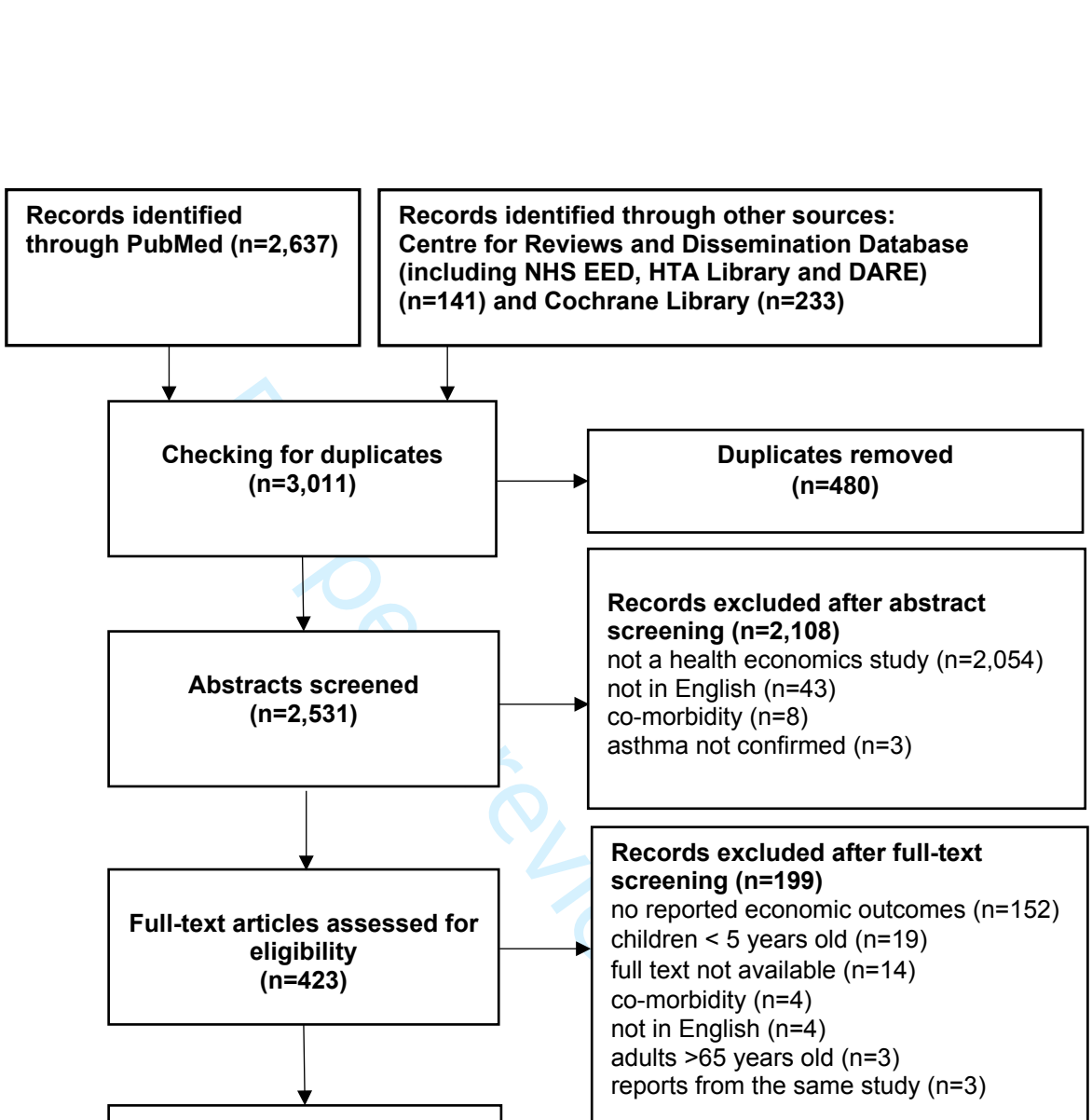


Figure 2. Proportional use of economic parameters in identified studies

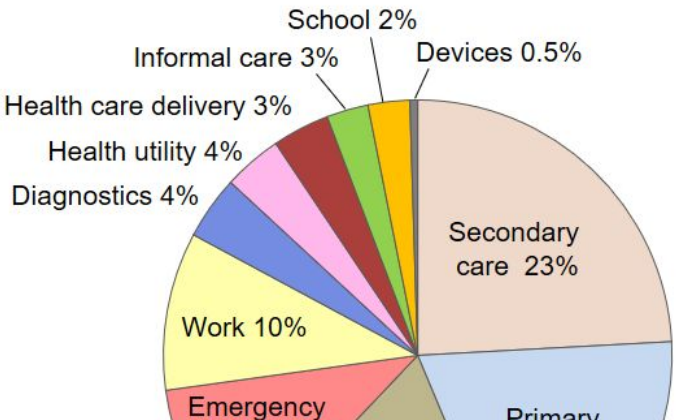


Figure 3. Analytical framework for realist synthesis

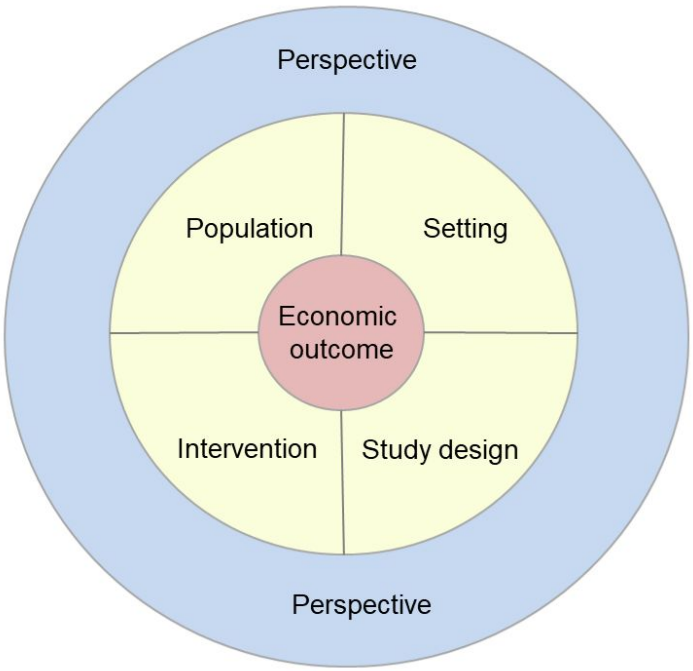
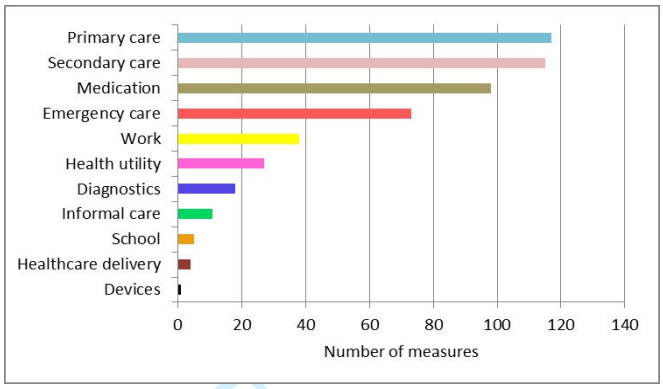
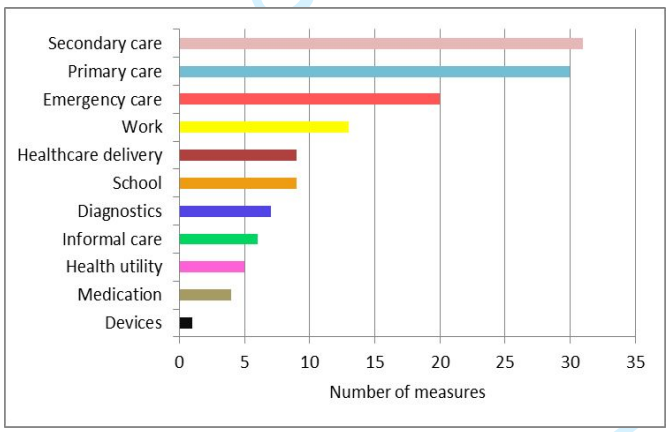


Figure 4. Use of economic parameters in studies with different types of interventions

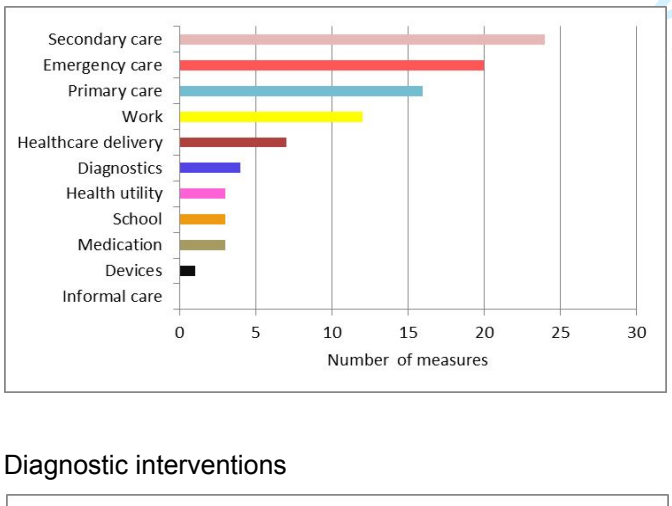
Medication interventions



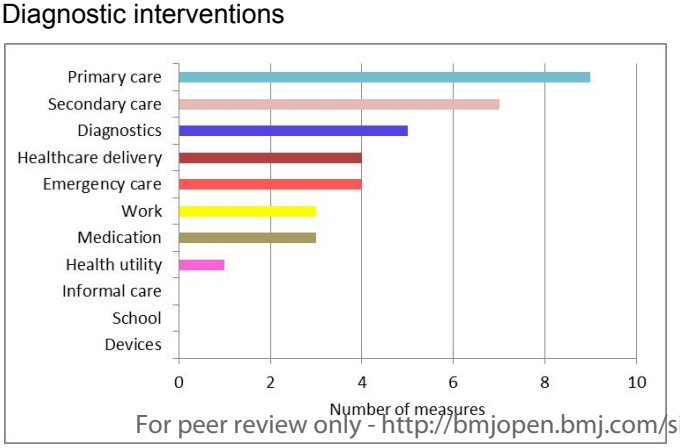
Procedure interventions



Educational interventions



Diagnostic interventions



Appendix 1. Keywords used for searching economic parameters.

Category	Keywords
Primary care	primary, GP, physician, nurse, specialist, home, telephone, physio, ambulatory, acupuncture, psychologist, unscheduled (visits)
Secondary care	hospital, outpatient, inpatient, clinic
Emergency care	A&E, emergency, ambulance, intensive, ICU, out-of-hours
Medication	medication, drug, adherence
Diagnostics	diagnostic, test
Work	work, productivity (loss), disability, retirement, absenteeism, presenteeism, earnings
School	school, nursery
Informal care	informal (care), parent, caregiver, carer, child care, family (help, care), house (help, worker)
Health care delivery	travel, waiting, supplies, education, admin, willingness (to pay), personnel, bedding, (home) improvements
Devices	device, inhaler, nebuliser
Health utility	QALY(quality-adjusted life years), HR-Qo (health-related quality of life), YLD (years lived with disability)

Appendix 2. List of studies included in the systematic review

1. Aballea S, Cure S, Vogelmeier C, Wiren A. A retrospective database study comparing treatment outcomes and cost associated with choice of fixed-dose inhaled corticosteroid/long-acting β2-agonists for asthma maintenance treatment in Germany. International journal of clinical practice. 2008;62(12):1870-9.
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Appendix 3. Ranking of economic outcomes

Population

Adults	**N**	**Rank**
Secondary care	74	1
Primary care	63	2
Medication use	59	3
Emergency care	41	4
Work	36	5
Diagnostics	18	6
Health utility	14	7
Healthcare delivery	9	8
Informal care	2	9
Devices	1	10
School	1	11

Children	**N**	**Rank**
Secondary care	57	1
Primary care	49	2
Medication use	40	3
Emergency care	32	4
Work	17	5
School	16	6
Diagnostics	11	7
Healthcare delivery	11	8
Informal care	9	9
Health utility	6	10
Devices	1	11

Setting

Primary care	**N**	**Rank**
Secondary care	113	1
Primary care	102	2
Medication use	87	3
Emergency care	70	4
Work	38	5
Diagnostics	22	6
Healthcare delivery	17	7
Health utility	14	8
School	13	9
Informal care	8	10
Devices	5	11

Secondary care	**N**	**Rank**
Secondary care	68	1

Primary care	49	2
Medication use	41	3
Emergency care	33	4
Work	30	5
Diagnostics	12	6
Health utility	11	7
Healthcare delivery	10	8
Informal care	6	9
School	5	10
Devices	0	11

Study design

RCT	**N**	**Rank**
Primary care	106	1
Secondary care	81	2
Medication use	66	3
Emergency care	60	4
Work	34	5
Diagnostics	12	6
School	9	7
Health utility	9	8
Informal care	8	9
Healthcare delivery	7	10
Devices	1	11

Cohort study	**N**	**Rank**
Secondary care	92	1
Medication use	66	2
Primary care	55	3
Emergency care	48	4
Work	36	5
Diagnostics	16	6
School	12	7
Informal care	12	8
Healthcare delivery	11	9
Health utility	4	10
Devices	0	11

Model	**N**	**Rank**
Secondary care	55	1
Medication use	42	2
Primary care	42	3
Emergency care	33	4
Health utility	23	5
Work	18	6

Diagnostics	14	7
Healthcare delivery	11	8
Informal care	5	9
School	3	10
Devices	0	11

Asthma severity

Mild	**N**	**Rank**
Secondary care	44	1
Medication use	38	2
Primary care	38	3
Emergency care	31	4
Work	19	5
Diagnostics	13	6
School	7	7
Health utility	7	8
Healthcare delivery	7	9
Informal care	5	10
Devices	2	11

Moderate	**N**	**Rank**
Secondary care	57	1
Primary care	49	2
Medication use	48	3
Emergency care	39	4
Work	28	5
Diagnostics	14	6
Health utility	10	7
Healthcare delivery	8	8
School	7	9
Informal care	7	10
Devices	2	11

Severe	**N**	**Rank**
Secondary care	56	1
Medication use	43	2
Primary care	42	3
Emergency care	37	4
Work	19	5
Diagnostics	18	6
Health utility	13	7
Healthcare delivery	9	8
Informal care	7	9
School	5	10
Devices	2	11

Type of intervention

Medication use	N	Rank
Primary care	117	1
Secondary care	115	2
Medication use	98	3
Emergency care	73	4
Work	38	5
Health utility	27	6
Diagnostics	18	7
Informal care	11	8
School	5	9
Healthcare delivery	4	10
Devices	1	11

Education	N	Rank
Secondary care	24	1
Emergency care	20	2
Primary care	16	3
Work	12	4
Healthcare delivery	7	5
Diagnostics	4	6
Medication use	3	7
School	3	8
Health utility	3	9
Devices	1	10
Informal care	0	11

Procedures	N	Rank
Secondary care	31	1
Primary care	30	2
Emergency care	20	3
Work	13	4
School	9	5
Healthcare delivery	9	6
Diagnostics	7	7
Informal care	6	8
Health utility	5	9
Medication use	4	10
Devices	1	11

Test	N	Rank
Primary care	9	1
Secondary care	7	2
Diagnostics	5	3

Emergency care	4	4
Healthcare delivery	4	5
Medication use	3	6
Work	3	7
Health utility	1	8
Devices	0	9
School	0	10
Informal care	0	11

Type of economic analysis

CA	N	Rank
Secondary care	109	1
Medication use	72	2
Emergency care	71	3
Primary care	57	4
Work	48	5
School	17	6
Diagnostics	14	7
Healthcare delivery	13	8
Informal care	11	9
Devices	2	10
Health utility	0	11

CEA	N	Rank
Primary care	112	1
Secondary care	91	2
Medication use	74	3
Emergency care	53	4
Work	34	5
Diagnostics	19	6
Healthcare delivery	11	7
Informal care	10	8
Health utility	10	9
School	6	10
Devices	2	11

CUA	N	Rank
Primary care	42	1
Secondary care	39	2
Medication use	35	3
Health utility	33	4
Emergency care	31	5
Work	16	6
Diagnostics	12	7
Healthcare delivery	5	8

Informal care	3	9
School	2	10
Devices	1	11

Perspective

Health care provider	**N**	**Rank**
Secondary care	134	1
Primary care	131	2
Medication use	104	3
Emergency care	93	4
Work	46	5
Health utility	26	6
Diagnostics	23	7
Healthcare delivery	17	8
Informal care	15	9
School	14	10
Devices	3	11

Societal	**N**	**Rank**
Primary care	74	1
Secondary care	66	2
Work	66	3
Medication use	54	4
Emergency care	46	5
Informal care	17	6
School	16	7
Diagnostics	15	8
Healthcare delivery	15	9
Health utility	12	10
Devices	1	11

Third party payer	**N**	**Rank**
Secondary care	48	1
Medication use	30	2
Emergency care	27	3
Primary care	20	4
Work	14	5
Diagnostics	6	6
Health utility	3	7
Informal care	2	8
Healthcare delivery	2	9
Devices	1	10
School	1	11

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Pages 3 and 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Protocol paper
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 4, Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Pages 4 and 5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 5 and Protocol paper (Appendix 3)
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A, explained on Page 4

PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (I^2) for each meta-analysis.	Page 5

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 6 Figure 1 Appendix 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 6 Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A, explained on Page 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 7 and Page 8, Table 2 Appendix 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A, explained on Page 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 9-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 10

PRISMA 2009 Checklist

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 9-11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 11

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Developing core economic parameter sets for asthma studies: A realist review and an analytical framework

Chris Roukas[1], Zahidul Quayyum[2], Anita Patel[3], Deborah Fitzsimmons[4], Ceri Phillips[4], Natalia Hounsome[5].

[1]Pragmatic Clinical Trials Unit, Centre of Primary Care and Public Health, Queen Mary University of London, London, UK
[2]BRAC James P Grant School of Public Health, BRAC University, Dhaka, Bangladesh
[3]Anita Patel Health Economics Consulting Ltd, London, UK
[4]Asthma UK Centre for Applied Research, Swansea Centre for Health Economics, Swansea University, Swansea, UK
[5]Brighton and Sussex Medical School, University of Sussex, Falmer, Brighton, UK

Correspondence to: Natalia Hounsome, Brighton and Sussex Medical School, University of Sussex, Falmer, Brighton, UK. Email: n.hounsome@bsms.ac.uk

Abstract

Objective: To develop a standardised set of economic parameters (core economic parameter set) for economic evaluations in asthma studies.

Design: A systematic literature review and an analytical framework.

Outcome measures: Economics parameters used to evaluate costs and cost-effectiveness of healthcare interventions for people with asthma.

Data sources: PubMed, the Cochrane Database of Systematic Reviews (CDSR), the NHS Economic Evaluation Database (EED), the Database of Abstracts of Reviews of Effects (DARE) and the HTA Library starting from 1990.

Review methods: Research methods were based on the realist review methodology and included a number of non-sequential, iterative and overlapping components, such as: developing an analytical framework for the realist review; systematic literature review of economic parameters; identifying and categorising economic parameters; producing preliminary list of core economic parameters.

Results: Database searches found 2,531 publications of which 224 were included in the systematic review. We identified 65 economic parameters which were categorised into 11 groups to enable the realist synthesis. Parameters related to secondary care, primary care, medication use, emergency care and work productivity comprised 84% of all economic parameters. An analytical framework was used to investigate the rationale behind the choices of economic parameters in these studies. The main framework domains included: type of intervention, research population, study design, study setting, and a stakeholder perspective.

Conclusion: Past research thus suggests that in asthma studies parameters depicting the use of secondary care, primary care, medication, emergency care and work productivity can be considered as core economic parameters, since they apply to different types of studies. Parameters including diagnostics, healthcare delivery, school activity, informal care, medical devices and health utility apply to a particular type of study (or research question), and thus can be recommended as supplemental parameters.

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Keywords: asthma studies, health economics, core parameters

Word count: 5,111

Strengths and limitations of this study

1. Research methods were based on the realist review methodology;
2. We developed an analytical framework to investigate the rationale behind the choices of economic parameters in asthma studies;
3. We identified the most frequently used economic parameters;
4. We derived a preliminary list of core economic parameters;
5. The main limitation of this study – lack of stakeholder involvement in identifying economic parameters - will be addressed in the next stage using Delphi methodology.

Background

Asthma is a common disease characterised by recurrent attacks of breathlessness and wheezing. It affects 5.4 million people in the UK: one in 11 children and one in 12 adults.[1,2] According to the International Clinical Trials Registry Platform [3] there are currently 4,391 registered trials for asthma. Many of these studies report different health outcomes, which has consequently made it difficult for researchers to compare the available evidence.[4,5] Selecting appropriate health outcomes at the study design stage is essential to ensure comparability between different studies, to reduce heterogeneity between reported outcomes, to facilitate evidence synthesis, and to minimise the risk of outcome reporting bias.[4-6]

In the last decade, there has been general move towards developing core outcome sets for use in clinical trials. The Core Outcome Measures in Effectiveness Trials (COMET) Initiative, launched in 2010, 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. The COMET initiative provides a methodological platform for developing core outcome sets for different diseases and medical conditions.[7]

In recent years, economic evaluation has become an essential part of clinical studies to assist decision makers with allocating resources in healthcare. Economic evaluation involves a "comparative analysis of alternative courses of action in terms of both their costs and consequences".[8] Therefore, economic evaluations necessarily need to collate information on both economic outcomes and health outcomes. Health outcomes represent health benefits (e.g. symptom relief, faster recovery or better quality of life) and may be either of a generic nature or specific to the condition being examined. Economic outcomes may include resource use (e.g. number of prescriptions, or days in hospital), costs (e.g. cost of medication and diagnostic equipment), or combined metrics of costs and outcomes (e.g. incremental cost-effectiveness ratio, probability of intervention being cost-effective). In the context of economic evaluations, preference-based health outcomes (e.g. quality-adjusted life years or disability-adjusted life years), can be also considered as economic outcomes. To differentiate between health outcomes and economic outcomes we will use the term "economic parameter".

While currently there are no core parameter sets available for economic evaluations in asthma trials, a number of studies have identified a range of parameters used to evaluate costs and cost-effectiveness

of healthcare interventions for people with asthma.[4, 9-12] Standardising these parameters is essential to ensure consistency in data collection, analyses, reporting and thus to enable valid comparison and evidence synthesis to appropriately inform resource allocation decisions.

We thus set out to develop a core parameter set for economic evaluation of asthma interventions. This paper reports results from the first stage of this process – a systematic literature review and an analytical framework. The aim of this stage was to identify economic parameters which are already in use, and to establish a preliminary list of reported items to be considered for inclusion in the core parameter set. Due to the scope of the review, neither qualitative nor quantitative analyses would produce meaningful results. Therefore, we applied a realist review methodology, which combines quantitative and qualitative approaches and focuses on contextual mechanisms that inform decisions and actions.[13-15] The protocol for this review was published elsewhere.[16]

Methods

Research strategy

The development of economic core parameter will be conducted in three stages. The first stage (described in this paper) includes a systematic literature review to determine what economic parameters are already in use, and to establish a preliminary list of reporting items to be considered for inclusion in the core parameter set. In the second stage, we will use Delphi methodology to determine which economic parameters should be included in effectiveness studies. A national expert panel will be convened for round-table discussions including wide range of stakeholders (health care professionals, people with mild to severe and brittle asthma, as well as parents, relatives and carers of people with asthma) to identify important economic parameters. In the third stage, an international workshop will be convened to discuss the applicability of the Delphi-generated core economic parameter set across international settings and relevant disciplines.

Systematic literature review

The systematic literature review was based on the realist review methodology[13-15] and included a number of non-sequential, iterative and overlapping components, such as: developing an analytical framework for the realist review; systematic literature review of economic parameters; identifying and categorizing economic parameters; producing preliminary list of core economic parameters. The realist methodology uses a mixed methods approach (both quantitative and qualitative) to addressing relationships between context, mechanisms and outcomes. It asks the question “What works for whom, in what circumstances and why?”[13] The realist approach has been used to analyse the effectiveness of complex interventions in health care.[15] In this study we applied the realist framework to address the questions: What economic parameters are used in asthma studies? For what type interventions and populations? In what kind of settings? From what stakeholder perspectives? A systematic literature review was conducted according to the protocol described elsewhere.[16]

Literature searches

We conducted literature searches using PubMed, the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE) and the HTA Library for the period January 1990 - January 2019 and the NHS Economic Evaluation Database (EED) for the period January 1990 - March 2015 (stopped updating). Titles and abstracts were searched for inclusion of the MESH term “asthma” as well as health economics key terms such as “economic”, “cost” and “resource” (Appendix 1). More information about the search strategy is provided in the published protocol.[16] Records from different databases were merged and duplicate publications were removed.

Study selection

Study selection was conducted by three reviewers (including a researcher with experience of asthma) and comprised of two stages. In the first stage, the titles/abstracts were screened according to the pre-specified checklist (Appendix 2) to ensure that the selected studies reported economic parameters, included the relevant population, and were written in English. The second stage was full text screening of studies which fulfilled the above criteria, as well as studies classified as “unsure” in the first stage. Studies were excluded at this stage if they did not report economic parameters, or included people with co-morbidities, or if the full text of study was not available. We also excluded studies conducted with children < 5 years (due to challenges of confirmation of asthma diagnosis) and adults >65 years (who are likely to have a COPD-asthma overlap syndrome), in accordance with the protocol for the systematic review.[16] Studies including children <5 years or adults >65 years among other age groups were marked as “unsure” for further scrutiny. Upon data extraction it was found that studies including children <5 years and adults >65 years along with other age groups comprised more than a half of identified publications. Consequently, a decision was made to include these studies in the systematic review, as this reflects the real-world research context in which a core economic parameter set would be required. Any discrepancies regarding whether a study was relevant for inclusion in the review were resolved via involving the third reviewer.

Ideally, in the realist synthesis no literature should be excluded,[15] unless the paper is not relevant, or provides insufficient information. Therefore, we assessed the studies with respect to their relevance rather than scientific rigor (research question, validity, generalizability, etc.). This approach is consistent with our aim to identify economic parameters which are already in use. However, we excluded studies which provided insufficient information about economic parameters (e.g. reported total costs, but did not specify what these costs included). Figure 1 shows a diagram depicting the flow of papers through the selection process.

Data extraction

Data extraction was conducted by three researchers. All identified economic parameters were tabulated together with the major study characteristics: population; age; asthma severity; number of subjects; country; setting; type of study; type of intervention/comparators; type of economic evaluation; perspective of economic evaluation; costs; sources and instruments used to collect economic parameters

Identifying economic parameters

Economic parameters were identified through term search in Microsoft Excel 2016 using wildcards and keywords (detailed in Appendix 3). Identified parameters were then aggregated into eleven resource groups according to their explicit and implicit meaning. For example, economic parameters such as “accident and emergency”, “emergency department”, “emergency room”, “intensive care unit”, “ambulance”, and “out-of-hours visits” were thought to represent the same group “emergency care”. Aggregating parameters into resource groups was necessary to reduce the number of parameters to enable the realist synthesis.

Ranking economic parameters

Economic parameters were allocated to one of 11 resource groups: “primary care”; “secondary care”, “emergency care”, “informal care”, “medication”, “medical devices”, ”diagnostics”, “work”; “school”, “health care delivery” and “health utility”. For example, if a study reported contacts with primary care doctors and nurses, these were counted as two outcomes, allocated to “primary care”. Results were presented as a frequency of using economic parameters for each resource group.

A ranking of resource groups was conducted to identify the most frequently used parameters which can be considered for inclusion in the core parameter set. The ranking was based on parameter counts. Some studies used more than one economic parameter belonging to the same resource group. The ranking was conducted in two ways: (i) ranking resource groups across all studies included in the systematic review (ii) ranking resource groups among studies with different types on interventions, study designs, population groups, settings and stakeholder perspectives (see below analytical framework).

Analytical framework

An analytical framework was developed using the conceptual framework analysis,[17] which included the following steps:

i) Initial scoping using group discussions with stakeholders and reviewing the literature;

ii) identifying and naming the concepts;

iii) deconstructing and integrating the concepts;

iv) synthesising concepts into a theoretical framework.

The initial scope for the analytical framework was identified from round table discussions within the research team. Initial discussions were carried out at the Asthma UK Centre for Applied Research (AUKCAR) Methodology Workshop "Maximising Information from Empirical Studies" (London, 23 January, 2017). Workshop discussions set out to understand the rationale behind the choices of economic parameters. Subsequent discussions were focused on identifying contexts in which different economic parameters were used (e.g. population age, asthma severity, study characteristics, type of economic analysis). The relationship between different contexts was analysed, and the contexts were integrated into framework domains. The hierarchy between framework domains was established and the domains were arranged into an analytical framework.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans at this stage.

Results

Selected studies

Literature searches identified a total of 3,011 entries before checking for duplicates (Figure 1). The PubMed searches were set deliberately broad and included, alongside specific terms such as "asthma" and "economic", a full range of general terms associated with healthcare resources, for example: "clinician", "nurse", "emergency", "attendance". These searches generated a large number of studies which did not include economic parameters. Therefore, our further searches of CDSR, NHS EED, DARE and the HTA Library included mainly economic terms such as "economic", "cost", "resource", "service", "productivity", etc. Removing duplicates generated 2,531 publications and abstracts were screened using the pre-defined checklist.[16] Approximately 81% of publications were excluded since these were not economic evaluations (e.g. clinical effectiveness studies, service delivery studies, editorials, protocols or methods papers). We also excluded papers which were not in English (n=43), included patients with co-morbidities (n=8), or non-confirmed asthma (n=3). The remaining 423 studies were selected for full-text screening. Out of these, the text was not available for 14 publications; 152 were not full-size papers or did not report economic parameters (e.g. abstracts, commentaries, editorials, reviews); 26 studies were excluded due to populations characteristics (included only children <5 years, adults >65 years old or people with co-morbidity); 4 publications were not in English; 3 reported parameters from the same study. Economic parameters were extracted for 224 studies (listed in Appendix 4).

Characteristics of selected studies

The summary characteristics of studies included in the systematic review are shown in Table 1. The majority (82%) were conducted in the USA, Europe (including the UK) and Canada. Studies undertaken in other countries (Australia, Brazil, Columbia, India, Japan, Thailand and Turkey) comprised 9% of identified studies. Approximately 8% of studies were multinational.

Approximately a third of selected studies (33%) involved both adult and child participants. Thirty percent of studies included only adults and 21% studies included only children. Population age was not specified in 16% of papers, including those based on economic models. The number of participants varied in wide range: 8% of studies included <100 individuals, 42% included 100-1,000 individuals, and 25 % included >1,000 individuals. Sample size was not specified in 25% of studies, including economic models, systematic reviews and cost-of-illness studies. With respect to asthma severity, the majority of studies included mixed populations. Participants with mild, moderate and severe asthma were presented in similar proportions (14%, 18% and 17%, respectively). However, a number of studies used different asthma severity classifications e.g. Global Initiative for Asthma (GINA) classification (intermittent, mild persistent, moderate persistent, and severe persistent), or British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS-SIGN) classification (mild, moderate, severe and life-threatening). A substantial proportion of studies (44%) did not specify asthma severity. In terms of study design, 37% were cohort studies, 33% randomized controlled trials, 23% economic models and 7% were population-level surveys and literature reviews. Half were conducted from a healthcare provider perspective (included costs to healthcare system), 27% considered a societal perspective (e.g. included school absence or parental days off work); 15% pursued a third party payer perspective (e.g. included health insurance claims) and only 2% considered patient or employer perspectives (e.g. included costs to patients or employers). The most common type of economic evaluation was cost analysis (41%), followed by cost effectiveness analysis (36%) and cost utility analysis (18%). Other types of economic analyses (cost benefit, cost consequences etc.) were used in less than 7% of studies.

Economic parameters were measured using wide range of instruments: study records (e.g. preference-based and resource use questionnaires, diaries, case report forms) 38%; registries and databases (e.g. primary care records, hospital databases, medical insurance claims) 33%; published literature (e.g. research papers, systematic reviews, meta-analyses, guidelines, tariffs) 22%; population surveys (6%); expert panels (1%).

Characteristics of economic parameters

We identified 65 economic parameters which we aggregated into 11 groups, each containing from 3 to 10 items: medication, primary care, secondary care, emergency care, diagnostics, drug delivery devices, health care delivery, informal care, work productivity, school activity and health utility (Table 2)

Medication use was the largest group of economic parameters, capturing use of asthma medication (e.g. long-acting beta agonists, short-acting beta agonists, inhaled corticosteroids, allergen immunotherapy and monoclonal antibodies), combination therapies, concomitant medication, treatment of drug adverse events, and over-the-counter medication.

Primary care parameters included scheduled and unscheduled contacts with general practitioners and nurses (face-to-face appointments, telephone contacts and home visits), specialty consultations (e.g. chest physician, allergy/internal medicine specialist or ENT doctor), acupuncture and physiotherapy, and medical claims. Specialty consultations can be also provided as outpatient hospital appointments, depending on the health care system. Where outpatient/hospital appointments were not specifically mentioned, we allocated specialty consultations to primary care.

Secondary care parameters were used to measure hospital-based care, including outpatient appointments, hospital admissions and re-admissions, hospital supplies, room charges, and medical claims.

Emergency care parameters included ambulance calls and attendances, emergency department visits, intensive care costs, and out-of-hours contacts. While emergency services are mainly provided by the secondary care sector, these are usually analysed as a separate group.

Diagnostics parameters capture resources and costs associated with asthma diagnosis and monitoring, such as procedures (e.g. peak expiratory flow measurements), equipment (e.g. exhaled nitric oxide monitor) and laboratory tests (e.g. IgE test).

Drug delivery parameters apply to medical devices used to deliver drugs directly to the airways. These include inhalers (pressurised metered dose inhalers, breath-actuated aerosol inhalers and dry powder inhalers), nebulizers (which create mist breathed in through a mask or mouthpiece), spacers (extension devices that are placed at the interface between the patient and the inhaler) and valved holding chambers (extensions which allow inhalation and prevent exhalation into the chamber). Parameters related to drug delivery devices include cost and number of prescribed items and cost of respiratory therapy.

Health care delivery parameters include time and cost associated with attending health care appointments (e.g. travel and waiting), health care programme delivery costs (e.g. telemetry), and willingness to pay for services.

Informal care parameters capture burden and costs related to care (usually unpaid) provided by family or friends to people with asthma. These parameters include: caregivers' time off work, productivity losses, early retirement, housekeeping costs. We also allocated to this group household modifications (e.g. air filters or dehumidifiers), due to small number of such parameters.

Work productivity parameters capture the effect of asthma on work activity, for example, time off work due to illness, income loss, disability payments and premature retirement.

School activity parameters capture the effect of asthma on school attendance, number of sickness episodes, school clinic consultations, cost of school nurses and school fees lost.

Health utility parameters are preference-based health-related quality of live values which people attach to the overall health status. We included in this group quality-adjusted life years and years lived with disability. It should be mentioned that health utilities are used as health outcomes as well as economic outcomes in asthma studies.

Figure 2 shows the proportional use of economic parameters in asthma studies. Secondary care parameters were the most frequently used group (24%), followed by primary care (20%) medication use (18%), emergency care (11%) and work (10%). Other parameter groups (informal care, school, diagnostics, healthcare delivery and health utilities) were found in 0.5% - 4% of studies.

Framework analysis

An analytical framework was developed to examine the use of economic parameters in different contexts of economic evaluation. The framework includes five domains (perspective of economic evaluation, intervention, population, study design and study setting; Figure 3) and is further described below alongside analysis of the identified economic parameters.

Perspective of economic evaluation reflects the stakeholders' viewpoint from which economic evaluation is conducted. Some studies adopt narrow perspectives such as that of patient, or health insurance provider. Wider perspectives include those of society, health care and social care. The following perspectives were identified: healthcare provider (n=122); societal (n=68); third-party payer (e.g. health insurance providers and government plans) (n=39); patient (n=5). Thirty-nine studies adopted multiple perspectives, such as healthcare provider and societal. In studies conducted from a healthcare provider perspective, the top three most frequently used parameters were: secondary care, primary care and medication use. In studies conducted from a societal perspective these were: primary care, secondary care and work. Studies which adopted a third-party payer perspective included secondary care, medication use and emergency care among the most frequently used parameters (Appendix 5).

Intervention is a health technology under investigation which may or may not be compared to an alternative technology. The types of interventions used in asthma studies included: medication (n=107), procedures (n=28), educational interventions (n=21) diagnostics (n=8) environmental interventions (n=2), adherence interventions (n=1) and non-interventional studies (e.g. surveys, cost of illness n=57). The most frequently used parameters for medication interventions were primary care, secondary care and medication use; for procedure interventions - secondary care, primary care and emergency care; for educational interventions – secondary care, emergency care and primary care; for diagnostics interventions – primary care, secondary care and diagnostics. The use of economic parameters in studies with different interventions is depicted in Figure 4. The full ranking of economic parameters is shown in Appendix 5.

Population refers to characteristics of study participants such as sample size, age, gender, severity of asthma, etc. We were able to isolate three age groups: children (<18 years) (n=46), adults (18+ years) (n=68), and a mixed population including both children and adults (n=75). More detailed breakdowns were not possible due to studies reporting aggregated age data. Secondary care, primary care, medication use and emergency care were the most frequently used parameters in all age groups. Studies with children also included parameters on school absence and informal care, while studies with adult population reported sick leave, productivity loss, work absenteeism and presenteeism. Secondary care, primary care, medication use and emergency care were also the most frequently reported parameters in patients with different asthma severity (mild, moderate and severe asthma, Appendix 5).

Study design refers to the methods and procedures of data gathering. The most frequently used research designs were cohort studies (n=83), randomized controlled trials (n=75) and economic modelling studies (n=51). Other designs such as surveys and literature reviews were used in 16 studies. Secondary care, primary care, medication use and emergency care were the most frequently used parameters across different study designs (Appendix 5).

Setting refers to different sites, facilities and providers of health and social care, such as GP practice, hospital, school, pharmacy, etc. The majority of experimental studies were conducted in primary care settings (n=100) and secondary care settings (n=80). Secondary care, primary care, medication use and emergency care were the most commonly used economic parameters in these settings. A small number of studies were conducted in schools (n=9), community (n=7), pharmacy (n=4) and A&E (n=2). These studies also included work- and school-related parameters (e.g. sick leave, productivity loss, school absence) among the most frequently used parameters.

Preliminary list of core economic parameters

To derive a preliminary list of core economic parameters used in past studies, we ranked 11 resource groups based on the frequency of usage of economic parameters. Parameters related to secondary care, primary care, medication use, emergency care and work (ranks 1-5, Table 3) comprised 84% of all economic parameters used in asthma studies. The less frequently used parameters were related to diagnostics (4.2%) health utility (3.5%), healthcare delivery (3.4%), informal care (2.5%), school (2.4%) and devices (0.5%). Additional ranking was performed using the analytical framework to categorize economic parameters with respect to different types of interventions, populations, study designs, settings and stakeholder perspectives (Table 4). The ranking shows that groups representing secondary care, primary care, medication use, emergency care and work productivity (ranks 1-5) were the most frequently used groups of economic outcomes across different studies. These followed by diagnostics (median rank 6), health utility and health care delivery (median ranks 8), school and informal care (median ranks 9) and drug delivery devices (median rank 11).

The above results suggest that economic parameters related to secondary care, primary care, medication use, emergency care and work productivity can be considered as the core parameters in

asthma studies. Parameters related to asthma diagnostics, drug delivery devices, healthcare delivery, informal care, school and health utility can be considered as supplementary parameters, which apply to certain types of interventions, populations, study designs or stakeholder perspectives.

Discussion

This paper describes the first step in developing core parameters sets specifically for asthma-related economic evaluations. Based on the systematic literature review, we identified the most frequently used economic parameters, classified these parameters into resource groups, and applied ranking of resource groups to derive a preliminary lists of parameters for inclusion in the core and supplementary parameter sets. Our examination of past research demonstrates a wide range of parameters used for measuring resource utilisation, costs and cost-effectiveness of health care interventions for people with asthma. In total, 65 different economic parameters were used in 224 studies included in this review. The most frequently used parameters were those capturing use of specialised hospital-based (secondary) care and general practice-based (primary) care, followed by parameters quantifying the use of medication, emergency services and work activity. The above parameters can be potentially considered as core economic parameters in future asthma studies.

Approaches to standardising economic parameters

The methodology of developing core outcome sets is well developed and thoroughly described in literature.[4,6,18-21] It includes a range of qualitative techniques such as systematic literature reviews, interviews with stakeholders, group discussions, surveys, conceptual frameworks, Delphi studies, and combinations of these.[4,18,19,21]

The process of developing core outcome sets usually includes following steps:[6]

1. Defining a scope for developing core outcome set;
2. Identifying existing knowledge (e.g. using systematic literature reviews);
3. Involving key stakeholders (e.g. using surveys, interviews and focus groups);
4. Achieving consensus (e.g. using Delphi process);
5. Validating core outcome set (e.g. using reviews and feedback);
6. Implementing core outcome set.

While our work follows the approach set out by Willamson and co-authors [6], which specifically focuses on developing core outcome sets for defined clinical areas, we acknowledge alternative approaches to generalize the use of economic parameters in clinical studies.

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) initiative proposed a checklist of items to be reported in economic evaluations of healthcare interventions.[22] This included economic parameters such as incremental costs and effectiveness estimates, health utility, characteristics of uncertainty and heterogeneity. However, the checklist is necessarily general in nature because it aims to address all economic evaluations and it primarily focuses on improving *reporting* standards and thus provides limited guidance on the *choice* of parameters to be used.

The Database of Instruments for Resource Use Measurement (DIRUM) project aimed to develop a database of instruments for collecting economic parameters in clinical trials.[23.] The database currently contains 84 validated and non-validated instruments, including resource use questionnaires for asthma studies (http://www.dirum.org/instruments/all). Included questionnaires are unlikely to be used off the shelf, but they provide a good starting point in selecting and standardising parameters for new studies.

The Outcome Measures in Rheumatology (OMERACT) initiative focuses on developing effectiveness outcomes for rheumatology studies and its analytical framework incorporates economic outcomes such as direct, indirect and intangible costs, and impacts on society, individuals and healthcare system.[24] It recommends including at least one domain describing resource use in clinical trials, but it does not specify the set of economic parameters to be collected.

Within the asthma area, the first attempt to standardise economic outcomes was undertaken at a National Institutes of Health workshop in March 2010.[12] The outcomes were classified as core (required in future studies), supplemental (used according to study aims and standardised), and emerging (requiring validation and standardisation). Core economic outcomes included asthma-specific hospital admissions, emergency department visits, outpatient visits and medication use. Supplemental parameters included primary care visits (scheduled and unscheduled), specialty and respiratory care; work and school absences. The emerging parameters were identified as patient-initiated remote care event (such as e-mail or telephone consultations), student achievements and test results. However, the above study[12] did not attempt to characterise the usage of economic parameters in asthma studies, as we have done here.

Realist review approach

We conducted a mixed-methods research which included a systematic literature review and an analytical framework. The methodology was based on a realist review approach to address the complexity of contexts and the heterogeneity of economic parameters.[13,14] Realist reviews have been previously used to analyse the effectiveness of complex policy interventions in health and social care, for example, providing school meals,[25] internet-based health education,[26] smoking cessation,[27] and managing diabetes in people with dementia.[28] We felt that the realist methodology can be equally applied to deriving core parameter sets, given that neither qualitative nor quantitative analyses alone would produce meaningful results.

We used an analytical framework analysis to identify contextual factors which inform the choice of economic parameters in asthma studies. These factors were: type of intervention, study design, target population, research setting and stakeholder perspective. The above framework was used to analyse economic parameters identified by the systematic literature review. The process of developing the framework was non-sequential and iterative in nature; the framework was changing as the new evidence was uncovered. The analytical framework was subsequently used to rank economic parameters identified by the systematic review. Sixty-five economic parameters were grouped into eleven economic categories to enable the analysis. This allowed identifying the most frequently used

economic parameters across different intervention, study designs, target populations, research settings and stakeholder perspectives. These categories included parameters representing secondary care, primary care, medication use, emergency care and work, and can be identified as core economic parameters. Supplementary parameter categories such as health utility, healthcare delivery, school, informal care and devices could apply to a certain types of studies (e.g. community- and school-based interventions, uncontrolled asthma, organizational changes and drug delivery devices).

Conclusions

1. The systematic literature review identified a wide range of economic parameters applied in asthma studies to capture the usage of health care services, medication, work and school activities, informal care and health utility. Multiple parameters were used to measure the same economic category (e.g. work activity or medication use).

2. Due to large number of economic parameters and a variety of economic categories identified in asthma studies, an analytical framework is required to enable data synthesis. The mixed-methods analysis based on the realist review methodology is a useful tool for systematising economic parameters.

3. Identifying contextual factors which inform the choices of economic parameters in asthma studies and applying ranking approach can be helpful in identifying economic parameters for inclusion in the preliminary core outcome set.

4. Economic parameters depicting the use of secondary care, primary care, medication, emergency care and work productivity can be considered as core economic parameters, since they apply to different types of studies. Parameters including diagnostics, healthcare delivery, school activity, informal care, medical devices and health utility apply to a particular type of study (or research question), and thus can be recommended as supplemental parameters.

Study Limitations

This study has following limitations:

1. Limited range of data sources. The study focused on peer-reviewed studies and did not include other data sources (e.g. online forums, interviews and focus groups).

2. Ranking based on frequency of usage of economic parameters was the only criteria for inclusion in the preliminary list of core outcomes. Other inclusion criteria can be considered, e.g. based on stakeholder opinions, or on consensus of opinions.

3. Lack of stakeholder involvement in identifying relevant economic parameters (e.g. patients and health care professionals).

These limitations will be addressed in the next stage of developing economic parameter sets – refining core economic outcomes using Delphi study. It will involve a national panel including health care professionals, people with asthma, parents, relatives and carers of people with asthma. Each participant will have an opportunity to rank each parameter as important or unimportant to them, as well as to nominate economic parameters of potential relevance that have not been identified from past studies. After the first round, any parameters that are universally considered to be unimportant will be removed. In the following round, participants will be given a feedback on how other stakeholders ranked the remaining parameters and have the opportunity to alter their ratings. Upon reaching consensus on parameters sets, an international workshop will be organised to discuss the applicability of proposed sets for asthma studies nationally and worldwide. To ensure uptake of the core parameters sets we will engage with clinical guideline developers, research funders, trial registries, ethics committees, patients and public representatives.

Abbreviations

AUKCAR: Asthma UK Centre for Applied Research; COMET: Core Outcome Measures in Effectiveness Trials; CHEERS: Consolidated Health Economic Evaluation Reporting Standards; DIRUM, Database of Instruments for Resource Use Measurement; OMERACT: Outcome Measures in Rheumatology; HR-QoL: Health-Related Quality of Life; QALY: Quality Adjusted Life Years, YLD: Years Lived with Disability.

Contributors

CR, ZQ and NH conducted database searches, literature selection and data extraction. AP conceived and provided intellectual leadership to the project and chaired group discussions at the Methodology Workshop “Maximising Information from Empirical Studies” (London, 23 January, 2017). NH conducted data analyses. NH and CR wrote the first draft of the manuscript and integrated comments from co-authors. AP, DF, CP and ZQ critically revised the manuscript and provided methodological input.

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Competing interests

The authors declare that they have no competing interests.

Patient consent

Not required

Ethics approval

Not required

Data sharing statement

No additional data are available

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Table 1. Summary characteristics of studies included in the systematic review (N=224)

Study characteristics	N	%
Country		
Europe (incl. Denmark, Finland, France, Germany, Ireland, Italy, Netherlands, Spain, Sweden, Switzerland)	83	37
UK	31	14
USA	82	37
Canada	20	9
Multinational	19	8
Other	20	9
Population		
adults only	68	30
children	46	21
adults and children	75	33
not specified *(incl. hypothetical cohorts)*	35	16
Sample size		
<100	19	8
100-1000	95	42
>1000	56	25
not specified *(incl. economic models)*	54	24
Asthma severity		
mild	41	18
moderate	53	24
severe	50	22
other classification (*incl. allergic, acute, persistent, uncontrolled*)	56	25
not specified	99	44
Type of study		
cohort study	83	37
RCT	75	33
economic model	51	23
survey	10	4
literature review	6	3
Type of intervention		
medication	107	48
procedures	28	13
educational interventions	21	9
tests	8	4
other interventions (*e.g. environmental, adherence*)	3	1
non-interventional studies *(e.g. surveys, cost-of-illness study)*	57	25
Perspective of economic analysis		
healthcare provider	122	54
societal	68	30
third-party payer *(e.g. insurance companies, managed care organisations)*	39	17
other perspectives *(e.g. patients, employer)*	6	3
not specified	21	9
Type of economic analysis		
cost analysis	94	42
cost effectiveness	84	38
cost utility	41	18
cost benefit	6	3
cost consequences	2	1
cost minimization	2	1
other analysis (*e.g. resource use, literature review of economic analysis*)	4	2
Sources of economic outcomes		
study records	89	40
registries and databases	77	34

published sources	51	23
population surveys	13	6
expert panels	3	1
not specified	2	1

*rounded to the nearest whole number. Some studies may belong to several groups, therefore percentages may not add to 100%

Table 2. Economic parameters identified by the systematic review

Resource group	Economic parameter
Secondary care	hospital admissions duration of stay in hospital use of hospital services/beds supplies and room charges outpatient visits/consultations re-admissions medical claims
Primary care	physician/GP visits contacts with nurse physiotherapy sessions specialist consultations home visits telephone consultations unscheduled consultations physiotherapy sessions acupuncture sessions medical claims
Medication use	drugs number/dose/frequency/cost number of items prescribed/number of prescriptions net ingredient cost combination therapies and concomitant medication treatment cost of drug-related adverse events pharmacy costs cost savings from medication averted pharmacy claims over-the-counter medication rescue/acute medication
Emergency care	emergency department visits and admissions intensive care ambulance calls and attendances out-of-hours services
Work	time off work due to illness number of sickness episodes productivity loss due to absenteeism and presenteeism lost income workers' compensations and disability payments inability to perform usual activities unpaid work premature retirement
Diagnostics	diagnostic procedures diagnostic equipment laboratory tests
Health utility	QALY YLD HR-QoL
Healthcare delivery	travel time/cost time spent by patient attending hospital/clinic time spent by accompanying person attending hospital/clinic waiting time/cost cost of care delivery programme willingness to pay for services
School	days off school number of sickness episodes school fees lost school clinic consultations

	cost of school nurse
Informal care	time off work for caregivers parents'/caregivers' work productivity losses loss of work/income for parents/caregivers early retirement of caregivers housekeeping costs household modifications (e.g. air filters, dehumidifiers)
Devices	type of inhaler device/cost number of items prescribed cost of respiratory therapy (nebuliser)

Table 3. Ranking of economic parameters according to the frequency of their usage in studies included in the systematic review

Parameter group	Count of use	% of total use	Rank
Secondary care	246	22.8	1
Primary care	215	19.9	2
Medication	185	17.1	3
Emergency care	153	14.2	4
Work	102	9.5	5
Diagnostics	45	4.2	6
Health utility	38	3.5	7
Healthcare delivery	37	3.4	8
Informal care	27	2.5	9
School	26	2.4	10
Devices	5	0.5	11

The ranking was based on parameter counts. The total number of parameters can be larger than the number of studies.

Table 4. Ranking of economic parameters (groups) in studies with different characteristics

Framework domain	Study characteristics	Secondary care	Primary care	Medication use	Emergency care	Work	Diagnostics	Health utility	Healthcare delivery	School	Informal care	Devices
Population	Adults	1	2	3	4	5	6	7	8	11	9	10
	Children	1	2	3	4	5	7	10	8	6	9	11
	Mild asthma	1	3	2	4	5	6	8	9	7	10	11
	Moderate asthma	1	2	3	4	5	6	7	8	9	10	11
	Severe asthma	1	3	2	4	5	6	7	8	10	9	11
Study design	RCT	2	1	3	4	5	6	8	10	7	9	11
	Cohort study	1	3	2	4	5	6	10	9	7	8	11
	Economic model	1	3	2	4	6	7	5	8	10	9	11
	Cost analysis	1	4	2	3	5	7	11	8	6	9	10
	Cost-effectiveness analysis	2	1	3	4	5	6	9	7	10	8	11
	Cost-utility analysis	2	1	3	5	6	7	4	8	10	9	11
Intervention	Medication	2	1	3	4	5	7	6	10	9	8	11
	Education	1	3	7	2	4	6	9	5	8	11	10
	Procedure	1	2	10	3	4	7	9	6	5	8	11
	Test	2	1	6	4	7	3	8	5	10	11	9
Setting	Primary care	1	2	3	4	5	6	8	7	9	10	11
	Secondary care	1	2	3	4	5	6	7	8	10	9	11
Perspective	Health care provider	1	2	3	4	5	7	6	8	10	9	11
	Societal	2	1	4	5	3	8	10	9	7	6	11
	Third party payer	1	4	2	3	5	6	7	9	11	8	10
Median rank		**1**	**2**	**3**	**4**	**5**	**6**	**8**	**8**	**9**	**9**	**11**

Figure legends

Figure 1. Flow diagram showing the process of identifying and selecting relevant studies.

Figure 2. Proportional use of economic parameters in identified studies.

Figure 3. Analytical framework for the realist synthesis.

Figure 4. Use of economic parameters in studies with different types of interventions.

Figure 1. Flow diagram showing the process of identifying and selecting relevant studies

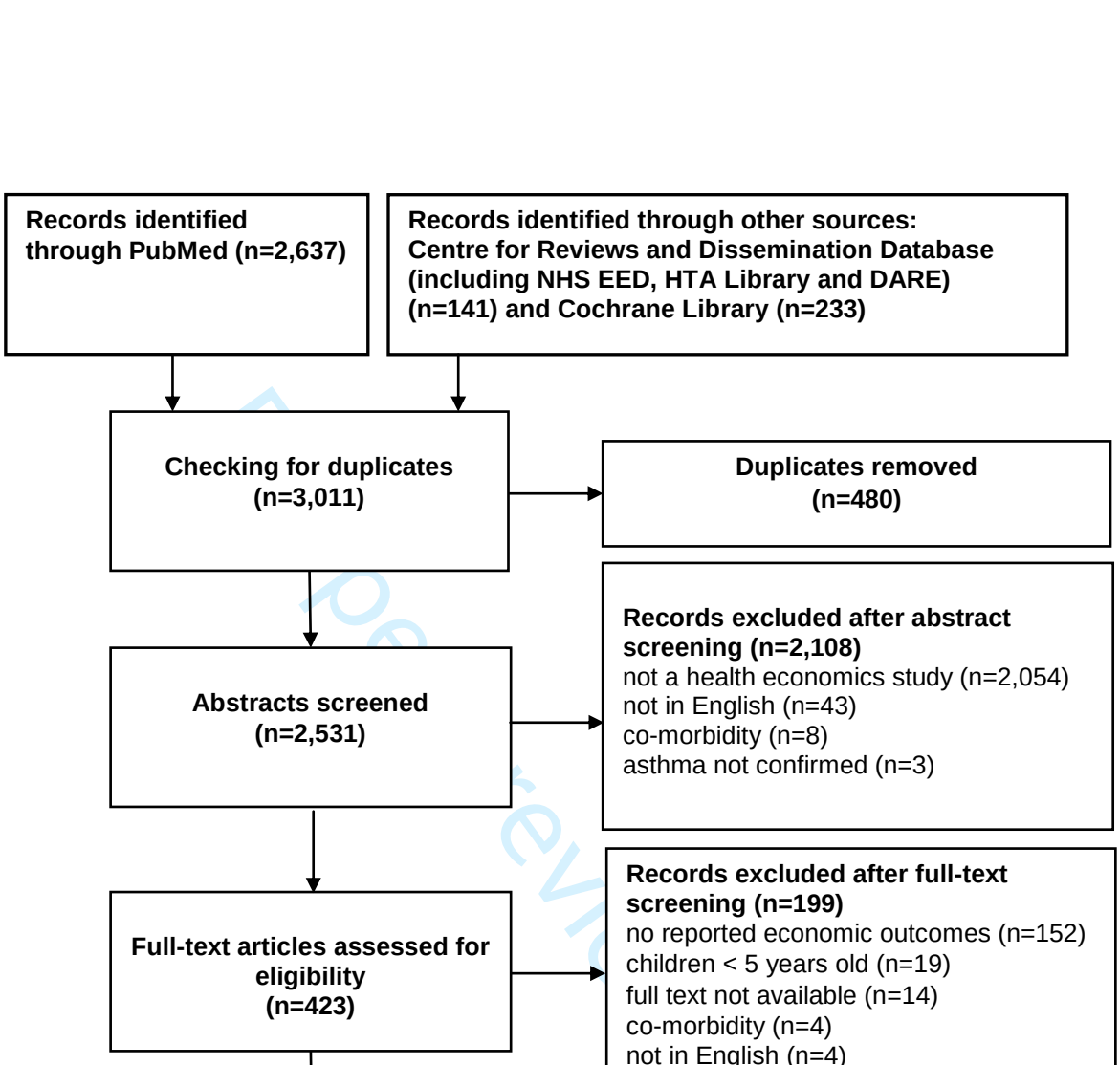


Figure 2. Proportional use of economic parameters in identified studies

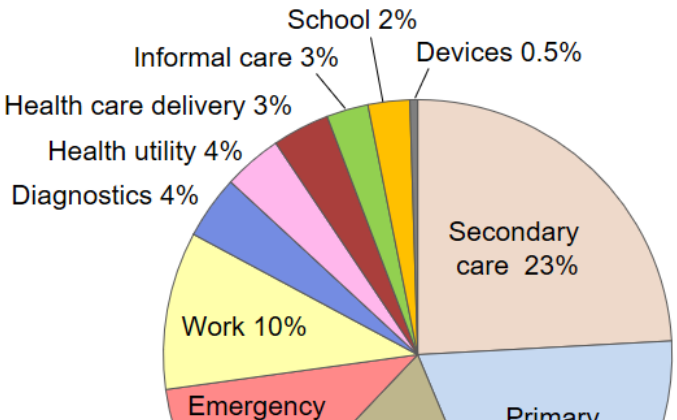


Figure 3. Analytical framework for realist synthesis

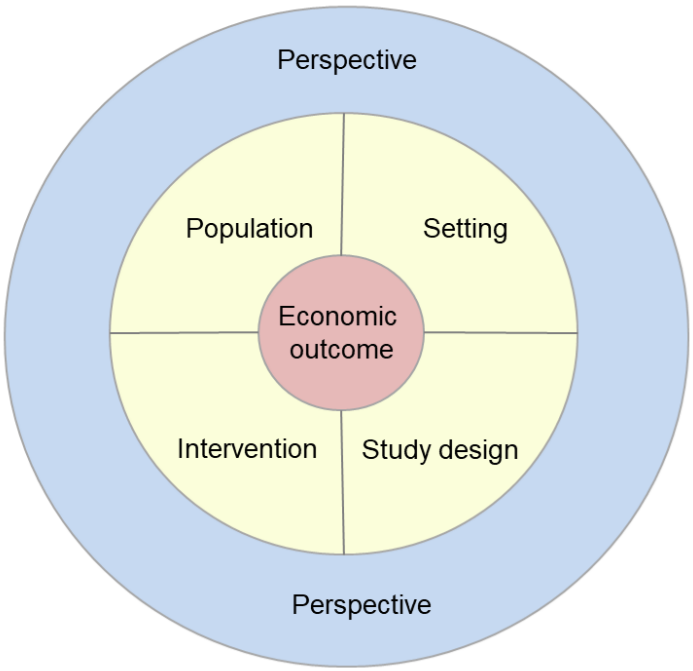
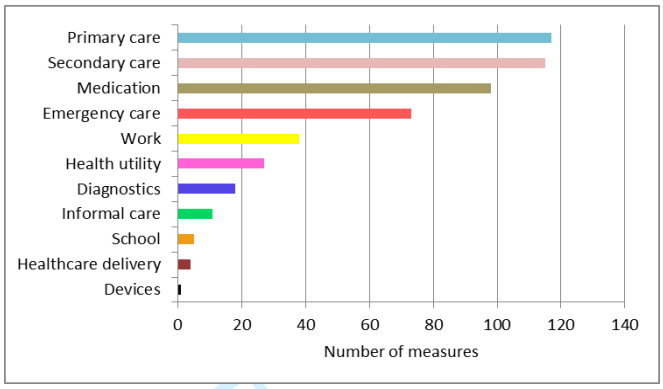
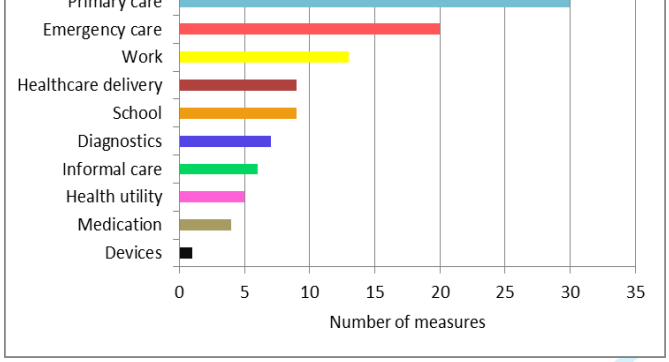


Figure 4. Use of economic parameters in studies with different types of interventions

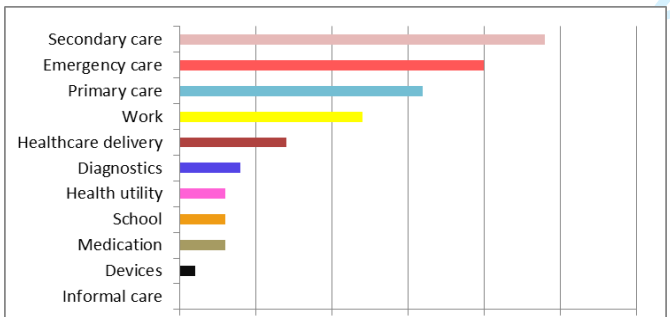
Medication interventions



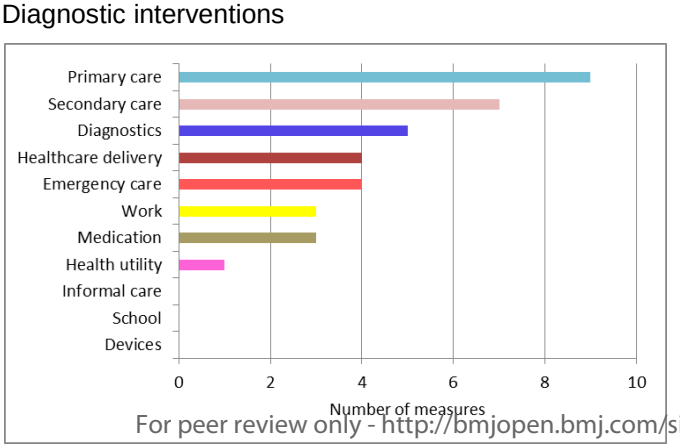
Procedure interventions



Educational interventions



Diagnostic interventions



Appendix 1. PubMed search strategy

1. Search ((asthma[MeSH Terms]) AND economic*[MeSH Terms]) AND outcome[Title/Abstract] Filters: Review; Full text; Publication date from 1990/01/01; Humans; English
2. 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[Title/Abstract] 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: Full text; Publication date from 1990/01/01; Humans; English
3. 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: Full text; Publication date from 1990/01/01; Humans; English
4. 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: Full text; Publication date from 1990/01/01; Humans; English
5. Search (asthma[MeSH Terms]) AND (work[Title/Abstract] OR school[Title/Abstract] OR primary[Title/Abstract] OR secondary [Title/Abstract] OR tertiary[Title/Abstract] OR social [Title/Abstract] OR home[Title/Abstract] OR intensive[Title/Abstract] OR community[Title/Abstract] OR ambulatory[Title/Abstract] OR private[Title/Abstract] OR social[Title/Abstract] OR care[Title/Abstract] OR support[Title/Abstract] OR travel[Title/Abstract]) Filters: Full text; Publication date from 1990/01/01; Humans; English
6. 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 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: Full text; Publication date from 1990/01/01; Humans; English

7. Search (asthma[MeSH Terms]) AND (work[Title/Abstract] OR school[Title/Abstract] OR primary[Title/Abstract] OR secondary[Title/Abstract] OR tertiary[Title/Abstract] OR social[Title/Abstract] OR home[Title/Abstract] OR intensive[Title/Abstract] OR community[Title/Abstract] OR ambulatory[Title/Abstract] OR private[Title/Abstract] OR social[Title/Abstract] OR care[Title/Abstract] OR support[Title/Abstract] OR travel[Title/Abstract]) Filters: Full text; Publication date from 1990/01/01; Humans; English
8. 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 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: Full text; Publication date from 1990/01/01; Humans; English

Appendix 2. Control questions and results of abstract screening (n=2,532)

Question Number	Question	Answer	Action	Number of studies
Q1	Is this a health economics study? (does it report resource use, costs, cost-effectiveness ratios, QALYs?)	No	Exclude	2,054
		Yes or unsure	Go to Q2	477
Q2	Does the study include the population with asthma?	No	Exclude	3
		Yes or unsure	Go to Q3	474
Q3	Does the study include the population with co-morbidities?	Yes	Exclude	8
		No or unsure	Go to Q4	466
Q4	Is the paper written in English?	No	Exclude	43
		Yes	Proceed to the full text selection	423

Appendix 3. Keywords used for searching economic parameters.

Category	Keywords
Primary care	primary, GP, physician, nurse, specialist, home, telephone, physio, ambulatory, acupuncture, psychologist, unscheduled (visits)
Secondary care	hospital, outpatient, inpatient, clinic
Emergency care	A&E, emergency, ambulance, intensive, ICU, out-of-hours
Medication	medication, drug, adherence
Diagnostics	diagnostic, test
Work	work, productivity (loss), disability, retirement, absenteeism, presenteeism, earnings
School	school, nursery
Informal care	informal (care), parent, caregiver, carer, child care, family (help, care), house (help, worker)
Health care delivery	travel, waiting, supplies, education, admin, willingness (to pay), personnel, bedding, (home) improvements
Devices	device, inhaler, nebuliser
Health utility	QALY(quality-adjusted life years), HR-QoL (health-related quality of life), YLD (years lived with disability)

Appendix 4. List of studies included in the systematic review

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Appendix 5. Ranking of economic parameters with respect to the frequency of their usage in studies with different characteristics (e.g. population, setting, study design). The ranking was based on parameter counts. N represents the number of counts for each resource group. Some studies used more than one economic parameter from each resource group.

Population

Adults	**N**	**Rank**
Secondary care	74	1
Primary care	63	2
Medication use	59	3
Emergency care	41	4
Work	36	5
Diagnostics	18	6
Health utility	14	7
Healthcare delivery	9	8
Informal care	2	9
Devices	1	10
School	1	11

Children	**N**	**Rank**
Secondary care	57	1
Primary care	49	2
Medication use	40	3
Emergency care	32	4
Work	17	5
School	16	6
Diagnostics	11	7
Healthcare delivery	11	8
Informal care	9	9
Health utility	6	10
Devices	1	11

Setting

Primary care	**N**	**Rank**
Secondary care	113	1
Primary care	102	2
Medication use	87	3
Emergency care	70	4
Work	38	5
Diagnostics	22	6
Healthcare delivery	17	7
Health utility	14	8
School	13	9
Informal care	8	10

Devices	5	11

Secondary care	**N**	**Rank**
Secondary care	68	1
Primary care	49	2
Medication use	41	3
Emergency care	33	4
Work	30	5
Diagnostics	12	6
Health utility	11	7
Healthcare delivery	10	8
Informal care	6	9
School	5	10
Devices	0	11

Study design

RCT	**N**	**Rank**
Primary care	106	1
Secondary care	81	2
Medication use	66	3
Emergency care	60	4
Work	34	5
Diagnostics	12	6
School	9	7
Health utility	9	8
Informal care	8	9
Healthcare delivery	7	10
Devices	1	11

Cohort study	**N**	**Rank**
Secondary care	92	1
Medication use	66	2
Primary care	55	3
Emergency care	48	4
Work	36	5
Diagnostics	16	6
School	12	7
Informal care	12	8
Healthcare delivery	11	9
Health utility	4	10
Devices	0	11

Model	**N**	**Rank**
Secondary care	55	1
Medication use	42	2

Primary care	42	3
Emergency care	33	4
Health utility	23	5
Work	18	6
Diagnostics	14	7
Healthcare delivery	11	8
Informal care	5	9
School	3	10
Devices	0	11

Asthma severity

Mild	**N**	**Rank**
Secondary care	44	1
Medication use	38	2
Primary care	38	3
Emergency care	31	4
Work	19	5
Diagnostics	13	6
School	7	7
Health utility	7	8
Healthcare delivery	7	9
Informal care	5	10
Devices	2	11

Moderate	**N**	**Rank**
Secondary care	57	1
Primary care	49	2
Medication use	48	3
Emergency care	39	4
Work	28	5
Diagnostics	14	6
Health utility	10	7
Healthcare delivery	8	8
School	7	9
Informal care	7	10
Devices	2	11

Severe	**N**	**Rank**
Secondary care	56	1
Medication use	43	2
Primary care	42	3
Emergency care	37	4
Work	19	5
Diagnostics	18	6
Health utility	13	7

Healthcare delivery	9	8
Informal care	7	9
School	5	10
Devices	2	11

Type of intervention

Medication use	**N**	**Rank**
Primary care	117	1
Secondary care	115	2
Medication use	98	3
Emergency care	73	4
Work	38	5
Health utility	27	6
Diagnostics	18	7
Informal care	11	8
School	5	9
Healthcare delivery	4	10
Devices	1	11

Education	**N**	**Rank**
Secondary care	24	1
Emergency care	20	2
Primary care	16	3
Work	12	4
Healthcare delivery	7	5
Diagnostics	4	6
Medication use	3	7
School	3	8
Health utility	3	9
Devices	1	10
Informal care	0	11

Procedures	**N**	**Rank**
Secondary care	31	1
Primary care	30	2
Emergency care	20	3
Work	13	4
School	9	5
Healthcare delivery	9	6
Diagnostics	7	7
Informal care	6	8
Health utility	5	9
Medication use	4	10
Devices	1	11

Test	N	Rank
Primary care	9	1
Secondary care	7	2
Diagnostics	5	3
Emergency care	4	4
Healthcare delivery	4	5
Medication use	3	6
Work	3	7
Health utility	1	8
Devices	0	9
School	0	10
Informal care	0	11

Type of economic analysis

CA	N	Rank
Secondary care	109	1
Medication use	72	2
Emergency care	71	3
Primary care	57	4
Work	48	5
School	17	6
Diagnostics	14	7
Healthcare delivery	13	8
Informal care	11	9
Devices	2	10
Health utility	0	11

CEA	N	Rank
Primary care	112	1
Secondary care	91	2
Medication use	74	3
Emergency care	53	4
Work	34	5
Diagnostics	19	6
Healthcare delivery	11	7
Informal care	10	8
Health utility	10	9
School	6	10
Devices	2	11

CUA	N	Rank
Primary care	42	1
Secondary care	39	2
Medication use	35	3
Health utility	33	4

Emergency care	31	5
Work	16	6
Diagnostics	12	7
Healthcare delivery	5	8
Informal care	3	9
School	2	10
Devices	1	11

Perspective

Health care provider	**N**	**Rank**
Secondary care	134	1
Primary care	131	2
Medication use	104	3
Emergency care	93	4
Work	46	5
Health utility	26	6
Diagnostics	23	7
Healthcare delivery	17	8
Informal care	15	9
School	14	10
Devices	3	11

Societal	**N**	**Rank**
Primary care	74	1
Secondary care	66	2
Work	66	3
Medication use	54	4
Emergency care	46	5
Informal care	17	6
School	16	7
Diagnostics	15	8
Healthcare delivery	15	9
Health utility	12	10
Devices	1	11

Third party payer	**N**	**Rank**
Secondary care	48	1
Medication use	30	2
Emergency care	27	3
Primary care	20	4
Work	14	5
Diagnostics	6	6
Health utility	3	7
Informal care	2	8
Healthcare delivery	2	9

Devices	1	10
School	1	11

List of items required when reporting a realist synthesis (RAMESES checklist)

	Reporting item	Description of item	Reported on page(s)
Title			
1		In the title, identify the document as a realist synthesis or review	Page 1
Abstract			
2		While acknowledging publication requirements and house style, abstracts should ideally contain brief details of: the study's background, review question or objectives; search strategy; methods of selection, appraisal, analysis and synthesis of sources; main results; and implications for practice	Page 2
Introduction			
3	Rationale for review	Explain why the review is needed and what it is likely to contribute to existing understanding of the topic area	Pages 3-4
4	Objectives and focus of review	State the objective(s) of the review and/or the review question(s). Define and provide a rationale for the focus of the review	Page 4
Methods			
5	Changes in the review process	Any changes made to the review process that was initially planned should be briefly described and justified	Page 5
6	Rationale for using realist synthesis	Explain why realist synthesis was considered the most appropriate method to use	Page 4
7	Scoping the literature	Describe and justify the initial process of exploratory scoping of the literature	Pages 5-7
8	Searching processes	While considering specific requirements of the journal or other publication outlet, state and provide a rationale for how the iterative searching was done. Provide details on all of the sources accessed for information in the review. Where searching in electronic databases has taken place, the details should include, for example, name of database, search terms, dates of coverage and date last searched. If individuals familiar with the relevant literature and/or topic area were contacted, indicate how they were identified and selected	Pages 5-7
9	Selection and appraisal of documents	Explain how judgements were made about including and excluding data from documents, and justify these	Page 5
10	Data extraction	Describe and explain which data or information were extracted from the included documents and justify this selection	Page 6
11	Analysis and synthesis processes	Describe the analysis and synthesis processes in detail. This section should include information on the constructs analysed and describe the analytic process	Pages 6-7

Results			
12	Document flow diagram	Provide details on the number of documents assessed for eligibility and included in the review, with reasons for exclusion at each stage, as well as an indication of their source of origin (e.g. from searching databases, reference lists and so on). You may consider using the example templates (which are likely to need modification to suit the data) that are provided	Appendix 1
13	Document characteristics	Provide information on the characteristics of the documents included in the review	Pages 7-8 Table 1
14	Main findings	Present the key findings with a specific focus on theory building and testing	Pages 7-11
Discussion			
15	Summary of findings	Summarise the main findings, taking into account the reviews objective(s), research question(s), focus and intended audience(s)	Page 12
16	Strengths, limitations and future research directions	Discuss both the strengths of the review and its limitations. These should include (but need not be restricted to) (a) consideration of all the steps in the review process and (b) comment on the overall strength of evidence supporting the explanatory insights which emerged The limitations identified may point to areas where further work is needed	Pages 14-15
17	Comparison with existing literature	Where applicable, compare and contrast the reviews findings with the existing literature (e.g. other reviews) on the same topic	Pages 12-13
18	Conclusion and recommendations	List the main implications of the findings and place these in the context of other relevant literature. If appropriate, offer recommendations for policy and practice	Pages 14-15
19	Funding	Provide details of funding source (if any) for the review, the role played by the funder (if any) and any conflicts of interests of the reviewers	Page 15