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Healthcare costs of asthma comorbidities: a systematic review protocol

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Keywords: Asthma, co-morbidity, multi-morbidity, burden of disease, cost, health economics, global health.

ABSTRACT

Introduction: Asthma is associated with many comorbid conditions that have the potential to impact on its management and control, increase healthcare expenditure, and heightened societal burden. We plan to undertake a systematic review to synthesise the evidence on the healthcare costs associated with asthma co-morbidity.

Methods and analysis: We will systematically search the following electronic databases: Medline, EMBASE, ISI Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), NHS Economic Evaluation Database, Google Scholar, AMED, Global Health, and PsychINFO between 2000 and 2016. Additional literature will be identified through searching the references in included studies, by contacting experts in the field, and through searching registers of ongoing studies. The review will include cost-effectiveness and economic modelling/evaluation studies, and analytical observational epidemiology studies that have investigated the healthcare and economic burden of asthma co-morbidity. Two reviewers will independently screen studies and extractrelevant data from included studies. Methodological quality of epidemiological studies will be assessed using the Effective Public Health Practice Project (EPHPP) tool, while that of economic evaluation studies will be assessed using the Drummond checklist. This protocol has been published in PROSPERO database (No. CRD42016051005).

Ethics and dissemination: The findings of this systematic review will be disseminated in a peer-reviewed journal and presented at a relevant conference.

Strengths and limitations:

- This is the first systematic review to synthesise the evidence on the healthcare costs attributable to asthma co-morbidity.
- We anticipate difficulties in identifying information on the additional costs expended by patients and their carers associated with asthma co-morbidity.

Introduction

Asthma is a highly prevalent condition that is responsible for considerable morbidity and, in some cases, mortality [1, 2]. Asthma management and control can be influenced, among other things, by the presence of other disease conditions in asthma patients, including psychological disorders, chronic obstructive pulmonary disease (COPD), cardiovascular diseases, hypertension, diabetes, cancer and other respiratory diseases [3-7].

Co-morbid conditions can have a major impact on functionality, disease burden, quality of life, healthcare utilisation and healthcare costs [3, 8]. Controlling these co-morbid conditions may improve asthma outcomes [6, 8-10]. Whilst several studies have now assessed the healthcare, economic, and societal burden associated with asthma co-morbidity [11-13], there has hitherto been no systematic attempt to synthesise and summarise the evidence that has emanated from existing studies.

This review builds on our earlier work [14], which provides a scoping review of the recent landscape of asthma co-morbidity; in the current work, we seek to identify, appraise and synthesise the evidence on healthcare costs associated with asthma co-morbidity [11-13].

Methods

This protocol has been prepared following the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) approach [15]. It has been published in PROSPERO database (No. CRD42016051005).

Types of studies

We will include economic modelling/evaluation and analytical epidemiological studies – i.e. cohort, case-control, and cross-sectional studies – that have investigated the healthcare costs of asthma co-morbidity. Editorials, animal studies, reviews, case studies, and case-series studies will be excluded.

Participants

We are interested in studies on participants with evidence of clinician-diagnosed asthma. There will be no restriction concerning age or sex of participants.

Co-morbidities of interest

Co-morbidity has been defined as "any distinct additional clinical entity that has existed or may occur during the clinical course of a patient who has the index disease under study" [16].

We are interested in co-morbidities that are not related to natural causes such as ageing, but rather those that are patho-physiologically related to asthma and have the potential to impact on asthma control, management and/or prognosis. These include, but are not limited to: allergic diseases, COPD, autoimmune disorders (e.g. type 1 diabetes), metabolic disorders (e.g. type 2 diabetes, obesity), cardiovascular diseases, psychological dysfunction (anxiety, depression), hypertension, cardiovascular diseases and gastroesophageal reflux disease (GORD).

Outcome

Healthcare costs of asthma comorbidities.

Search methods

Databases

We will identify published studies from the following databases: Medline, EMBASE, ISI Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), NHS Economic Evaluation Database, Google Scholar, AMED, Global Health and PsychINFO. Additional literature will be identified by searching the reference list of identified eligible studies and by searching the repositories of international conference proceedings, including ISI Conference Proceeding Citation Index, and ZETOC (British Library). Additional literature will identified through searching the references in included studies, by contacting experts in the field, and through searching of registers of ongoing studies. Unpublished literature and on-going studies will be identified by searching the following registries: ISI Conference Proceedings Citation Index via Web of Knowledge, Current Controlled Trials (http://www.controlled-trials.com), ClinicalTrials.gov (http://www.clinicaltrials.gov), Australian and New Zealand Clinical Trials Registry (http://www.anzctr.org.au).

Search strategy:

We have developed a strategy in MEDLINE (see appendix) to retrieve relevant literature on the topic. This search strategy will be adapted in searching other databases. There will be no language restriction and, where possible, studies in languages other than English will be translated.

The databases will be searched for the period January 2000 to November 2016. We have chosen a 2000 start date as whilst we are aware that there was limited work before the 2000s

on the healthcare and economic burden of asthma [17], these studies focused exclusively on asthma without taking any co-morbid conditions into consideration.

Study selection

The articles retrieved from the database searches will be exported into EndNote reference management program. Screening will be undertaken according to the inclusion and exclusion criteria. Two reviewers (KF and EV) will independently undertake the screening of the records (by title and/or abstract) for eligibility and a third reviewer (BN or AS or AP) will arbitrate in case of any disagreement to reach a consensus. Full text of potentially eligible papers after the first screening will be retrieved and reviewed again to confirm that the papers meet the inclusion and exclusion criteria. The screening process will be undertaken and reported according to the PRISMA recommendation [18].

Data extraction

A customised data extraction form is being constructed to extract relevant data from all studies meeting our inclusion criteria. The form will first be piloted to evaluate its reliability in capturing the study data of interest. The data abstracted will include: author(s), publication year, geographical location of data collection, study design, aims and research questions, settings, population/participants (N, mean age, gender), co-morbidities studied, time period specific costs included, cost unit(s), and estimates of total costs, currency, price year, whether discounting was applied where relevant and key findings. Data extraction will be undertaken independently by two reviewers (KF and EV). Any disagreements will be resolved by discussion or if necessary arbitration by a third reviewer (BN or AS or AP).

Data assessment and synthesis

Quality assessment

Two reviewers (KF and EV) will independently assess the quality of included studies and the potential for risk of bias will be evaluated. We will use the Drummond checklist [19] for assessing the methodological quality of economic evaluation and cost studies. Although there are many economic evaluation and reporting checklists, a lot of them have overlapping aspects. The Drummond checklist focuses on the quality of the designs. Consensus will be reached through discussion and arbitration by a third reviewer (BN or AS or AP) in event of any disagreement.

The quality of the broader study design will be evaluated using the Effective Public Health Practice Project (EPHHP) tool [20]. The EPHPP tool assesses different components of studies: design, biases and methods. The overall study rating will be judged as strong, moderate or weak based on the component ratings.

Data synthesis

We anticipate considerable methodological and statistical heterogeneity across studies, which will make it hard to conduct meta-analyses of the evidence base. A narrative synthesis will thus be employed as the primary approach to synthesise the data, but we will also consider the possibility of meta-analysis using random-effects modelling if the data allow. If that is the case, then we will evaluate potential for publication bias using funnel plots and Begg and Egger tests [21, 22].

Subgroup analysis

Where possible, we will conduct subgroup analyses based on the categories of relevant socio-demographic characteristics reported in the studies, particularly by age groups and gender.

- Age (will depend on how authors have reported it, but may include categorisation as follows):
    - Children and young people <18 years
    - Adults (≥18 years old)
- Gender
    - Male
    - Female

If the number of studies and data available show significant statistical heterogeneity, then we will conduct sensitivity analyses with regards to study quality, by excluding studies at high risk of bias.

Conclusion

Asthma co-morbidities have the potential to impact on asthma management, healthcare utilisation and outcomes. We anticipate that this systematic review will build on our previous work on the epidemiology and outcomes of asthma [14, 23, 24], and provide important

insights into patterns of asthma co-morbidity and the economic consequences of these co-morbid disorders.

Ethics and Dissemination

As there are no primary data collected, formal NHS ethical review is not necessary. Findings from the systematic review will be presented at a relevant conference and be published in a peer-reviewed journal.

Protocol registration

This review's protocol will be registered in International Prospective Register of Systematic Reviews (PROSPERO) database.

Footnotes

Funding: This work is supported by the Chief Scientist's Office of the Scottish Government and Asthma UK as part of the Asthma UK Centre for Applied Research [AUK-AC-2012-01]. BN and AS are supported by the Farr Institute and Asthma UK Centre for Applied Research.

Conflicts of interest: None declared.

Contributorship: All authors have made substantive intellectual contributions to the development of this protocol. KF wrote this protocol. AS, AP, CG and BN commented critically on several drafts of the manuscript. KF, AS, AP and BN were involved in conceptualising this review.

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Appendix

Search Strategy

(Medline)

1. exp Asthma/
2. asthma$.mp
3. (antiasthma$ or anti-asthma$).mp
4. Respiratory Sounds/
5. wheez$.mp
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp
9. bronchoconstrict$.mp
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp
16. **or/1-15**
17. exp Comorbidity/ or co-morbidity.mp.
18. multimorbidity.mp.
19. allergic rhinitis.mp. or exp Rhinitis, Allergic/

20. chronic obstructive pulmonary disease.mp. or exp Pulmonary Disease, Chronic Obstructive/

21. .exp Obesity/ or exp Diabetes, Type 2/ or metabolic disorder.mp.

22. . exp Gastroesophageal Reflux/ or gastro-oesophageal reflux disease.mp.

23. cardiovascular disease.mp. or exp Cardiovascular Diseases/

24. exp Hypertension/ or hypertension.mp.

25. exp Depression/ or exp Mental Disorder/ or exp Stress, Psychological/ or psychological dysfunction.mp. or Stress Disorder, Post-Traumatic/

26. .exp Anxiety/ or anxiety.mp.

27. panic disorders.mp. or exp Panic Disorder/

28. or/17-25

29. 16 and 28

30. economics/

31. "costs and cost analysis"/

32. cost allocation/

33. cost-benefit analysis/

34. cost control/

35. cost savings/

36. cost of illness/

37. cost sharing/

38. "deductibles and coinsurance"/

39. medical savings accounts/

40. health care costs/

41. direct service costs/

42. drug costs/

43. employer health costs/

44. hospital costs/

45. health expenditures/

46. capital expenditures/

47. value of life/

48. exp economics, hospital/

49. exp economics, medical/

50. economics, nursing/

51. economics, pharmaceutical/

52. exp "fees and charges"/

53. exp budgets/

54. (low adj cost).mp.

55. (high adj cost).mp.

56. (health?care adj cost$).mp.

57. (fiscal or funding or financial or finance).tw.

58. (cost adj estimate$).mp.

59. (cost adj variable).mp.

60. (unit adj cost$).mp.

61. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.

62. or/30-61

63. 29 and 62

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

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

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Appndx
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6-7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6-7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6-7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	4
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	6-7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Methods and analysis: We will systematically search the following electronic databases: Medline, EMBASE, ISI Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), NHS Economic Evaluation Database, Google Scholar, AMED, Global Health, and PsychINFO between January 2000 and January 2017. Additional literature will be identified through searching the references in included studies, by contacting experts in the field, and through searching registers of ongoing studies. The review will include cost-effectiveness and economic modelling/evaluation studies, and analytical observational epidemiology studies that have investigated the healthcare costs of asthma comorbidity. Two reviewers will independently screen studies and extract relevant data from included studies. Methodological quality of epidemiological studies will be assessed using the Effective Public Health Practice Project (EPHPP) tool, while that of economic evaluation studies will be assessed using the Drummond checklist. This protocol has been published in PROSPERO database (No. CRD42016051005).

Ethics and dissemination: The findings of this systematic review will be disseminated in a peer-reviewed journal and presented at relevant conferences.

Strengths and limitations:

- This is the first systematic review to synthesise the evidence on the healthcare costs attributable to asthma comorbidity.
- A major limitation is that it may be difficult to employ meta-analysis as we anticipate studies with different study designs, definitions of costs, and time periods.
- Based on previous work, we anticipate considerable difficulties in identifying information on the indirect costs associated with asthma comorbidities such as productivity loss and social and intangible costs. This review will therefore be focused on direct healthcare costs only, we recognise that it is a subset of overall costs.

Introduction

Asthma is a highly prevalent condition that is responsible for considerable morbidity and, in some cases, mortality [1, 2]. Asthma management and control can be influenced, among other things, by the presence of other comorbid conditions [3-7]. Our recently completed scoping review investigating the prevalence of comorbidities among asthma patients identified a number of conditions including, but not limited to depression, anxiety, rhinitis, gastro-esophageal reflux disease (GERD) and obesity, may occur more frequently in people with asthma than in those without, leading to potential additional difficulties in asthma management [8-10]. These comorbid conditions may be associated with poor functionality, poor asthma control, impaired health-related quality of life (HRQoL) and increased health utilisation [3, 6, 9-15], and controlling these may improve asthma outcomes [6, 12, 14, 15].

The findings of these international studies vary depending on the population targeted and the particular comorbid conditions studied [16-18]. Whilst these studies have now assessed the healthcare, and economic burden associated with asthma comorbidity [19-21], there has hitherto been no systematic attempt to synthesise and summarise the evidence that has emanated from existing studies.

This review builds on our earlier work [8], which involved a scoping review of the recent landscape of asthma comorbidity; the purpose of the current work is to identify, appraise and synthesise the evidence on healthcare costs associated with asthma comorbidity [19-21].

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Comorbidity has been defined as "any distinct additional clinical entity that has existed or may occur during the clinical course of a patient who has the index disease under study" [23]. We are interested in comorbidities that are not related to natural causes such as ageing, but rather those that are patho-physiologically related to asthma and have the potential to impact on asthma control, management and/or prognosis, regardless of whether they develop before or after asthma. These include, but are not limited to: allergic diseases, COPD, autoimmune disorders (e.g. type 1 diabetes), metabolic disorders (e.g. type 2 diabetes, obesity), cardiovascular diseases, psychological dysfunction (anxiety, depression), hypertension, and GERD. We grouped comorbidities according to the latest version of the International Classification of Diseases (ICD-10) diagnosis codes [24].

Outcome

Healthcare costs of asthma comorbidities.

Search methods

Databases

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The articles retrieved from the database searches will be exported into EndNote reference management program. Screening will be undertaken according to the inclusion and exclusion criteria. Two reviewers (KF and EV) will independently undertake the screening of the records (by title and/or abstract) for eligibility and a third reviewer (BN or AS or AP) will arbitrate in case of any disagreement to reach a consensus. Full text of potentially eligible papers after the first screening will be retrieved and reviewed again to confirm that the papers meet the inclusion and exclusion criteria. The screening process will be undertaken and reported according to the PRISMA recommendation [26].

Data extraction

A customised data extraction form is being constructed to extract relevant data from all studies meeting our inclusion criteria. The form will first be piloted to evaluate its reliability in capturing the study data of interest. The data abstracted will include: author(s), publication year, geographical location of data collection, study design, aims and research questions, settings, population/participants (N, mean age, gender), comorbidities studied, time period specific costs included, cost unit(s), and estimates of total costs, currency, price year, whether discounting was applied where relevant and key findings. Data extraction will be undertaken independently by two reviewers (KF and EV). Any disagreements will be resolved by discussion or if necessary arbitration by a third reviewer (BN or AS or AP).

Data assessment and synthesis

Quality assessment

Two reviewers (KF and EV) will independently assess the quality of included studies and the potential for risk of bias will be evaluated. We will use the Drummond checklist [27] for assessing the methodological quality of economic evaluation and cost studies. Although there are many economic evaluation and reporting checklists, a lot of them have overlapping aspects. The Drummond checklist focuses on the quality of the designs. Consensus will be reached through discussion and arbitration by a third reviewer (BN or AS or AP) in event of any disagreement.

The quality of the broader study design will be evaluated using the Effective Public Health Practice Project (EPHHP) tool [28]. The EPHPP tool assesses different components of studies: design, biases and methods. The overall study rating will be judged as strong, moderate or weak based on the component ratings.

Data synthesis

We anticipate considerable methodological and statistical heterogeneity across studies, which will make it hard to conduct meta-analyses of the evidence base. A narrative synthesis will thus be employed as the primary approach to synthesise the data, but we will also consider the possibility of meta-analysis using random-effects modelling if the data allow. If that is the case, then we will evaluate potential for publication bias using funnel plots and Begg and Egger tests [29, 30].

Subgroup analysis

Where possible, we will conduct subgroup analyses based on the categories of relevant socio-demographic characteristics reported in the studies, particularly by age groups and gender.

- Age (will depend on how authors have reported it, but may include categorisation as follows):
    - Children and young people <18 years
    - Adults (≥18 years old)
- Gender
    - Male
    - Female

If the number of studies and data available show significant statistical heterogeneity, then we will conduct sensitivity analyses with regards to study quality, by excluding studies at high risk of bias.

Conclusion

Asthma comorbidities have the potential to impact on asthma management, healthcare utilisation and outcomes. We anticipate that this systematic review will build on our previous work on the epidemiology and outcomes of asthma [8, 31, 32], and provide important insights into patterns of asthma comorbidity and the economic consequences to health systems of these comorbid disorders.

Ethics and Dissemination

As there are no primary data collected, formal NHS ethical review is not necessary. Findings from the systematic review will be presented at a relevant conference and be published in a peer-reviewed journal.

Conflicts of interest: None declared.

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Appendix

Search Strategy

(Medline)

1. exp Asthma/
2. asthma$.mp
3. (antiasthma$ or anti-asthma$).mp
4. Respiratory Sounds/
5. wheez$.mp
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp
9. bronchoconstrict$.mp
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp
16. **or/1-15**
17. exp Comorbidity/ or co-morbidity.mp.
18. multimorbidity.mp.
19. allergic rhinitis.mp. or exp Rhinitis, Allergic/

20. chronic obstructive pulmonary disease.mp. or exp Pulmonary Disease, Chronic Obstructive/

21. .exp Obesity/ or exp Diabetes, Type 2/ or metabolic disorder.mp.

22. . exp Gastroesophageal Reflux/ or gastro-oesophageal reflux disease.mp.

23. cardiovascular disease.mp. or exp Cardiovascular Diseases/

24. exp Hypertension/ or hypertension.mp.

25. exp Depression/ or exp Mental Disorder/ or exp Stress, Psychological/ or psychological dysfunction.mp. or Stress Disorder, Post-Traumatic/

26. .exp Anxiety/ or anxiety.mp.

27. panic disorders.mp. or exp Panic Disorder/

28. or/17-25

29. 16 and 28

30. economics/

31. "costs and cost analysis"/

32. cost allocation/

33. cost-benefit analysis/

34. cost control/

35. cost savings/

36. cost of illness/

37. cost sharing/

38. "deductibles and coinsurance"/

39. medical savings accounts/

40. health care costs/

41. direct service costs/

42. drug costs/

43. employer health costs/

44. hospital costs/

45. health expenditures/

46. capital expenditures/

47. value of life/

48. exp economics, hospital/

49. exp economics, medical/

50. economics, nursing/

51. economics, pharmaceutical/

52. exp "fees and charges"/

53. exp budgets/

54. (low adj cost).mp.

55. (high adj cost).mp.

56. (health?care adj cost$).mp.

57. (fiscal or funding or financial or finance).tw.

58. (cost adj estimate$).mp.

59. (cost adj variable).mp.

60. (unit adj cost$).mp.

61. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.

62. or/30-61

63. 29 and 62

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

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

sources		literature sources) with planned dates of coverage	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Appndx
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	6-7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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