## BMJ OPEN Correctioned Palliative care for the management of chronic illness: a systematic review study protocol

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## ABSTRACT

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Introduction: Chronic illnesses are marked by fluctuations and variations over time. Individuals with chronic illness experience pain and other symptoms that are not always adequately managed. Their caregivers often have to deal with enormous burden as the illness progresses. Palliative care can serve as an intervention to manage chronic illness, not just at the end of life but also in the early phases of illness. Methods and analysis: Randomised and nonrandomised studies will be included in the systematic review. The focus will be on non-cancer chronic illness. Sources of data will be from PubMed and other databases and will include the reference list of studies included in the systematic review. The primary outcome will be to assess the efficacy of palliative care on chronic illness. Secondary outcomes will include health-related quality of life, care giver burden, quality of care and cost-effectiveness of interventions. The study population will consist of patients aged 18 years or over.

Ethics and dissemination: For purposes of privacy and confidentiality, the systematic review will be limited to studies with de-identified data. The systematic review will be published in a peer-reviewed journal. It will also be disseminated electronically and in print. Brief reports of review findings will be disseminated directly to appropriate audiences via email and other modes of communication. Updates of the review will be conducted to inform and guide healthcare practice and policy.

## **Trial registration**

number: PROSPEROCRD42011001794.

## **INTRODUCTION**

The World Health Organization (WHO) defines palliative care as an intervention that improves the quality of life of patients and their families experiencing intermittent illness, with the ultimate goal being to offer pain and symptom relief, as well as spiritual and psychosocial support.<sup>1</sup> Chronic illnesses are characterised by fluctuations in trajectory, uncertainty in prognoses, extended disease timelines and stress. The Centers for Disease

## **ARTICLE SUMMARY**

#### **Article focus**

- Will a systematic review of palliative care for the management of chronic illness reveal any palliative care disparities between non-cancer patients and cancer patients?
- Does palliative care lead to symptom improvement and pain control in chronically ill patients?
- How does palliative care impact health-related quality of life?

#### Key messages

- A primary focus of the study is on non-cancer chronic illness.
- Study examines eight different domains of palliative care.
- Does palliative care lead to better or worse outcomes in chronic illness?

## Strengths and limitations of this study

- This study concerns palliative care for the management of chronic illness. To our knowledge, this is the first protocol of a systematic review that will attempt to assess the eight different domains of palliative care.
- We will be including observational studies in the systematic review because we believe that observational studies will provide us with valid and useful information (that might be lacking in randomized studies) to address key messages of this study.
- The risk for bias might be heightened by the inclusion of non-randomized studies; however, we have made it clear that we will give priority to high-quality evidence, where it exists, and will interpret results that are highly prone to bias with great caution.

Control states that chronic diseases—such as heart disease, stroke, cancer, diabetes and arthritis—are among the most common, costly and preventable of all health problems.<sup>2</sup> Chronic diseases are also the leading causes of disability and death in the USA.<sup>2</sup>

Murray *et al* posit that health, social and palliative care services are continuing to fail many people with progressive chronic illnesses in whom death may be approaching,

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reflecting a failure to think proactively and holistically about their care.<sup>3</sup> In the absence of adequate interventions aimed at caring for patients with chronic illness, the quality of life and symptom burden faced by such patients are bound to be subpar and excessive.<sup>4</sup> It is important to mention that while the terms chronic illness and chronic disease are used interchangeably. they convey slightly different meanings. Chronic disease is defined on the basis of the biomedical disease classification,<sup>5</sup> for example, asthma, sickle cell, depression and diabetes. Chronic illness is the personal experience of living with the affliction that accompanies chronic disease. Chronic illness is often not recognised in health systems because it does not fit into a biomedical or administrative classification.<sup>6</sup>

In order to alleviate the debilitating symptoms and enhance the quality of life of chronically ill patients, palliative care serves as an effective tool for pain relief, symptom improvement and existential well-being. Furthermore, several studies have shown that patients with non-cancer chronic illness have significantly impaired quality of life and emotional well-being that may often not be as well met as those of patients with cancer nor do they receive holistic care that is appropriate to their needs.<sup>7–9</sup> Unrelieved pain is more than a symptom and has a pathophysiology that, if left unchecked, can ultimately become a disease itself.<sup>9</sup>

While the focus of palliative care has been end of life, we suggest that the palliative care model be used for patients with chronic illness, not just at the end of life but in the early phases of illness.

Several systematic reviews have been conducted on palliative care, but they have focused strictly on end-of-life issues or in some cases have failed to adequately address symptom prevalence in chronically ill patients or to assess quality of care or all domains of palliative care.<sup>10-12</sup>

This protocol is for a systematic review that will attempt to assess the eight different domains of palliative care, as laid out by The National Consensus Project (NCP) for Quality Palliative Care in the USA and which also cover the WHO definition of palliative care.<sup>13</sup> These domains are structure and process of care; physical aspects of care; psychological and psychiatric aspects of care; social aspects of care; spiritual, religious and existential aspects of care; cultural aspects of care; care of the imminently dying patient and ethical and legal aspects of care. The primary objective of this systematic review will be to assess the efficacy of integrated and standard palliative care on symptom improvement (eg, dyspnoea relief). In addition, secondary outcome such as health-related quality of life and care giver burden will be assessed. The cost-effectiveness of palliative care interventions in the management of chronic illness will be examined.

#### Methods and analysis

For the systematic review, we will not be limiting the studies selected to randomised controlled trials. Data from randomised controlled trials are often insufficient to address all aspects of palliative care practice, and

randomised controlled trials on palliative care are sometimes unethical or difficult to conduct.<sup>14</sup> Further, Norris *et al*<sup>15</sup> state that the default strategy in systematic reviews should be to consider including observational studies and the decision rests on the answer to two questions: (1) are there gaps in the trial evidence for the review questions under consideration? And (2) will observational studies provide valid and useful information to address key questions?<sup>16 17</sup>

In view of the above, we have decided a priori to develop a protocol that does not rule out the use of observational studies to assess the effectiveness and limitations of palliative care interventions on chronic illness. In doing so, we are cognizant of the fact that non-randomised studies as well as non-double blind studies are prone to bias. Therefore, we will give the utmost priority to high-quality evidence, when and where it exists, and will interpret with maximum caution, bias-prone studies and study designs. uding

In designing the study, the following questions and objectives will take precedence:

- Will a systematic review of palliative care for chronically ill patients reveal disparities in palliative care between non-cancer and cancer patients?
- Will such a systematic review also reveal the efficacy of palliative care in chronic illness symptom improvement?
- To assess the efficacy of palliative care on healthrelated quality of life.
- Identify the efficacy of palliative care on patient, care giver and provider satisfaction.
- What is the cost-effectiveness of palliative care for non-cancer chronic illness?
- To answer these questions, a literature search of the following databases will be conducted:
- MEDLINE
- EMBASE ►
- The Cochrane Central Register of Controlled Trials (CENTRAL)
- Cochrane Database of Systematic Reviews (CDSR)
- ► Database of Abstracts of Reviews of Effects (DARE)
- ► PubMed
- Health Economic Evaluations Database (HEED)
- The Latin American and Caribbean Literature on Health Sciences Database (LILACS)
- African Index Medicus ►
- In order to minimise bias, we will also conduct a search of pertinent grey literature.
- Two search strategies for MEDLINE are available in appendices 1 and 2 of this protocol.

## **Inclusion criteria**

Primary studies involving patients with non-cancer chronic illness: randomised controlled trials, guasirandomised controlled trials, observational studies and large registry studies that address chronic illness and palliative care. Study population with a mean age of 18 years or older (or identified subgroup of people >18 years); articles written in English; articles published

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in peer-reviewed journals; conference abstracts and other grey literature; articles focusing mainly on palliative care and its domains including assessment and management of physical, psychological and spiritual symptoms, quality of care, quality of life and advance care planning; studies that were a minimum of 12-week duration with at least 10 participants per group.

#### **Exclusion criteria**

Studies focusing strictly on individual components of palliative care, such as advance care planning or care giver burden, studies focused solely on cancer patients admitted or referred to palliative care, studies focused on patients under 18 years of age, studies with a high risk of bias (based on a predefined threshold) and studies of <12 weeks duration with <10 participants per group.

Studies published before 2000 will also be excluded because palliative care was recognised as a specialty and service in 2000.<sup>18</sup> Furthermore, palliative care practice has changed significantly since 2000;<sup>18</sup> however, we will reference systematic reviews that addressed the pre-2000 literature, including key intervention studies included in those reviews.<sup>18</sup>

Studies will be characterised by intervention, outcomes measured, study population, settings and quality of research design.

#### Types of interventions

Interventions will be classified based on whether they incorporate standard or integrative palliative care or whether they incorporate usual care. Such interventions must address more than one of the eight domains of palliative care that are relevant to this study. If necessary, interventions that do not satisfy this taxonomy will be given a post hoc classification.

#### Types of outcome measures

#### **Primary outcomes**

- ► Efficacy of integrated palliative care on symptom improvement (eg, pain relief).
- Efficacy of standard palliative care on symptom improvement (eg, pain relief).

#### Secondary outcomes

- ► Health-related quality of life (of patient).
- Quality of care (eg, structure and process of care; physical aspects of care; psychological and psychiatric aspects of care; spiritual, religious and existential aspects of care; cultural aspects of care; care of the imminently dying patient or ethical and legal aspects of care).
- ► Care giver burden (eg, physical or psychological distress).
- Cost-effectiveness of interventions: we suggest that the rendition of effective and timely palliative care will provide the following economic benefits:
- 1. Individual medical cost reduction including costs of hospitalisation, drugs, feeding expenses and opportunity cost of long hospital inpatient accommodation.

- 2. Effective control and management of professional time that could be translated into lower operational cost including overtime payment to service attendants.
- 3. Decreasing social cost of medical and professional service delivery.
- 4. Reduced aggregate cost of funeral expenses.
- 5. Effective prediction or estimation of budgets for nononcologic and cancer patients healthcare delivery.
- 6. Alleviation of burden of excessive and extended charges of patient's medical expenses to insurance companies.
- 7. Reduced social security expenses by the governments emanating from lower claims of health benefits by patients.
- 8. Longer life span for chronically ill patients, who might subsequently contribute positively to the community in other social service areas.

Therefore, in attempting to evaluate the cost-effectiveness of palliative care interventions used in the management of chronic illness, we will take into account how included studies address the effects of palliative care on these benefits and the final outcomes that were obtained at the conclusion of these studies.

All primary and secondary outcomes measured in the systematic review will be assessed using a validated or substantiated scale or tool, for example: Care giver Burden Scale, McGill Pain Questionnaire, Palliative Outcomes Scale and EQ-5D. Cost-effectiveness studies will be appraised for quality based on a grading scheme that will encompass definition and presentation of the problem, measurement and data and analytic methodology.<sup>19</sup> In the process of assessing the cost-effectiveness, we will highlight the potential opportunity costs involved because recommendations that ignore opportunity costs will either not be relevant to decision makers or, if blindly followed, may result in inappropriate adoptions or rejections of treatments.<sup>20</sup>

The overall aim of the systematic review will be to provide a summary of the data available in the studies included and perhaps suggestions for practice, policy and research.

#### Data extraction (selection and coding)

Standardised data extraction forms will be created for the study. Two researchers will independently perform the data extraction. One researcher will extract the data with the second researcher independently checking the data extraction forms for accuracy and detail. If disagreements occur between assessors, they will be resolved according to a predetermined strategy using consensus and arbitration, as necessary. Relevant missing data will be sought by contacting original authors of included studies. Similarly, we will deal with missing data for patients not completing a study, by imputing the missing data and accounting for the fact that they were imputed with uncertainty. In specific, we will use multiple imputation methods to handle missing data.

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The potential impact of missing data on the findings of the review will be addressed in the 'discussion' section.<sup>21</sup>

#### Risk of bias (quality) assessment

The Cochrane Collaboration's tool for assessment of risk of bias will be used. A risk of bias table will be generated with the following entries: adequate sequence generation, allocation concealment, blinding, incomplete outcome data addressed, free of selective reporting, and free of other bias. Only studies meeting specific criteria will be included in the primary analysis. The threshold for study selection adopted in this protocol will be used in the systematic review. Data from unpublished studies will be analysed and included (if appropriate) with the aim of reducing bias. For non-randomised studies, focus on specific aspects of the studies (eg, outcome assessment) and the extent to which they are susceptible to bias also be used to assess risk of bias. Notably, either the Risk of Bias Assessment tool for Non-Randomised Studies (RoBANS) developed by The Cochrane Collaboration as a component of The Cochrane Collaboration's tool for assessing risk of bias in randomised trials<sup>22</sup> or the Newcastle-Ottawa Scale will be used to assess risks of bias in non-randomised studies.<sup>23</sup>

RoBANS is available in Review Manager (RevMAN). In using RoBANS, certain items in the Risk of Bias table will be changed, for example, adequate sequence generation will be changed to allocation concealment (in order to minimise allocation and selection bias)<sup>24</sup> and selection of participants will be changed to confounding variables.

#### List of potential confounding factors

- ► Demographic characteristics<sup>25</sup>
- Prognostic factors
- Severity of illness
- Symptom burden
- Comorbidities
- Functional status
- Social support
- Financial resources
- ► Factors existent at baseline
- Individual preferences towards avoidance of high-cost settings
- Values and preferences for quality of life and lifesustaining treatments
- Clinician practice characteristics
- Urban/rural location of institution
- ► Type of institution
- Values and preferences towards treatment options and goals of care
- Team/family dynamics

### Methods to control potential confounding factors

Multivariable regression modelling or propensity scores will be used to control for potential confounding factors.<sup>25</sup>

# Methods to assess the susceptibility of primary studies to confounding

We will attempt to select the best set of confounding variables that include the most relevant factors likely to account for differences between intervention and comparison groups and provide a balance in the tradeoff between bias and variance to obtain more precise estimates of the treatment effects.<sup>25 26</sup>

#### **Evaluating uncertainty**

We will evaluate uncertainty through sensitivity analysis and statistical tests comparing effects, costs or costeffectiveness.<sup>26</sup>

#### Strategy for data synthesis

Due to the diversity of included studies, a narrative approach will be used for synthesis. Quantitative synthesis of results will be considered in the presence of several high-quality studies of similar design. Sources of heterogeneity will be investigated using the  $I^2$  statistic.<sup>22</sup>

#### Ethics and dissemination

For purposes of privacy and confidentiality, the systematic review will be limited to studies with de-identified data.

The systematic review will be published in a peerreviewed journal. It will also be disseminated electronically and in print. Brief reports of review findings will be disseminated directly to appropriate audiences via email and other modes of communication. Updates of the review will be conducted to inform and guide healthcare practice and policy.

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**Contributors** AE: drafted the protocol, conceived and designed the study protocol; is primary and contact author for the study; supervised the revisions and approved the final manuscript and critically revised earlier drafts of the manuscript for intellectual content. AIE: assisted in drafting and preparation of the manuscript; provided feedback on study protocol format; was involved in the conception and design of the study and approved the final manuscript.

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Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

#### REFERENCES

- World Health Organization (WHO). National Cancer Control Programmes: policies and Managerial Guidelines. 2nd edn. Geneva: World Health Organization, 2002. http://www.who.int/cancer/media/ en/408.pdf (accessed 26 Mar 2012).
- Centers for Disease Control (CDC). Chronic disease and health promotion. http://www.cdc.gov/chronicdisease/overview/index.htm (accessed 26 Mar 2012).
- Murray SA, Boyd K, Kendall M, et al. Dying of lung cancer or cardiac failure: prospective qualitative interview study of patients and their carers in the community. BMJ 2002;325:929–32.
- 4. Kim A, Wang D. Palliative care: optimizing quality of life. *J Am Osteopath Assoc* 2005;105:S9–14.
- Carmel MM. Chronic disease and illness care: adding principles of family medicine to address ongoing health system redesign. *Can Fam Physician* 2012;53:2086–90.
- Walker Ć. Recognizing the changing burdens of illness in defining terms of chronic illness: a prelude to understanding the changing

needs of people with chronic illness. Aust Health Rev 2001;24:207-14

- Gore JM, Brophy CJ, Greenstone MA. How well do we care for 7. patients with end stage chronic obstructive pulmonary disease (COPD)? A comparison of palliative care and quality of life in COPD and lung cancer. Thorax 2000;55:1000-6.
- Stewart S. Palliative care for heart failure. BMJ 2002;325:915. 8
- 9 Benjamin L. Pain management in sickle cell disease: Palliative care begins at birth? Hematology Am Soc Hematol Educ Program 2008;2008:466-74.
- Lorenz KA. Lvnn J, Dy SM, et al. Evidence for improving palliative 10. care at the end of life: a systematic review. Ann Intern Med 2008;48:147-59.
- Janssen DJA. Daily symptom burden in end-stage chronic organ 11. failure: a systematic review. Palliat Med 2008:22:938-48.
- Pasman HR, Brandt HE, Deliens L, et al. Quality indicators for 12 palliative care: a systematic review. J Pain Symptom Manage 2009;38:145-56.
- 13 Clinical Practice Guidelines For Quality Palliative Care. National Consensus Project For Quality Palliative Care. 2nd edn. 2009. http://www.nationalconsensusproject.org/guideline.pdf
- Bee W, Hadley G, Derry S. How useful are systematic reviews for 14. informing palliative care practice? Survey of 25 cochrane systematic reviews. BMC Palliat Care 2008;7:13.
- Norris S, Atkins D, Bruening W, et al. Selecting observational studies 15. for comparing medical interventions. In: Agency for Healthcare Research and Quality. Methods Guide for Comparative Effectiveness Reviews. Rockville, MD, 2010. http://www.effectivehealthcare.ahrq. gov/ehc/products/196/454/MethodsGuideNorris\_06042010.pdf
- 16. Zaza S, Carande-Kulis VG, Sleet DA, et al. Methods for conducting systematic reviews of the evidence of effectiveness and economic efficiency of interventions to reduce injuries to motor vehicle occupants. Am J Prev Med 2001;21(4 Suppl):23-30.
- 17. Viswanathan M, Ansari MT, Berkman ND, et al. Assessing The Risk Of Bias Of Individual Studies In Systematic Reviews Of Health Care Interventions. Agency for Healthcare Research And Quality Methods Guide For Comparative Effectiveness Reviews. AHRQ Publication No. 12-EHC047-EF, 2012. http://www.effectivehealthcare.ahrq.gov/
- 18 Closing the Quality Gap. Revisiting the State of the Science End-Of-Life and Hospice Care. Evidence-Based Practice Center Systematic Review Protocol. 2007. http://www.effectivehealthcare. ahrq.gov (accessed 29 Mar 2012).
- 19 Soares M, Dumville JC. Critical appraisal of cost-effectiveness and cost-utility studies in health care. Evid Based Nurs 2008;11:99-102.
- 20 Donaldson C, Currie G, Mitton C. Cost effectiveness analysis in
- healthcare: contraindications. *BMJ* 2002;325:891. Higgins JPT, Deeks JJ, Altman DG, *et al*, eds. *Chapter 16: Special Topics In Statistics*. In: Higgins JPT, Green S, eds. *Cochrane* 21 Handbook for Systematic Reviews of Interventions. Version 5.0.1. The Cochrane Collaboration, 2008. http://www.cochrane-handbook. org (accessed 29 Mar 2012).
- Higgins JP, Atman DG, Gotzsche PC, et al. The cochrane 22. collaboration's tool for assessing risk of bias in randomized trials. BMJ 2011;343:d5928.
- 23. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.
- Sedgwick P. Allocation concealment. BMJ 2012;344:e156. 24.
- 25 Starks H, Diehr P, Curtis JR. The challenge of selection bias and confounding in palliative care research. J Palliat Med 2009;12:181-7.
- 26 Tacconelli E. Systematic reviews: CRD's guidance for undertaking reviews in health care. Centre for Reviews and Dissemination. CRD: University of York, York, 2009, p209.

## **APPENDIX 1**

#### Medline search strategy

- 1. Palliative Care/
- 2. pallia\$.tw.
- 3. or 1 2
- 4. Advance Care Planning/
- 5. (advance care planning).tw.
- 6. or 4-5
- 7. or 3,6
- 8. Chronic Disease/
- 9. (chronic disease).tw.
- 10. Arthritis/
- 11. arthritis.tw.
- 12. Asthma/

- 13. asthma.tw.
- 14. Anemia, Sickle Cell/
- 15. sickle cell.tw.
- 16. HIV Infections/
- 17. HIV.tw.
- 18. AIDS.tw.
- 19. Depressive Disorder/
- 20. depression.tw.
- 21. Diabetes Mellitus/
- 22. diabetes.tw.
- 23. Pulmonary Disease/Chronic Obstructive/
- 24. emphysema.tw.
- 25. (chronic bronchitis).tw.
- 26. Heart Diseases/
- 27. cardiac.tw.
- 28. (congestive heart failure).tw.
- 29. CHF.tw.
- 30. Hypertension/
- 31. Affective Disorders/Psychotic
- 32. bipolar.tw.
- 33. manic.tw.
- 34. Stroke/
- 35. stroke.tw.
- 36. or 8-35
- 37. and 7, 36
- 38. (symptom improvement).tw.
- 39. symptom.tw.
- 40. Quality of Life/
- 41. (quality of life).tw.
- 42. Quality of Health Care/
- 43. quality.tw.
- 44. Cost of Illness/
- 45. Caregivers/
- 46. (caregiver burden).tw.
- 47. or 38-46
- 48. and 37. 47
- 49. Young Adult/
- 50. adult.tw.
- 51. Adult/
- 52. Middle Aged/
- 53. Aged/
- 54. Aged, 80 and over
- 55. or 47-52
- 56. and 48, 55
- Facets per patron:
- Palliative Care or Advance Care Planning
- And

Chronic Disease or (Eleven conditions specifically named: Arthritis or Asthma or Sickle Cell or HIV/AIDS or Depression or Diabetes or Emphysema or Chronic Obstructive Pulmonary Disease or Heart similar Disease or High Blood Pressure or a mood disorder other than depression or Stroke) And

(Symptom improvement) or (Quality of Life) or (Cost of Illness) or (caregiver burden) And

Adults over age 18

## **APPENDIX 2**

- 1. Palliative Care/
- 2. pallia\$.tw.
- 3. or 1 2
- 4. Advance Care Planning/
- 5. (advance care planning).tw.
- 6. or 4-5
- 7. or 3,6
- 8. Chronic Disease/
- 9. (chronic disease).tw.
- 10. Arthritis/ 11. arthritis.tw.

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## Palliative care for the management of chronic illness: study protocol

- 12. Asthma/
- 13. asthma.tw.
- 14. Anemia, Sickle Cell/
- 15. sickle cell.tw.
- 16. HIV Infections/
- 17. HIV.tw.
- 18. AIDS.tw.
- 19. Depressive Disorder/
- 20. depression.tw.
- 21. Diabetes Mellitus/
- 22. diabetes.tw.
- 23. Pulmonary Disease/Chronic Obstructive/
- 24. emphysema.tw.
- 25. (chronic bronchitis).tw.
- 26. Heart Diseases/
- 27. cardiac.tw.
- 28. (congestive heart failure).tw.
- 29. CHF.tw.
- 30. Hypertension/
- 31. Affective Disorders/Psychotic
- 32. bipolar.tw.
- 33. manic.tw.
- 34. Stroke/
- 35. stroke.tw.
- 36. or 8-35
- 37. and 7, 36
- 38. (symptom improvement).tw.
- 39. symptom.tw.
- 40. Pain/

- 41. (pain).tw.
- 42. Dyspnea/
- 43. dyspnea.tw.
- 44. Fatigue/
- 45. fatigue.tw.
- 46. Constipation/
- 47. constipation.tw.
- 48. Nausea/ 49. nausea.tw.
- 50. Sleep Initiation and Maintenance Disorders/
- 51. insomnia.tw.
- 52. Quality of Life/
- 53. (quality of life).tw.
- 54. Quality of Health Care/
- 55. quality.tw.
- 56. Cost of Illness/
- 57. Caregivers/
- 58. (caregiver burden).tw.
- 59. or 38 58
- 60. and 37, 59
- 61. Young Adult/
- 62. adult.tw.
- 63. Adult/
- 64. Middle Aged/ 65. Aged/
- 66. Aged, 80 and over
- 67. or 61-66
- 68. and 60, 67