# Palliative Care for the Management of Chronic Illness

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Palliative Care for the Management of Chronic Illness: study protocol
Andem Effiong, Nazeem Muhajarine, Andem I. Effiong

Abstract

Introduction

Chronic illnesses are marked by fluctuations and variations over time. Individuals with chronic illness experience pain and other symptoms which 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

Randomized and non-randomized 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, caregiver burden, quality of care, and cost effectiveness of interventions. The study population will consist of patients 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.

Registration details

http://www.crd.york.ac.uk/PROSPERO/full_doc.asp?ID=CRD42011001794

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. Chronic illnesses are characterized by fluctuations in trajectory, uncertainty in prognoses, extended disease timelines, and stress. The Centers for
Disease Control (CDC) 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 (CDC 2010). Chronic diseases are also the leading causes of disability and death in the United States.

According to Murray et al., health, social, and palliative care services are continuing to fail many people with progressive chronic illnesses in whom death may be approaching, reflecting a failure to think proactively and holistically about their care. 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. 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, 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 recognized in health systems because it does not fit into a biomedical or administrative classification.

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. Further, several studies have shown that patients with non-cancer chronic illness have significantly impaired quality of life and emotional well being which 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. Unrelieved pain is more than a symptom and has a pathophysiology that, if left unchecked, can ultimately become a disease itself.

While the focus of palliative care has been end of life, we suggest that the palliative care model be utilized 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.

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 United States, and which also cover the WHO definition of palliative care. 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 (for example, pain relief). In addition, secondary
outcomes such as Health Related Quality of Life and Caregiver burden will be measured. 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 randomized controlled trials. Data from randomized controlled trials are often insufficient to address all aspects of palliative care practice, and randomized controlled trials on palliative care are sometimes unethical or difficult to conduct. Further, Norris et al. 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?

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

Will a systematic review of palliative care for chronically ill patients reflect the gaps in palliative care services that are known to exist between chronically ill patients with non-oncologic illness and those with cancer?

Will such a systematic review also address the impact of palliative care interventions on specific health outcome measures in chronic illness?

To identify systematically the quality measures and the evidence to support the use of palliative care for the management of 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

As a preliminary step to minimize bias, grey literature will also be searched.

The search strategy for MEDLINE is available in Appendix I of this protocol.

Inclusion criteria:

Primary studies involving patients with non-cancer chronic illness; randomized controlled trials, quasi-randomized controlled trials, observational studies, and large registry studies that address chronic illness and palliative care. A mean age of study population 18 years or older (or identified subgroup of people greater than 18 years); articles written in English; articles published in peer-reviewed journals; conference abstracts and other grey literature. Articles focusing mainly on palliative care and its domains, as well as assessment and management of physical, psychological and spiritual symptoms, quality of care, quality of life, and advance care planning.

Exclusion criteria:

Studies focusing strictly on individual components of palliative care, such as advance care planning or caregiver burden will be excluded. Studies focused solely on cancer patients admitted or referred to palliative care; studies focused on patients under 18 years of age; and studies with a high risk of bias (based on a predefined threshold) will also be excluded.

Studies will be characterized 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 integrated 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 (for example, pain relief)

Efficacy of standard palliative care on symptom improvement (for example, pain relief)

Secondary outcomes

Health Related Quality of Life (of patient)

Quality of Care (for example, 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)

Caregiver burden (for example, 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 hospitalization, drugs, feeding expenses, and opportunity cost of long hospital in- patient accommodation

2. Effective control and management of professional time which 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 non- oncologic and cancer patients health care delivery

6. Alleviation of burden of excessive and extended charges for patients 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 services 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:

Caregiver Burden Scale, McGill Pain Questionnaire, Palliative Outcomes Scale, EQ-5D. Cost effectiveness studies will be appraised for quality based on a grading scheme which will encompass definition and presentation of the problem, measurement and data, and analytic methodology. In the process of assessing 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.

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)

Standardized 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 through contacting of original authors of included studies.

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, 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 utilized in the systematic review. Data from unpublished studies will be included to reduce bias. For non-randomized studies, focus on specific aspects of the studies (for example, outcome assessment) and the extent to which they are susceptible to bias will also be used to assess risk of bias. Specifically, either the Risk of Bias Assessment tool for Non-Randomized Studies (RoBANS) developed by The Cochrane Collaboration as a component of The Cochrane Collaboration's tool for assessing risk of bias in randomized trials, or, the Newcastle-Ottawa Scale will be used to assess risks of bias in non-randomized studies.

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 minimize allocation and selection bias) and selection of participants will be changed to confounding variables.

**List of potential confounding factors**

Demographic characteristics

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 life-sustaining 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 modeling or propensity scores will be used to control for potential confounding factors. \(^{23}\)

**Methods to assess the susceptibility of primary studies to confounding** \(^{23}\)

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 trade-off between bias and variance to obtain more precise estimates of the treatment effects. \(^{23}\)

**Evaluating uncertainty**

We will evaluate uncertainty through sensitivity analysis and statistical tests comparing effects, costs or cost-effectiveness. \(^{24}\)

**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 the \(I^2\) statistic \(^{20}\)

**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.

Full References


6. Walker, C. Recognizing the changing burdens of illness in defining terms of chronic illness: a prelude to understanding the changing needs of people with chronic illness. Australian Health Review. 2001; 24(2): 207-14


8. EDITORIAL. Palliative care for heart failure BMJ 2002; 325:915


Authors’ contributions

Effiong, A: Drafted the manuscript, conceived and designed the study protocol. Is primary and contact author for the study.

Muhajarine, N: Helped in the conception and design of the study protocol.

Effiong, AI: Helped in the conception and design of the study protocol. Contributed to the drafting of the manuscript.

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Competing interests statement

None declared for all three authors.

Registration details

http://www.crd.york.ac.uk/PROSPERO/full_doc.asp?ID=CRD42011001794

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Appendix I

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/
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.
26. Heart Diseases/
27. cardiac.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 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
**Palliative Care for the Management of Chronic Illness: a systematic review study protocol.**

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Palliative Care for the Management of Chronic Illness: a systematic review study protocol

Andem Effiong, Andem I. Effiong

Abstract

Introduction
Chronic illnesses are marked by fluctuations and variations over time. Individuals with chronic illness experience pain and other symptoms which 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
Randomized and non-randomized 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, caregiver burden, quality of care, and cost effectiveness of interventions. The study population will consist of patients 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.

Registration details
PROSPERO CRD42011001794

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. [1] Chronic illnesses are characterized by fluctuations in
trajectory, uncertainty in prognoses, extended disease timelines, and stress. The
Centers for Disease Control (CDC) 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 (CDC 2010). [2] Chronic diseases are also the
leading causes of disability and death in the United States. [2]

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,
reflecting a failure to think proactively and holistically about their care. [3] 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.
[4] 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,[5] 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
recognized in health systems because it does not fit into a biomedical or administrative
classification. [6]

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. Further, several studies have shown that
patients with non-cancer chronic illness have significantly impaired quality of life and
emotional well-being which 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. [7-9]
Unrelieved pain is more than a symptom and has a pathophysiology that, if left
unchecked, can ultimately become a disease itself. [9]

While the focus of palliative care has been end of life, we suggest that, the palliative
care model be utilized 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. [10-12]

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 United States, and which also cover, the WHO definition of
palliative care. [13] 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 (for example, dyspnea relief). In addition, secondary
outcomes, such as, Health Related Quality of Life and Caregiver 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 randomized
controlled trials. Data from randomized controlled trials are often insufficient to address
all aspects of palliative care practice, and randomized controlled trials on palliative care
are sometimes unethical or difficult to conduct. [14] Further, Norris et al. 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:[15] (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?
[16-17]

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-randomized 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.

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 health related quality of life.

Identify the efficacy of palliative care on patient, caregiver, 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 minimize bias, we will also conduct a search of pertinent gray literature.

Two search strategies for MEDLINE are available in Appendix I and II of this protocol.

Inclusion criteria:
Primary studies involving patients with non-cancer chronic illness: randomized controlled trials, quasi-randomized controlled trials, observational studies, and large registry studies that address chronic illness and palliative care. A mean age of study population 18 years or older (or identified subgroup of people greater than 18 years); articles written in English; articles published in peer-reviewed journals; conference abstracts and other gray 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 weeks 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 caregiver 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); studies of less than 12 weeks duration with less than 10 participants per group.

Studies published before 2000 will also be excluded because palliative care was recognized as a specialty and service in 2000. [18] Further, palliative care practice has changed significantly since 2000.[18] however, we will reference systematic reviews that addressed the pre-2000 literature, including key intervention studies included in those reviews. [18]
Studies will be characterized 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 (for example: pain relief).
- Efficacy of standard palliative care on symptom improvement (for example: pain relief).

**Secondary outcomes**
- Health Related Quality of Life (of patient)
- Quality of Care (for example, 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).
- Caregiver burden (for example, 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 hospitalization, drugs, feeding expenses, and opportunity cost of long hospital in-patient accommodation.
  2. Effective control and management of professional time which 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 non-oncologic and cancer patients health care delivery.

6. Alleviation of burden of excessive and extended charges of patients 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: Caregiver Burden Scale, McGill Pain Questionnaire, Palliative Outcomes Scale, and EQ-5D. Cost-effectiveness studies will be appraised for quality based on a grading scheme which will encompass definition and presentation of the problem, measurement and data, and analytic methodology. [19] 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. [20]

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)

Standardized 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 utilize multiple imputation methods to handle missing data. The potential impact of missing data on the findings of the review will be addressed in the ‘discussion’ section. [21]
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 utilized in the systematic review. Data from unpublished studies will be analyzed and included (if appropriate) with the aim of reducing bias. For non-randomized studies, focus on specific aspects of the studies (for example, 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-Randomized Studies (RoBANS) developed by The Cochrane Collaboration as a component of The Cochrane Collaboration’s tool for assessing risk of bias in randomized trials,[22] or, the Newcastle-Ottawa Scale will be used to assess risks of bias in non-randomized studies. [23]

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 minimize allocation and selection bias)[24] and selection of participants will be changed to confounding variables.

List of potential confounding factors [25]
- Demographic characteristics
- 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 life-sustaining 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 modeling or propensity scores will be used to control for potential confounding factors. [25]

**Methods to assess the susceptibility of primary studies to confounding [26]**
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 trade-off between bias and variance to obtain more precise estimates of the treatment effects. [25]

**Evaluating uncertainty**
We will evaluate uncertainty through sensitivity analysis and statistical tests comparing effects, costs or cost-effectiveness. [26]

**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. [22]

**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.

**Full References**
2. Centers for Disease Control (CDC). Chronic disease and health promotion.


6. Walker C, 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(2):207-14


**Authors’ contributions**

Effiong A: 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.

Effiong, AI: Assisted in drafting and preparation of the manuscript; provided feedback on study protocol format; involved in conception and design of the study and approved the final manuscript.

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**Competing interests**

None

**Registration details**

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**Appendix I**

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/
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.
26. Heart Diseases/
27. cardiac.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/
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 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 II

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/
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.
26. Heart Diseases/
27. cardiac.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/
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