Systematic review and meta-analysis of the effectiveness and cost-effectiveness of inpatient specialist palliative care in acute hospitals for adults with advanced illness and their caregivers

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SUMMARY:

Background: The global burden of disease has increased with increasing longevity and reduced mortality. This change is placing considerable strain on healthcare systems with increases in healthcare costs observed globally, despite efforts to reduce acute hospital expenditure. Specialist palliative care in acute hospitals is common. Most adults die in hospitals and most die from advanced chronic illness. With an ageing population, the demand for specialist palliative care is likely to continue. Evidence shows that specialist palliative care improves clinical outcomes and quality of care, can reduce hospital costs, and help contain costs in the last year of life. A review of the evidence of the effectiveness and cost-effectiveness of specialist palliative care has the potential to aid the future development, funding and implementation of evidenced based inpatient specialist palliative care.

Aim: To determine the effectiveness (on improving pain and other symptoms) and cost-effectiveness of inpatient specialist palliative care for patients with advanced illness and their unpaid caregivers.

Methods

Design: Cochrane Systematic review, meta-analysis and meta-synthesis.

***P**articipants*: 1) adult patients admitted to an acute hospital receiving inpatient specialist palliative care or in a control group or 2) unpaid caregivers of these patients ***I**ntervention*: Inpatient specialist palliative care. ***C**omparator*: Best usual care ***O**utcome*: Primary Outcome- Pain measured using validated assessment scales. Secondary outcomes- Other symptoms, quality of life, experience/satisfaction of care, patient mortality/survival, caregiver burden, mental health and bereavement outcomes, health economic evaluation and adverse effects.

Studies: We will include intervention studies with quantitative primary outcomes. We will include randomised and non-randomised studies.

Search methods: We will identify studies through electronic searches (1947 to present) and appropriate health economic databases (1980-present), hand searching, electronic citation tracking, personal contact and searching of grey literature. We will use an adapted MEDLINE search strategy for all databases. *Data extraction and management*: Two researchers will assess studies for bias and independently extract and enter data from all included studies using a data extraction form. Disagreements will be resolved by discussion and consensus with a third researcher. Quality assessment will follow Cochrane handbook methods.

Analysis: We will conduct all analyses as per the Cochrane Collaboration handbook including assessment of quality of non-randomised studies. If appropriate, we will undertake meta-analysis of the primary and secondary outcomes. We will present characteristics of the included health economics studies. We will also present point estimates of measures of items of resource use and

cost and point estimates of incremental costs and/or cost-effectiveness, with associated measures of uncertainty. We will identify and report incremental cost per QALY (or equivalent) and cost-benefit ratios where relevant. We will conduct further cost-effectiveness analysis depending on the level of data retrieved. Should the eligible studies not be sufficiently homogenous to permit meta-analysis, we will extract quantitative data and techniques used in narrative synthesis will be employed to analyse the data. Where possible, we will include qualitative data from nested or embedded qualitative studies where qualitative data has been used as part of the trial to assess the effectiveness or cost-effectiveness of the intervention.

BACKGROUND AND RATIONALE:

What is the problem being addressed?

The global burden of disease has increased due to global demography of lowered fertility, increased longevity, and reduced childhood and infant infectious disease mortality. This change is placing considerable strain on healthcare systems internationally.(1) Most adults develop one or more chronic illnesses with which they may live for many years before they die. For a minority of patients with serious illness (for example, metastatic colon cancer), the time following diagnosis is characterised by a stable period of relatively good functional and cognitive performance, followed by a predictable and short period of functional and clinical decline. However, for most patients with serious illness (for example, heart or lung disease, Parkinson's disease, dementia, stroke, neuro-muscular degenerative diseases and many cancers), the time following diagnosis is characterised by months to years of physical and psychological symptom distress, progressive functional dependence and frailty, considerable family support needs and high healthcare resource use.(2) In addition to increased clinical complexity, the rise of ageing populations has led to considerable healthcare costs globally. This has occurred despite efforts to reduce acute hospital care expenditure in many high-income countries, including, for example, in the United States (3) and the United Kingdom. (4)

The current funding call for the HS & DR program is to identify cost-effective models of specialist palliative care. The research question we are addressing is "are in-patient specialist palliative care in acute hospitals effective and cost-effective for adults with advanced illness and their caregivers?". Our research examines the effectiveness and cost-effectiveness of specialist palliative care in the acute hospital setting. This directly answers the HS&DR call.

Why is this research important in terms of improving the health of patients and to the NHS?

It could be argued that increased staffing costs and the introduction or expansion of novel services in hospitals, such as specialist palliative care, plays a role in this increased expenditure. For example, in the United States, over the past 12 years, palliative care prevalence in hospitals with 50 or more beds has increased 164%, to 61% of hospitals.(5) Furthermore, the growth of specialist palliative care in acute hospitals is likely to continue in the foreseeable future as most older adults (≥65 years old) die in hospitals (71% of all hospital deaths in the United States) (6), the majority of deaths in hospital occur due to terminal illness (7), and also because deaths in institutional care persist into older stages of life, with one in five centenarians dying in hospital.(8) However, evidence shows that specialist palliative care improves clinical outcomes and quality of care.(9) Furthermore, specialist palliative care, which includes bereavement care and preparatory grief work, has the potential to help unpaid caregivers access the care they need related to the death of a loved one.(10)

Although increasingly recognised internationally as essential to healthcare, only 1 in 10 who needs palliative care receives it and palliative care remains on the margins. (11) This issue potentially places patients and their unpaid caregivers at risk of receiving care that focuses on disease-modification at the expense of optimal outcomes, holistic care and efficiency.

The numbers of inpatient specialist palliative care teams are increasing. (9, 12)This is occurring in response to unmet palliative needs of inpatients and their unpaid caregivers (12), yet clarity regarding the effective components of the intervention remains unknown. This review will provide

much-needed clarity regarding the effectiveness and cost-effectiveness of the component parts of specialist palliative care.

Why is this research needed now?

A previous systematic review in 2002 by Higginson et al showed that specialist palliative care improved clinical outcomes and quality of care and can reduce hospital costs.(13) However this review was small (nine studies) and only included cancer patients. The literature has not been reviewed systematically since this review despite a number of studies looking at effectiveness of inpatient palliative care in the last decade (APPENDIX 1) and no systematic review including non-malignant disease groups has been conducted. In addition, the models of palliative care in hospital have evolved since the previous review. Recent UK government (10) and commissioning guidance (14) has recommended that there ought to be delivery of a 24/7 palliative care service.(10) However, the recent End of Life Care Audit 2016 (15) showed that of the 142 acute NHS trusts in England participating, only 37% had specialist palliative care services available out of hours and this service varied with level of contact (telephone or on site visiting) and health professional involved (specialist nurse, junior doctor or Consultant). The recent research priorities identified by the James Lind Alliance (16)highlight the need for research into identifying the core palliative care services needed and the best way of providing palliative care outside of working hours. This Cochrane review will meet these priorities. It is important following the Liverpool Care Pathway and Neuberger review (17) that we examine the most effective methods and models of specialist palliative care for the acute hospital setting to ensure that there is an evidenced based approach to the delivery of inpatient palliative care. By understanding what component of inpatient specialist palliative care works, we are in a better position to instigate positive change. A recent Cochrane review has provided valuable synthesis of evidence on the effectiveness and cost-effectiveness of home palliative care services.(18) However, there is no such available evidence for inpatient specialist palliative care. This review is therefore important as it can assist with providing much-needed solutions to problems, and clarity regarding the effectiveness and cost-effectiveness of the component parts of specialist palliative care in the acute setting.

AIMS/OBJECTIVES

Aim

To determine the effectiveness (in improving pain and other symptoms) and cost-effectiveness of inpatient specialist palliative care in acute hospitals.

Objectives

- To determine the effectiveness of inpatient palliative care services compared with best usual care on pain.
- To determine the effectiveness of inpatient palliative care services compared with best usual care on quality of life and mortality/survival.
- To determine the effectiveness of inpatient palliative care services compared with best usual care on caregiver burden, mental health and bereavement.
- To determine the different models and out-of-hours arrangements of inpatient palliative care teams and their influence on effectiveness and cost-effectiveness.
- To determine effect of inpatient palliative care services on costs to the NHS
- To assess whether inpatient palliative care services result in adverse effects

RESEARCH QUESTION

Are inpatient specialist palliative care services in acute hospital effective and cost-effective?

METHODS

Design: Cochrane review, meta-analysis and meta-synthesis.

This project had previously been approved by Cochrane and had been published as a protocol:

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011619/abstract;jsessionid=0EFE71279F6E393305A10FC0721607B1.f03t04

The protocol was withdrawn by Cochrane as the deadline for the project had passed. A number of authors on the original protocol had left the project. In addition, we realised from our scoping that the body of literature was large and we did not have the resources to complete this without dedicated staff for the project. Therefore we sought funding and have closely liaised with Cochrane about this. We have now resubmitted the revised protocol (greatly strengthened by the HS&DR review process) and are awaiting acceptance. We will aim to start the project April 2017 and do not anticipate delay.

Participants

- Adult (≥ 18 years) patients admitted to an acute hospital for > 24 hours and those in receipt of inpatient specialist palliative care while an inpatient in an acute hospital
    - These patients will be diagnosed with advanced, life-limiting or life-threatening illness (malignant or non-malignant), which is likely to compromise the patient's quality of life in some way
- Unpaid caregivers of patients receiving inpatient specialist palliative care
    - Unpaid caregivers are likely to be family, friends or significant others associated with the patient (19)

Intervention

The intervention examined in this review is inpatient specialist palliative care. Inpatient specialist palliative care encompasses interventions delivered to patients with advanced (20), life-limiting (21), or life-threatening illness (22), which is likely to compromise their quality of life. The care is provided to the patient while they are admitted as inpatients to acute care hospitals. The intervention aims to prevent and/or relieve physical, psychological, social and spiritual problems. It is provided to patients with a malignant and/or non-malignant condition who may or may not be at the end of their life.(23) Population-based estimates of specialist palliative care have indicated which populations require specialist palliative care (24), including those with malignant neoplasms and non-malignant and other health-related conditions, specifically: heart disease, including cerebrovascular disease, renal disease, liver disease, respiratory disease, neurodegenerative disease (Huntington's disease, Parkinson's disease, multiple sclerosis, motor neuron disease, multi-system degeneration, progressive supranuclear ophathlmoplegia, Alzheimer's dementia and senility), and/or human immunodeficiency virus (HIV) infection/acquired immune deficiency syndrome (AIDS).

Inpatient specialist palliative care comprises of the following essential components:

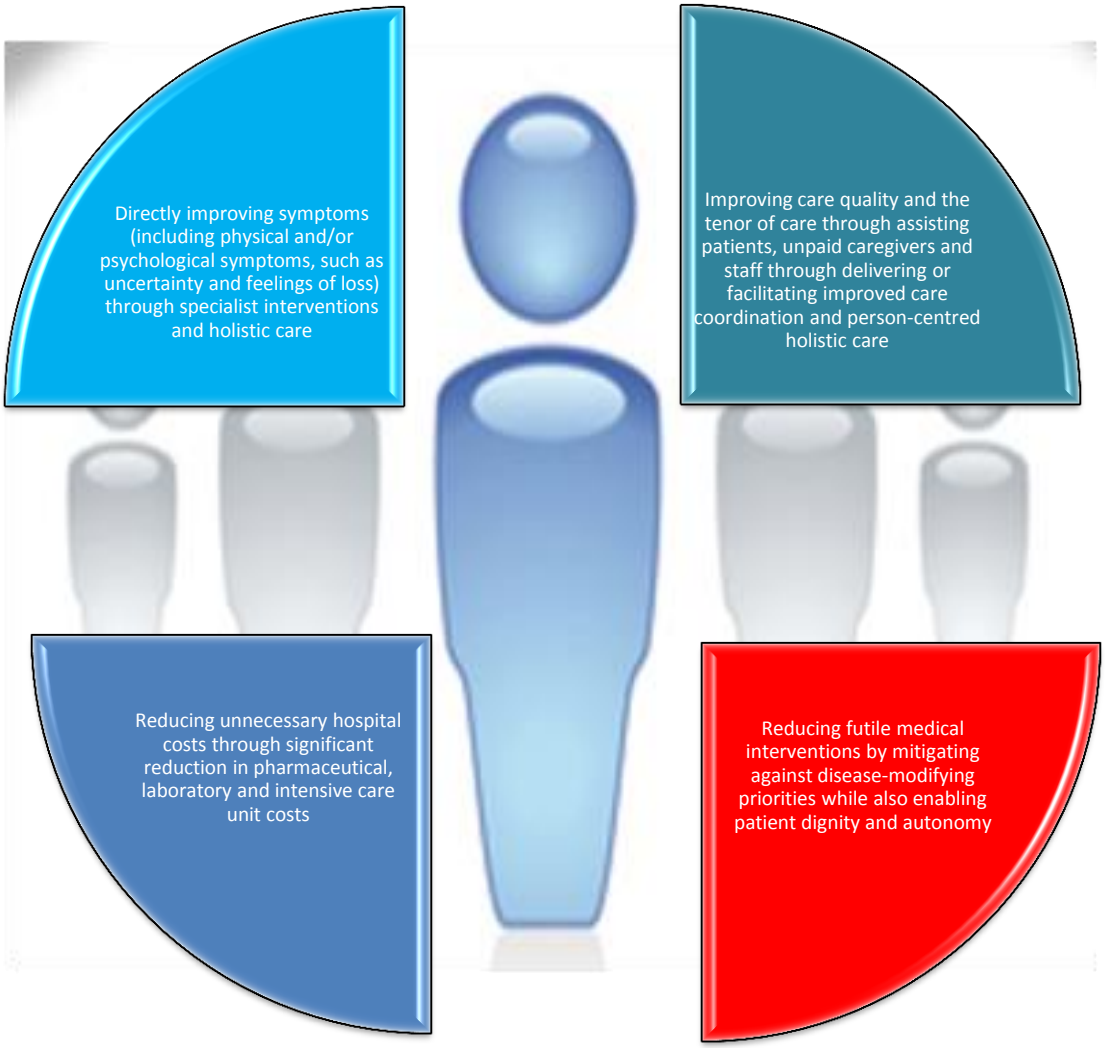
1. care coordinated by a multi-professional or multi-disciplinary team;
2. collaboration between specialist palliative care providers and generalist providers;
3. holistic care; and
4. complexity, feelings of loss and uncertainty.(22)

The intervention is provided to patients who are inpatients in an acute hospital and their families. Inpatient wards include, for example, palliative care units in the hospital, intensive care units, oncology wards, care of the elderly wards, or accident and emergency departments. The intervention is administered by hospital staff who have completed specialist training in palliative care or who have obtained clinical competencies and professional characteristics required for the delivery of inpatient specialist palliative care through clinical experience working.(14)

How the intervention might work

Although positive outcomes, such as symptom reduction, improved quality of care and care coordination, and reduced hospital costs can result from specialist palliative care, qualitative modelling and empirical testing is yet to definitively establish how inpatient specialist palliative care might work. Therefore, any descriptions of how specialist palliative care may work are speculative. That acknowledged, inpatient specialist palliative care may work with patients by improving symptoms (including pain) (25), improving care quality(26), reducing futile medical interventions (27) and reducing hospital costs.(28) Figure 1 demonstrates how inpatient specialist palliative care may work.

Figure 1 How inpatient specialist palliative care may work



Inpatient specialist palliative care varies between settings and countries. In order to allow for these differences, inpatient specialist palliative care will include care for patients with an advanced, life-limiting or life-threatening illness that is likely to compromise the patient's quality of life in some way with or without pre-bereavement care for unpaid caregivers (provided while the patient is alive and in hospital to either the unpaid caregiver alone or together with the patient). (9) The intervention must be aiming to address the primary outcome of this review and/or a secondary outcome. It must also be delivered by a specialist palliative care team or by a "specialist palliative care", "palliative care" (but not a generalist palliative care member, as defined in Shipman 2008 (29)).

Similarly to a previous Cochrane systematic review that has examined home palliative care (18), we will exclude trials evaluating inpatient specialist palliative care practitioners' provision of only a biomedical component of palliative care (for example, oxygen therapy) as this does not encompass the holistic nature of palliative care assessment or treatment. In addition, in order to limit the size of this review and heterogeneity, specialist palliative care delivered to patients by outreach hospital services or within hospital outpatient services will not be included in the review. Specialist palliative care provided to unpaid caregivers in hospital settings and/or hospital outpatients will be included.

This is because unpaid caregivers are likely to be seen as outpatients or in treatment rooms by hospital staff in the hospital to address pre-bereavement outcomes. Previous Cochrane reviews examining the effectiveness and cost-effectiveness of palliative care have been limited by the heterogeneity of both palliative care interventions and "usual care" .(18) Limiting our review in this way will help limit heterogeneity.

Comparator

Comparisons will be made with usual care. Usual care is defined as inpatient hospital care without any specialist palliative care input (for example, oncological care only), or community care (for example, primary or specialist care provided in the patient's place of residence). We will extract descriptive data on what is involved in each intervention. Detailing these items will help address different implications regarding associated cost-effectiveness and costs in studies with various study designs and diverse specialist palliative care and usual care interventions.

Outcome

The primary and secondary outcomes for this review are developed from previous reviews regarding the effectiveness of palliative care. (9, 18, 30, 31) They reflect the multi-component nature of palliative care and the provision of both direct (e.g. face-to-face delivery of patient care) and indirect patient care (e.g. concerning practitioners' prescribing rationale), and care for unpaid caregivers while the inpatient is still alive. We have chosen to measure pain as our primary outcome rather than quality of life. Research has shown that conducting meta-analysis on data from instruments that do not measure the same underlying constructs or ones that differ substantially due to responsiveness (as is possible for patient-reported quality of life instruments) may be problematic, leading to between-study heterogeneity and biased meta-analysis.(32) Pain control is a top priority for many potential palliative care patients and their unpaid caregivers in many countries (33), and can be assessed by either the patient or by a proxy i.e. a healthcare clinician or an unpaid caregiver. The use of pain as the primary outcome incorporates a patient-level clinical outcome as central to the review.

Primary outcome

- Pain, measured using validated assessment scales e.g. pain item of the Palliative care Outcome Scale

Secondary outcomes

- Patient other symptoms, specifically physical, psychological (for example, anxiety and/or depression or distress), social and/or spiritual domains, either patient or proxy-reported
- Quality of life, measured using generic and disease/condition specific health related quality of life measures.
- Satisfaction with care, measured using validated assessment scales.
- Patient mortality/survival

- Unpaid caregiver symptom control, specifically physical, psychological (for example, anxiety and/or depression), social or spiritual domains, either unpaid caregiver or proxy-reported
- Unpaid caregiver burden, including emotional strain, burden, distress, mastery or positive aspects of caregiving
- Unpaid caregiver pre- and post-bereavement outcomes
- Cost outcomes:
    - Inpatient hospital costs, including inpatient length of stay, consultations with healthcare professionals, investigations, treatments, equipment and medication prescribed by care provision (for example, usual care, specialist palliative care, usual care plus specialist palliative care)
    - Unpaid caregiver costs from a societal perspective wherever possible (costs of caregivers' time off work, patient and caregivers' out-of-pocket expenses e.g. travel and child care costs, and any lost-opportunity costs);
    - Measures of cost-effectiveness
    - Economic evaluation outcome measures incorporating incremental cost effectiveness ratios using service cost data and condition specific outcome measures or quality-adjusted life years (QALYS) or an equivalent
- Adverse effects
    - Increased clinical depression, increased psycho-social-emotional distress, and early and/or increased mortality

Criteria for considering studies for this review

Types of studies

We will examine both effectiveness and cost-effectiveness components. Although the number of randomised controlled trials (RCTs) in palliative and end-of-life care is steadily increasing (34), they remain few in number. Non-randomised studies can provide important understanding on the effectiveness of palliative care services (9), but only with careful attention paid to the likelihood of bias. (35)

We will include studies that examine inpatient specialist palliative care through a RCT or other trial design. Individual- and cluster-unit randomisation will also be included. The type of non-randomised studies we are interested in include: quasi-experimental studies, interrupted time series (ITS) studies, controlled before and after (CBA) studies, cohort and case-control studies. We will use the list of study design features given in the Cochrane Handbook for Systematic Reviews of Interventions to identify the characteristics of non-randomised studies in order to include all eligible studies.(36) We recognise that heterogeneity will be greater in a systematic review of non-randomised studies than in a systematic review of randomised trials. Therefore, we will consider very carefully the likely extent of heterogeneity between included studies when deciding whether to pool findings quantitatively (i.e. by meta-analysis). We expect pooling of effect estimates from non-randomised studies to be the exception, rather than the rule. We will use established approaches to include and analyse non-randomised studies following Chapter 13 of Cochrane Hand book for Systematic Reviews of Interventions 2011.(36)

All studies must evaluate effectiveness regarding one of the stated primary and/or secondary outcomes stipulated for this review. In the economic component of the review, studies to be included are those that are conducted alongside (or as part of) the main effectiveness trial and ones that also meet the eligibility criteria for the effectiveness component. Full economic evaluation (i.e. cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses); partial economic evaluations (i.e. cost analyses, cost-description studies, cost-outcome descriptions); and studies reporting more limited information, such as estimates of resource use or costs associated with service use are eligible for review.

Search methods for identification of studies

We will identify studies through electronic searches, hand searching, electronic citation tracking, personal contact and searching of grey literature. We will not place restrictions on language; non-English papers will be assessed with the assistance of a native speaker, wherever possible. Where non-English studies are located and not able to be included in the review (due to a lack of resources to enable data extraction, for example), we will report accordingly to ensure transparency.

Electronic searches
We will identify studies by searching the databases listed below, using a combination of key terms and MeSH terms:

- Cochrane Library (Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA)) (current issue);
- MEDLINE & MEDLINE-in-Process (1947 to present);
- EMBASE (1974 to present);
- CINAHL (1981 to present);
- PsycINFO (1806 to present);
- CareSearch, Australian Government's Department of Health and Ageing (http://www.caresearch.com.au/) (from inception to present).

We will also search the following health economic databases to identify further studies:

- National Health Service Economic Evaluation Database (NHS EED) (current issue);
- Health Economics Evaluation Database (HEED) (current issue);
- European Network of Health Economics Evaluation Databases (EURONHEED) (1980 to present).

We will modify the MEDLINE search strategy (which has been approved by Cochrane) for use in other databases (Appendix 2).

Searching other resources

Hand searching
We will screen the reference lists of all included studies and relevant reviews for additional studies.

Electronic citation tracking
We will use the "Citation tacking" option in MEDLINE for lateral searching on the included studies, as recommended for palliative care reviews.(19)

Personal contact
When indicated to support data analysis, we will attempt to contact key investigators identified from the included studies for unpublished data or knowledge of grey literature. The collective knowledge of the Cochrane Pain, Palliative and Supportive Care Group editorial team will also be used to identify potential investigators and their studies to approach regarding unpublished data and their knowledge of grey literature.

Data collection and analysis

Selection of studies
Two authors (SB and research assistant) will independently screen all titles and abstracts identified in our electronic searches. If, after reading the abstract, doubt persists regarding the eligibility of the study, we will retrieve the full-text articles for further assessment and again these full-text articles will be assessed by the two authors independently. A third author (CE) will adjudicate any discrepancies between the two authors' assessment of eligibility. Disagreements will be resolved by discussion and consensus. We plan to illustrate our study selection process using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (37), as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.(36)

Data extraction and management
Two authors (SB and research assistant) will independently extract and enter data from all included studies using a data extraction form developed for the review. Disagreements will be resolved by discussion and consensus with a third author (CE). The data extraction form has been adapted from a form used in a previous review on the effectiveness of home palliative care.(18) Drawing on an existing data extraction form enables future work comparing the effectiveness and cost-effectiveness of specialist palliative care across care settings.

Assessment of risk of bias in included studies
Two authors (SB and research assistant) will independently assess the quality of all selected RCTs using the Cochrane Effective Practice and Organisation of Care (EPOC) criteria for effectiveness studies.(38) For non-randomised studies, we will use the 'Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies of Interventions'.(39) For full economic evaluations, we will use a 35-item checklist employed by BMJ for authors and peer reviewers of economic submissions; a shorter version of this checklist will be used for partial economic evaluation.(40) In order to identify low quality evaluation, each item of the checklist will be equally weighted and scored either 1 (addressed), 0.5 (unclear) and 0 (not addressed)(41) and in order to allow for appraisal of each component of selected studies, we will complete an average score for each section (study design, data collection, analysis and interpretation of results). This is to avoid an overall average score, which may mask specific areas of weakness. If useful, we will also calculate an overall average score to provide some overall indication of quality. As used previously in palliative care systematic reviews

(18), an average score under 0.6 will be considered as low quality. (41) We will assess the quality of relevant economic modelling studies using the Philips Checklist.(42)
We will assess risk of bias in all other studies using the Cochrane Collaboration's tool for assessing risk of bias (36), which involves assessment of individual domains, such as allocation concealment and blinding. Blinding may not always be possible for many palliative care studies. In addition, as with any research project, attempts at blinding may be unsuccessful once implementation occurs. We will examine blinding in each study, including whether this occurred and whether it was compromised during study implementation. These factors will be considered when interpreting the results of the review. Similarly, we will report selection, performance, detection, attrition, reporting and other sources of bias (where relevant). A summary of bias in relation to each important outcome and also across studies will be provided as either low risk, unclear risk or high risk. We will prepare 'Risk of bias' tables using the Cochrane Collaboration's statistical software, Review Manager 2014.

Cochrane guidance provides scope for assessing the risk of bias based on the likelihood that the outcome will be influenced by lack of blinding. The guidance suggests that a common assessment of risk be completed for all subjective outcomes (e.g. distress) as compared to objective outcomes (e.g. mortality).(36) Accordingly, we will group all "subjective" primary and secondary outcomes as being at high-risk of bias if blinding is unsuccessful. However, the mortality outcome is unlikely to be influenced by lack of blinding. This will therefore be treated as a "low risk of bias" even if blinding is unsuccessful.

Measures of treatment effect
If appropriate, we will undertake meta-analysis of the primary and secondary outcomes using Review Manager 2014. We will evaluate the direction and size of the effect as well as looking at the consistency of the effect across the selected studies. We will appraise the strength of the evidence using the grading system recommended by the Cochrane Collaborative.(43) To measure treatment effect, we will calculate a summary statistic for each study followed by an overall average treatment effect. We will use odds ratios (ORs) with 95% confidence intervals (CIs) for each study to determine whether pain was reduced or not.
Our primary outcome will be treated as a binary outcome. This will aid interpretation of the findings for clinicians and address the heterogeneity of pain data. Pain outcome data in eligible studies is likely to be presented as binary or ordinal data. This will involve transforming data by aggregating adjacent categories. Decisions related to dichotomising data will be informed primarily by clinical considerations with reference to the study population. Even though ORs will be used to detect treatment effect, we will present findings as risk ratios (RRs) (or relative risk reduction) in order to aid the use and interpretation of the findings by end users.

We will use either a fixed-effect or a random-effects model for meta-analysis. It is likely that a random-effects model will be used as the true effect size may not be due to chance alone. Eligible studies will most probably have been conducted with different populations, countries and years, for example. It is therefore likely that we may incorporate the assumption of heterogeneity in our review. However, should one true underlying fixed effect size be detected, we will use a fixed-effect model.

For secondary outcomes, we will either calculate standardised mean differences (SMDs) with 95% CIs in both intervention(s) and comparator(s) in order to show the intervention effect involving continuous data. For measures in the form of binary data, we will calculate ORs with 95% CIs. Ordinal data may be transformed into dichotomous data by aggregating adjacent categories together (informed by clinical judgement). If the same continuous outcome measure is used in all studies and measured in the same way, then the results will be averaged and we will calculate a mean difference (MD). If the outcome measures are the same, but they are measured differently in each study, we will calculate the SMD. A SMD of less than or equal to 0.2 will constitute a small effect, 0.2 to 0.5 will constitute a moderate effect and ≥0.8 will constitute a large effect. Statistical significance will be assumed using a P value of < 0.05.

Measures of resource use and cost

We will present characteristics of the included health economics studies, such as year of study; details of interventions and comparators; study design; data sources; jurisdiction and setting; analytic perspective and time horizon, in the 'Characteristics of included studies' table as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.(36) We will provide additional tables, which summarise checklists completed to inform assessments of the methodological quality of included health economics studies. We will present point estimates of measures of items of resource use and cost with associated measures of uncertainty for both the target intervention and each of its comparators, as well as point estimates of incremental costs and/or cost-effectiveness, again with associated measures of uncertainty. We will convert costs to US dollars (USD) or Great British Pounds (GBP) (current year) based on Purchasing Power Parities (PPP) and gross domestic product (GDP) deflators.

Cost-effectiveness

We will identify and report incremental cost per QALY (or equivalent) and cost-benefit ratios where relevant. We will conduct further cost-effectiveness analysis depending on the level of data retrieved. We will assess the methodological quality of selected studies using the Drummond and Jefferson checklist for economic evaluations. (40, 44) We will supplement this with the Good Practice Guidance produced by the ISPOR Task Force on Economic evaluations (45) and the Philips checklist. (46)

We assume that few economic studies exist, therefore, the primary aim is to confirm or refute our assumption. Only those studies meeting eligibility criteria relating to the target populations, interventions, comparisons and outcomes will be included for the further analysis. We will report characteristics of excluded studies in tables with reasons for exclusion as well as those of the included studies.

We will proceed to meta-analysis for cost-effectiveness when at least three studies are included, which investigate homogeneous inpatient palliative care using the same outcome measure.

If meta-analysis is possible, studies would be combined using a fixed effects model to give relative risks with 95% confidence intervals (Cis) for binary outcomes and weighted or standardised mean differences with 95% CIs for continuous outcomes. We will examine statistical heterogeneity using

the chi-square and I-square statistics. In case these statistics indicate heterogeneity, we will use random effects model.

Unit of analysis issues

Issues in the analysis of studies with particular characteristics, for example cross-over trials and cluster randomised trials, will be addressed once, and if, such studies are identified. We will report intra-cluster correlations for cluster trials and adjustments will be completed where necessary. We intend to use the intra-class correlation coefficient (ICC) supplied in eligible studies to adjust for meta-analysis. If not supplied in the article, we will seek this information from the study authors. If still unavailable, we will estimate an intra-class correlation to allow for meta-analysis.

Dealing with missing data

When data are missing from a study, we will contact the original investigator for clarification and additional information where possible. Any strategy used for imputing missing data will be described, as well as justifying the choice of the strategy used. We are also expecting to find studies with missing intervention data (number of staff involved, skills and so on). The potential impact of these missing data on the findings of the review will be examined in the discussion section. We will seek clarity from authors regarding study population and interventions where required, especially to aid examination of the components of the intervention.

Assessment of heterogeneity

We will examine and assess heterogeneity through the following three measures:
1.inspecting the studies to examine for plausible areas of heterogeneity based on clinical factors that may influence findings of our meta-analysis;
2.inspecting the forest plots;
3.using the I^2statistics to examine the extent and impact of heterogeneity between included studies. We will explore reasons for heterogeneity n sensitivity analysis should high heterogeneity be identified (I^2 ≥75%).(36)

Assessment of reporting biases

In order to detect and manage reporting bias, we will take steps to attend to:
•multiple (publication) bias through contacting authors to ascertain whether duplication has occurred;
•location bias by searching relevant national and international trial registries for all relevant studies included (e.g. CENTRAL);
•language bias by including studies published in languages other than English, where possible, and if their inclusion is not feasible then we will report on these studies to identify that their data was not included in the review; and
•outcome reporting will be addressed through comparing the findings in eligible studies with published protocols where available.

In addition, if there are more than 10 included studies in our meta-analysis, we will use funnel plots and visually inspect them for a/symmetry as means of determining the effects of any eligible small study. We will also conduct relevant tests for asymmetry influenced by data type (e.g. continuous or

dichotomous), to assist with examining publication bias and to overcome any reliance on visual inspection.(47) Should small-study effects be identified, we will conduct sensitivity analysis to examine different assumptions and their impact on the review findings. We will determine fixed-effect and random-effects estimates of the intervention effect if it becomes evident that there is between-study heterogeneity. When asymmetry is observed, we will consider publication bias as one (of several) plausible explanations .(39)

As the potential for bias is greater in a non-randomised study than in a well-conducted randomised trial (48), we will pay particular attention to selection bias and reporting bias for non-randomised studies. We will critically appraise all studies and assess their risk of bias following guidance from the Cochrane Hand book for Systematic Reviews of Interventions.(36)
Non-randomised studies are generally assessed as low in quality, but can be appraised higher if indicated by a large magnitude of effect or lack of concern about confounding .(49) We expect pooling of effect estimates from non-randomised studies to be the exception, rather than the rule and will follow Cochrane Hand book for Systematic Reviews of Interventions (36) guidance at all times.

Data synthesis

Should the eligible studies not be sufficiently homogenous to permit meta-analysis, we will extract quantitative data (means, standard deviations, frequencies and proportions, test coefficients, 95% confidence intervals and effects sizes, where available) and techniques used in narrative synthesis will be employed to analyse the data, including:
•tabulation, which will involve inserting the main elements of extracted data into a table format;
•textual descriptions, which will involve collating a summary description of each included study;
•clustering of group textual descriptions according to attributes; and
•vote counting to determine how often certain attributes were reported .(50)
Where possible, we will include qualitative data from nested or embedded qualitative studies where qualitative data has been used as part of the trial to assess the effectiveness or cost-effectiveness of the intervention. We will analyse these through narrative synthesis methods.

Subgroup analysis and investigation of heterogeneity
As part of our primary objective, we will be identifying the effective components and determining the comparative effectiveness of inpatient specialist palliative care in acute hospitals for adults with advanced illness and their caregivers. We will compare the resources and costs associated with these services and determine their cost-effectiveness; compare the effectiveness by disease type (e.g. malignant and non-malignant groups) inpatient settings and country; examine other sources of heterogeneity, including interventions offering only single or few components of palliative care, and the applicability of meta-analysis. We will also examine how the different models and out of hours arrangements influence effectiveness and cost-effectiveness.

We will perform subgroup analysis using the following components known to influence the effectiveness of inpatient specialist care and in relation to particular patient groups.

1. Patient characteristic of disease type, including malignant and non-malignant disease to improve the evidence base for different types of palliative care populations .(31)
2. Frailty associated with advanced age due to how valuable these findings will be to society and future commissioning of services.
3. Inpatient specialist palliative care team composition (for example, physician-led as compared to nurse-led palliative care services) and organisation (for example, 24-hour access versus temporally restricted access) to examine the effectiveness of different models of service provision and to inform service delivery and configuration. This subgroup analysis will aid the identification of key components of inpatient specialist palliative care models.(31) In addition we will consider which models of specialist palliative care work best for which patients. During this review, we will measure what the authors are meaning by specialist in patient palliative care in each instance. We will aim to develop a taxonomy of the components. As such we will aim to fully understand what the intervention is and clearly present this, allowing clear and transparent conclusions about the data to be reached. In addition, this will provide an important methodological contribution to palliative care for future studies. The review will also generate insights into barriers and facilitators and the different points in the pathway in which specialist palliative care could have an impact.
4. Country of origin will also be explored due to differences in care structures and the availability of inpatient specialist palliative care, and any associated impact of this on effectiveness and cost-effectiveness.

Sensitivity analysis

We plan to conduct sensitivity analyses due to heterogeneity related to clinical (e.g. intervention type, patient population) and statistical reasons inherent within eligible studies. The I^2 statistic will help us examine the extent and impact of heterogeneity between included studies. We will explore reasons for heterogeneity using sensitivity analysis when high heterogeneity ($I^2 \geq 75\%$) is evident.(36)

Plan of investigation and timetable

Assuming a start date of May 2017, the project timetable will be as follows:
Form the advisory group – May 2017;
Literature searching and study retrieval –May 2017;
Assess studies for inclusion – June 2017 – July 2017;
Project Steering Group Meeting- July 2017;
Assessment of study quality and data extraction – August to November 2017;
Data synthesis – December to March 2018;
Updating of searches and systematic review – March 2018;
Project Steering Group Meeting- March 2018;
Drafting of Cochrane review– April 2018;

Patient and Public Involvement

Patient and public involvement led directly to the development of this review. In a study funded by NIHR and managed through the UK Medical Research Council (called MORECARE - Methods Of Researching End of life Care(51))we developed research based guidance to improve end of life care research. Patients and the public were included as integral in all stages, including several members who actively participated in the consultations, and also the project advisory group. In this the

patients and families identified the need for a systematic review, and then commented on and honed the questions, aims and objectives, including the priority questions. Based on this we developed the protocol and this application.
In addition, we have referred to the James Lind Alliance priorities (16) when developing our application: Our research specifically will help to answer "what are the core palliative care services that should be provided no matter what the patients' diagnoses are?" and "what are the best ways of providing palliative care outside of working hours?".
A patient (DM) and a carer (GB) are both co-applicants on this application and have both been involved in preparing this application. They will attend Project Steering group meetings and provide advice to the research team as needed. The patient and carer will be closely involved in dissemination of the research to ensure that as many of the end service users are reached. To support this, we have costed their time into the grant proposal. In addition, we have a PPI group at the Cicely Saunders Institute and we will present to the "Dragon's Den" group, receive feedback and change aspects as needed.
http://www.kcl.ac.uk/lsm/research/divisions/cicelysaunders/patients/ppi.aspx.

Expertise and justification of support required
The team is a multi-disciplinary collaboration between clinical academic teams throughout the UK. SB will lead the project, and oversee all aspects. She is a Consultant (hon senior lecturer) in palliative medicine. Her PhD trialled a hospital to home complex intervention in palliative care, and she has conducted systematic reviews of therapies and services. IJH is the senior co-applicant, and will support SB in all aspects, bring particular expertise in systematic review methods and complex evaluation design. IJH is Professor in Palliative Care and Policy, with a background in Palliative Medicine and Public Health Medicine, and a NIHR senior investigator. She has over 550 research papers in peer reviewed journals and extensive experience of conducting systematic reviews, empirical trials and health services research in end of life and palliative care. In particular she was senior investigator for a Cochrane review on the effectiveness and cost-effectiveness of home palliative care.(18) CE is a NIHR Senior Clinical Lecturer in palliative care, led the NIHR/MRC MORECare work on methods of Evaluating End of Life Care (51)and provides senior leadership for qualitative and nursing components. FM is a Consultant and Reader in Palliative Medicine. She is currently taking forward the NIHR funded C-CHANGE project (52) which amongst other things is testing the effectiveness and cost-effectiveness of different models of palliative care. CT is a Professor of Primary Care and Community Health and he was a co-PI on the MORECare project and will be leading on statistical aspects. Where needed we will approach our lead statistical colleagues for specialist advice. GG is Professor of Palliative Care and her research interests include factors contributing to inequity in access to palliative care services. DY is a palliative care health economist and will lead the assessment of health economics.
DM is a patient diagnosed with MND and COPD. GB is a carer for his father who has accessed palliative care services. Both DM and GB will provide valuable insight into the needs of patients and carers.
The support required and timetable to be followed for the proposed research are based on our estimates of the likely workload involved and reflect the scope of the project. The main cost for the proposed research is for staff time to undertake the systematic review. We have carried out scoping searches to identify potential studies of relevance and estimated the time cost for reviewing them.

In order to deliver the components of the project, a multi-disciplinary team with expertise clinical and palliative care research (especially previous Cochrane reviews).The day-to-day project work will be shared between the research assistant and SB. IJH, CE and FM, CT, GG, DY will assist in the interpretation of the research evidence, attend project meetings and support the dissemination plans for the research. Funding for travel, subsistence and conference fees for a national and international conference have been included to ensure the results of the review are widely disseminated .Costs of PCs and appropriate software are included at the Trust minimum cost. Funding for travel and catering expenses will be required for co-applicants for two project meetings to be held in London. In addition to staff costs we have included costs for PPI and dissemination plans including an open access journal publication.

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APPENDIX 1

Summary of potential studies to include in review

Study	Study Type	Number of patients	
		Intervention	Control
Back et al(53)	Cohort study	82	183
Bendaly et al (54)	Cohort study	61	55
Cassel et al(55)	Cohort study	91	20
Ciemins et al(56)	Cohort study	282	128
Cowan (57)	Cohort study	164	152
Engelhardt et al (58)	Randomised controlled trial	93	76
Gade et al (59)	Randomised controlled trial	275	237
Gomez-Batiste et al(60)	Cohort study	100	100
Hanson et al (61)	Cohort study	104	1813
Lo(62)	Cohort study	912	25,544
Morrison(63)	Cohort study	2630	18,427
Morrison, Dietrich(64)	Cohort study	475	1576
Penrod et al (65)	Cohort study	82	232
Penrod et al (66)	Cohort study	606	2715
Simoens et al (67)	Cohort study	88	53
Smith et al (68)	Cohort study	38	38
Ward-Smith et al(69)	Cohort study	9	9
White et al(70)	Cohort study	1774	520

In addition, the original nine studies in the Higginson et al (13) systematic review will be included.

APPENDIX 2

MEDLINE search strategy

1. exp palliative care/
2. exp terminal care/
3. exp terminally ill/
4. palliat*.mp.
5. (terminal* adj3 (care or caring)).mp.
6. ((advanced or end stage or terminal) adj3 (disease* or ill* or cancer* or malignan*)).mp.
7. (last year of life or LYOL or life's end or end of life).mp.
8. or/1-7
9. exp hospitals/
10. inpatients/
11. ((hospital* or inpatient*) adj2 (base* or care or center* or centre* or interven* or management or model* or nurs* or program* or service* or team* or therap* or treat*)).mp.
12. or/9-11
13. 8 and 12
14. randomized controlled trial.pt.
15. controlled clinical trial.pt.
16. randomized.ab.
17. placebo.ab.
18. drug therapy.fs.
19. randomly.ab.
20. trial.ab.
21. groups.ab.
22. (random* or control* or intervention* or evaluat*).tw.
23. ((before and after) or case control* or cohort study or or quasi experiment* or time series).tw.
24. or/14-23
25. 13 and 24
26. exp budgets/ or exp "costs and cost analysis"/ or economics/ or exp economics, hospital/ or exp economics, medical/ or economics, nursing/ or exp "fees and charges"/ or exp resource allocation/ or value of life/
27. (cost* or economic*).ti. or (cost* adj2 (effective* or utilit* or benefit* or minimi*)).ab. or economic model*.tw. or (budget* or fee* or financ* or price* or pricing or resourc* allocat* or (value adj2 (monetary or money))).ti,ab.
28. or/26-27
29. 13 and 28
30. 25 or 29
31. (animals not (humans and animals)).sh.
32. not 31
33. 32 and 30