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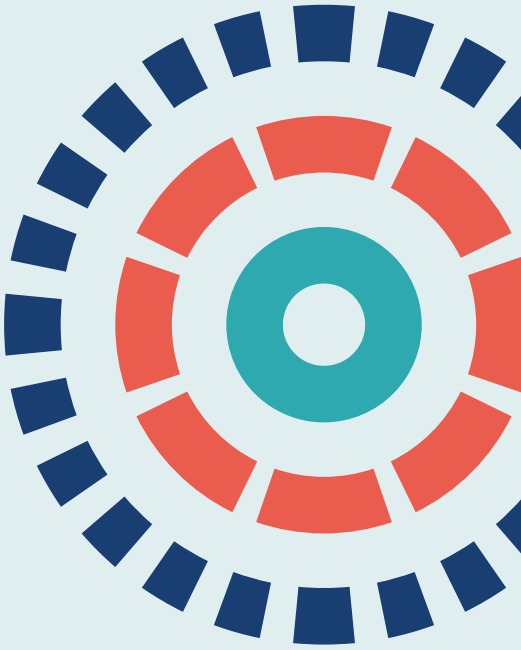

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Hospital-based specialist palliative care compared with usual care for adults with advanced illness and their caregivers: a systematic review

Adejoke O Oluyase,[1] Irene J Higginson,[1] Deokhee Yi,[1] Wei Gao,[1] Catherine J Evans,[1] Gunn Grande,[2,3] Chris Todd,[2,3,4] Massimo Costantini,[5] Fliss EM Murtagh[1,6] and Sabrina Bajwah[1*]

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Abstract

Hospital-based specialist palliative care compared with usual care for adults with advanced illness and their caregivers: a systematic review

Adejoke O Oluyase,[1] Irene J Higginson,[1] Deokhee Yi,[1] Wei Gao,[1] Catherine J Evans,[1] Gunn Grande,[2,3] Chris Todd,[2,3,4] Massimo Costantini,[5] Fliss EM Murtagh[1,6] and Sabrina Bajwah[1*]

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Background: Most deaths still take place in hospital; cost-effective commissioning of end-of-life resources is a priority. This review provides clarity on the effectiveness of hospital-based specialist palliative care.

Objectives: The objectives were to assess the effectiveness and cost-effectiveness of hospital-based specialist palliative care.

Population: Adult patients with advanced illnesses and their unpaid caregivers.

Intervention: Hospital-based specialist palliative care.

Comparators: Inpatient or outpatient hospital care without specialist palliative care input at the point of entry to the study, or community care or hospice care provided outside the hospital setting (usual care).

Primary outcomes: Patient health-related quality of life and symptom burden.

Data sources: Six databases (The Cochrane Library, MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, PsycINFO and CareSearch), clinical trial registers, reference lists and systematic reviews were searched to August 2019.

Review methods: Two independent reviewers screened, data extracted and assessed methodological quality. Meta-analysis was carried out using RevMan (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark), with separate synthesis of qualitative data.

Results: Forty-two randomised controlled trials involving 7779 participants (6678 patients and 1101 unpaid caregivers) were included. Diagnoses of participants were as follows: cancer, 21 studies; non-cancer, 14 studies; and mixed cancer and non-cancer, seven studies. Hospital-based specialist palliative care was offered in the following models: ward based (one study), inpatient consult (10 studies), outpatient (six studies), hospital at home or hospital outreach (five studies) and multiple settings that included hospital (20 studies). Meta-analyses demonstrated significant improvement favouring hospital-based specialist palliative care over usual care in patient health-related quality of life (10 studies,

standardised mean difference 0.26, 95% confidence interval 0.15 to 0.37; $I^2 = 3\%$) and patient satisfaction with care (two studies, standardised mean difference 0.36, 95% confidence interval 0.14 to 0.57; $I^2 = 0\%$), a significant reduction in patient symptom burden (six studies, standardised mean difference −0.26, 95% confidence interval −0.41 to −0.12; $I^2 = 0\%$) and patient depression (eight studies, standardised mean difference −0.22, 95% confidence interval −0.34 to −0.10; $I^2 = 0\%$), and a significant increase in the chances of patients dying in their preferred place (measured by number of patients with home death) (seven studies, odds ratio 1.63, 95% confidence interval 1.23 to 2.16; $I^2 = 0\%$). There were non-significant improvements in pain (four studies, standardised mean difference −0.16, 95% confidence interval −0.33 to 0.01; $I^2 = 0\%$) and patient anxiety (five studies, mean difference −0.63, 95% confidence interval −2.22 to 0.96; $I^2 = 76\%$). Hospital-based specialist palliative care showed no evidence of causing serious harm. The evidence on mortality/survival and cost-effectiveness was inconclusive. Qualitative studies (10 studies, 322 participants) suggested that hospital-based specialist palliative care was beneficial as it ensured personalised and holistic care for patients and their families, while also fostering open communication, shared decision-making and respectful and compassionate care.

Limitation: In almost half of the included randomised controlled trials, there was palliative care involvement in the control group.

Conclusions: Hospital-based specialist palliative care may offer benefits for person-centred outcomes including health-related quality of life, symptom burden, patient depression and satisfaction with care, while also increasing the chances of patients dying in their preferred place (measured by home death) with little evidence of harm.

Future work: More studies are needed of populations with non-malignant diseases, different models of hospital-based specialist palliative care, and cost-effectiveness.

Study registration: This study is registered as PROSPERO CRD42017083205.

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Report Supplementary Material 1 Characteristics of included studies, resource use data and studies with qualitative components

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/hsdr09120).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

Glossary

Effect size A way of quantifying the difference between two groups by calculating the size of the difference. An effect size of 0.2 to < 0.5 constituted a small effect, 0.5 to < 0.8 constituted a moderate effect and ≥ 0.8 constituted a large effect.

Hospital-based specialist palliative care This was defined as specialist palliative care delivered by a palliative care team that is based in a hospital providing holistic care, co-ordination by a multidisciplinary team, and collaboration between hospital-based specialist palliative care providers and generalists. Hospital-based specialist palliative care is provided to patients while they are admitted as inpatients to acute care hospitals, to outpatients or to patients receiving care from hospital outreach teams at home. It may also involve caregivers who might be family members, friends or significant others associated with the patient.

Multidisciplinary team A group of health-care workers who are members of different disciplines and who each provide a specific service to a patient.

***p*-value** The probability value is used to indicate whether or not research results are statistically significant. A *p*-value of < 0.05 means that there is a $< 5\%$ chance that the results of the study occurred by chance alone.

Risk ratio The probability of an event taking place.

Usual care This includes inpatient or outpatient hospital care without specialist palliative care input at the point of entry to the study, or community care or hospice care provided outside the hospital setting.

List of abbreviations

A&E	accident and emergency
AIDS	acquired immunodeficiency syndrome
BIS	Breathlessness Intervention Service
BPI	Brief Pain Inventory
CENTRAL	Cochrane Central Register of Controlled Trials
CES-D	Center for Epidemiologic Studies Depression Scale
CHEC	Consensus on Health Economic Criteria
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CQOL	Caregiver Quality of Life Index
CRQ	Chronic Respiratory Disease Questionnaire
CSRI	Client Service Receipt Inventory
DARE	Database of Abstracts of Reviews of Effects
ED	emergency department
EORTC QLQ-C30	European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D	EuroQol-5 Dimensions
ESAS	Edmonton Symptom Assessment Scale
EURONHEED	European Network of Health Economic Evaluation Databases
FACIT-Pal	Functional Assessment of Chronic Illness Therapy for Palliative Care
FACT-L	Functional Assessment of Cancer Therapy-Lung
FS-ICU	Family Satisfaction in the Intensive Care Unit
GP	general practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale-Anxiety
HADS-D	Hospital Anxiety and Depression Scale-Depression
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
HSPC	hospital-based specialist palliative care
HTA	Health Technology Assessment
ICC	intracluster correlation coefficient
ICD-10	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
INMB	incremental net monetary benefit
IQR	interquartile range
KCCQ	Kansas City Cardiomyopathy Questionnaire
MBCB	Montgomery–Borgatta Caregiver Burden
MCOHPQ	Modified City of Hope Patient Questionnaire
MD	mean difference
MDT	multidisciplinary team
NHS EED	NHS Economic Evaluation Database
NRS	Numeric Rating Scale

OR	odds ratio	QALY	quality-adjusted life-year
PG-13	Prigerson Inventory of Complicated Grief-Short Form	RCT	randomised controlled trial
PHQ-9	Patient Health Questionnaire-9 items	SD	standard deviation
POS	Palliative care Outcome Scale	SE	standard error
PREFER	Palliative advanced home caRE and heart FailurE caRe	SEIQoL-DW	Schedule for the Evaluation of Individual Quality of Life-Direct Weighting
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses	SEK	Swedish krona
		SMD	standardised mean difference
		ZBI	Zarit Burden Interview

Plain English summary

Although most people prefer to die at home, most deaths still occur in hospital. Hospital-based specialist palliative care involves the provision of palliative care services by specialist palliative care providers to people while admitted as inpatients to acute care hospitals, as outpatients or as patients receiving care from hospital outreach teams at home. Usual care could be inpatient or outpatient hospital care without specialist palliative care input at the point of entry to the study, or community care or hospice care provided outside the hospital setting. Hospital-based specialist palliative care is a growing area. However, it is unclear what components and models of hospital-based specialist palliative care work best. The need for clarity on these important features, as well as effective use of resources, has been raised. Consequently, this systematic review was carried out to address these areas.

We identified and studied all the key data from relevant randomised controlled trials. We included 42 randomised controlled trials with 7779 participants (6678 patients and 1101 caregivers). Twenty-one studies involved patients with cancer, 14 studies involved patients with other advanced illness (non-cancer) and seven involved patients who had a combination of cancer and non-cancer diagnoses (mixed diagnoses).

Results showed that hospital-based specialist palliative care may improve patient health-related quality of life, symptom burden and depression, while improving satisfaction with care and helping patients die where they want (measured by home death). Interviews exploring views and experiences of hospital-based specialist palliative care suggest that hospital-based specialist palliative care may be beneficial because it ensures personalised and holistic care for patients and their families, while also fostering open communication and shared decision-making, with respectful and compassionate care. There was no evidence that hospital-based specialist palliative care caused serious harm or cost more than usual care.

Further research is needed to look at the effectiveness of hospital-based specialist palliative care for caregivers, those with non-cancer diagnoses and whether it is more economical than usual care.

Scientific summary

Background

Serious illness is often characterised by physical/psychological problems, family support needs and high rates of health-care resource use. Hospital-based specialist palliative care has developed to assist in better meeting the needs of patients and their families, and, potentially, reduces hospital care expenditure. There is a need for clarity on the effectiveness and optimal models of hospital-based specialist palliative care, given that most people still die in hospital, and also to allocate scarce resources judiciously.

Objectives

The study had the following objectives:

- to determine the effectiveness of hospital-based specialist palliative care services compared with best usual care on –
    - patient and caregiver health-related quality of life
    - patient symptom burden
    - patient and caregiver satisfaction with care
    - achieving a patient's preferred place of care or death
    - patient mortality/survival
    - pain
    - patient symptoms such as anxiety, depression and breathlessness
    - caregiver burden, mental health and bereavement
- to determine the different models and out-of-hours arrangements of hospital-based specialist palliative care teams and their influence on effectiveness
- to assess whether or not hospital-based specialist palliative care services result in adverse effects
- to critically appraise and summarise current evidence on resource use and costs associated with hospital-based specialist palliative care services compared with best usual care services for adults with advanced illness and their caregivers/families.

Methods

A systematic review of randomised controlled trials assessing the impact of hospital-based specialist palliative care on outcomes for adults with advanced illness or their caregivers, or both, was undertaken.

Search strategy and data sources

We searched The Cochrane Library [Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment], MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature, PsycINFO, CareSearch, the NHS Economic Evaluation Database and trial registers to August 2019. Search terms included a combination of medical subject headings and free-text terms, refined with the assistance of the information specialist of the Cochrane Pain, Palliative and Supportive Care group. We checked reference lists of all included studies and of three relevant systematic reviews, searched citations and contacted 15 experts to identify additional studies.

Study selection

The inclusion and exclusion criteria used were as follows:

- Target population – patients with advanced illnesses and their unpaid caregivers.
- Target interventions – hospital-based specialist palliative care involving any of the following models: ward-based models, inpatient consulting models, outpatient models, hospital at home or hospital outreach models, and models involving multiple settings that included hospital. Hospital-based specialist palliative care consisted of the following essential elements –
    - care co-ordinated by a multiprofessional or multidisciplinary team
    - collaboration between specialist palliative care providers and generalist providers
    - holistic care.
- Control/comparators – usual care was the comparator. It was defined as inpatient or outpatient hospital care without any specialist palliative care input at the point of entry to the study (e.g. oncological care only), community care (e.g. primary or specialist care provided in a patient's place of residence) or hospice care provided outside the hospital setting. When usual care was compared with hospital-based specialist palliative care (plus or minus usual care), we extracted descriptive data on what was involved in the intervention.
- Outcome measures –
    - primary outcomes:
        - patient health-related quality of life, measured using validated assessment scales, which may be generic or disease-/condition-specific health-related quality-of-life measures
        - patient symptom burden, specifically, a collection of two or more symptoms, which could be physical (e.g. pain), psychological (e.g. anxiety, depression), social or spiritual, either patient- or proxy-reported through validated generalised assessment scales.
    - secondary outcomes:
        - patient satisfaction with care through validated assessment scales
        - caregiver satisfaction with care through validated assessment scales
        - achieving patient's preferred place of death
        - achieving patient's preferred place of care
        - patient mortality/survival
        - pain measured using validated assessment scales
        - patient anxiety and depression measured using validated assessment scales
        - patient breathlessness measured using validated assessment scales
        - adverse events among participants and unpaid caregivers
        - unpaid caregiver symptom control, specifically of physical, psychological (e.g. anxiety and depression), social or spiritual domains, reported through validated assessment scales and burden, including emotional strain, burden, distress, mastery or positive aspects of caregiving through validated assessment scales
        - unpaid caregiver pre- and post-bereavement outcomes, reported using validated outcome scales of multidimensional caregiving experiences (strain, distress, positive appraisals and family well-being), caregiver prolonged grief, multidimensional grief responses (despair, panic behaviour, blame and anger, detachment, disorganisation and personal growth) and quality of life.

Data extraction

Full texts of studies that met the inclusion criteria were read and data extraction was carried out by two independent reviewers. We resolved any disagreements by discussion and consensus.

Assessment of quality

Assessment of methodological quality was carried out by two independent reviewers using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.1 [Updated March 2011]*. London: The Cochrane Collaboration; 2011. URL: www.handbook.cochrane.org), with any disagreements resolved by discussion. We completed a 'risk of bias' table for each included study using the Cochrane Risk of Bias tool for randomised controlled studies.

Strength of the evidence

Two reviewers independently rated the quality of the evidence for each outcome using recommendations from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system and guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins and Green, 2011). Four levels were specified: very low, low, moderate and high. Evidence of very low certainty means that we have very little confidence in the effect estimate. Evidence of low certainty means that our confidence in the effect estimate is limited; evidence of moderate certainty means that we are moderately confident in the effect estimate; and evidence of high certainty reflects high confidence in the effect estimate.

Data synthesis

If appropriate, we undertook meta-analyses of the primary and secondary outcomes using RevMan (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). We used a random-effects model for meta-analyses to incorporate the assumption of heterogeneity, as eligible studies were conducted with different populations, in different countries and years. To account for use of different scales across studies, we calculated standardised mean differences with 95% confidence intervals for continuous data. If the same scales were used, we calculated mean differences. We used an inverse variance random-effects model. For binary data, we calculated odds ratios with 95% confidence intervals.

Results

A total of 42 randomised controlled trials involving 7779 participants (6678 patients and 1101 caregivers/family members) were included. We included 13 economic studies (2103 participants). The designs included parallel, fast-track and cluster randomised controlled trials. Almost half (19) of the studies were set in the USA. Twenty-one studies were with cancer populations; 14 and seven studies were with non-cancer, and mixed cancer and non-cancer populations, respectively. Six of the 14 non-cancer studies were on heart failure. Hospital-based specialist palliative care was offered in different ways, and included the following models: ward based (one study), inpatient consult (10 studies), outpatient (six studies), hospital at home or hospital outreach models (five studies) and service provision across multiple settings that included hospital (20 studies). For our main analyses, we pooled data from studies reporting adjusted end-point values. Seven studies included multidisciplinary hospital-based specialist palliative care teams led by nurses, whereas none of the studies included physician-led hospital-based specialist palliative care teams. Multidisciplinary team members ranged from two to eight professionals, mainly comprising nurses, physicians and, sometimes, social workers. Five studies included hospital-based specialist palliative care that had provision for out-of-hours services. In 20 studies, usual care included involvement of palliative care professionals if needed; in one study, usual care incorporated hospice care. Early palliative care was evaluated in 19 studies.

Meta-analyses demonstrated improvement in patient health-related quality of life (10 studies, 1344 participants, standardised mean difference 0.26, 95% confidence interval 0.15 to 0.37; $I^2 = 3\%$) and patient satisfaction with care (two studies, 337 participants, standardised mean difference 0.36, 95% confidence interval 0.14 to 0.57; $I^2 = 0\%$), as well as a significant reduction in patient symptom burden (six studies, 761 participants, standardised mean difference –0.26, 95% confidence interval –0.41 to

−0.12; $I^2 = 0\%$) and patient depression (eight studies, 1096 participants, standardised mean difference −0.22, 95% confidence interval −0.34 to −0.10; $I^2 = 0\%$). There was a significant increase in the chances of patients dying in their preferred place (measured by number of patients with home death) (seven studies, 861 participants, odds ratio 1.63, 95% confidence interval 1.23 to 2.16; $I^2 = 0\%$), favouring hospital-based specialist palliative care.

Non-significant improvement in favour of the control group was observed for caregiver satisfaction with care: the mean satisfaction in the hospital-based specialist palliative care group was 81.1 (95% confidence interval 78.3 to 83.9) (range 0–100, 100 = best caregiver satisfaction), whereas that in the usual-care group was 84.3 (95% confidence interval 81.3 to 87.3). Non-significant improvement in favour of the hospital-based specialist palliative care group was observed for pain (four studies, 525 participants, standardised mean difference −0.16, 95% confidence interval −0.33 to 0.01; $I^2 = 0\%$), patient anxiety (five studies, 384 participants, mean difference −0.63, 95% confidence interval −2.22 to 0.96; $I^2 = 76\%$), caregiver depression (two studies, 413 participants, standardised mean difference −0.02, 95% confidence interval −0.21 to 0.18; $I^2 = 0\%$) and patient breathlessness (five studies, 616 participants, standardised mean difference −0.04, 95% confidence interval −0.19 to 0.12; $I^2 = 0\%$).

The evidence on mortality/survival in 36 studies (7103 participants) was inconsistent, as some studies showed an increase in mortality/survival, whereas others showed a decrease. One study showed that all the patients who died in the hospital-based specialist palliative care group [$n = 8$ (100%)] achieved their preferred place of care, compared with 11 patients (84%) in the control group who died by the end of the study. Two studies presented data on caregiver burden, but they could not be pooled in a meta-analysis. They both found non-significant differences between hospital-based specialist palliative care and usual care. One of the studies assessed caregiver burden using the Montgomery–Borgatta Caregiver Burden scale and presented results for three different subscales of the scale, namely the objective burden scale (range 6–30, 30 = worst), the stress burden scale (range 4–20, 20 = worst) and the demand scale (range 4–20, 20 = worst). On the objective burden scale of the Montgomery–Borgatta Caregiver Burden scale, the mean caregiver burden score was 0.3 points higher (range 6–30, 30 indicates worst) for the hospital-based specialist palliative care group than for the control group, with adjustment for patient death ($p = 0.64$). On the stress burden scale of the Montgomery–Borgatta Caregiver Burden scale, the mean caregiver burden score was 0.5 points lower (range 4–20, 20 indicates worst) for the hospital-based specialist palliative care group than for the control group, with adjustment for patient death ($p = 0.29$). There was no difference in the mean caregiver burden score with adjustment for patient death on the demand scale of the Montgomery–Borgatta Caregiver Burden scale ($p = 0.97$). The second study assessed caregiver burden using the Zarit Burden Interview (range 0–88; 88 = highest burden) and reported a mean caregiver burden of 12.9 (standard error 1.3) in the hospital-based specialist palliative care group and of 14.8 (standard error 1.4) in the control group at 12 months ($p = 0.30$).

One study reported non-significant worsening of caregiver anxiety with hospital-based specialist palliative care. The study assessed caregiver anxiety using the Hospital Anxiety and Depression Scale-Anxiety (seven items; scale of 0–21, 21 = maximum distress), and found higher mean caregiver anxiety in the hospital-based specialist palliative care group (mean 7.2, 95% confidence interval 6.6 to 7.9) than in the control group at 3 months (mean 6.4, 95% confidence interval 5.7 to 7.1); on adjusting for baseline and multiple respondents, the mean difference was 0.8 (95% confidence interval −0.1 to 1.8; $p = 0.09$). Adjustments for three variables (baseline, multiple respondents and study sites) and six variables (baseline, multiple respondents, study sites, race, sex and primary/additional surrogate) also produced similar results with p-values of 0.11 and 0.12, respectively. Another study found a non-significant reduction in caregiver grief in favour of hospital-based specialist palliative care. The study assessed caregiver grief using the Prigerson Inventory of Complicated Grief-Short Form and reported a mean caregiver grief score in the hospital-based specialist palliative care group that was 2.2 points lower (range 11–55, 55 indicates highest grief) than that of the control group ($p = 0.21$). There was no evidence of a difference on adjusting for religious preference ($p = 0.40$), baseline depression levels ($p = 0.51$) or patient hospice use ($p = 0.51$). One study reported non-significantly better caregiver

quality of life in the hospital-based specialist palliative care group. The study assessed caregiver quality of life using the Caregiver Quality of Life Index (range 0–140, 140 = worse caregiver quality of life), and found a mean caregiver quality-of-life score in the hospital-based specialist palliative care group that was 2 points better than that of the control group at 3 months, with adjustment for patient death ($p = 0.39$). Among decedents' caregivers, a terminal decline analysis indicated a mean difference of −4.9 points between the hospital-based specialist palliative care group and the control group ($p = 0.07$).

Eight studies with 1252 participants reported on adverse events. Overall, hospital-based specialist palliative care showed no evidence of causing serious adverse events. One study reported a non-significant increase in adverse events in the hospital-based specialist palliative care group: 15 serious adverse events in 13 patients in the hospital-based specialist palliative care group (compared with seven adverse events in seven patients in the control group) ($p = 0.78$). Another study found that more patients in the hospital-based specialist palliative care group had the mild adverse event of poorer appetite compared with the control group ($p = 0.04$).

The evidence on cost-effectiveness of hospital-based specialist palliative care, compared with usual care, was not consistent among the four full economic studies and was, at best, equivocal. Other studies that used only partial economic analysis and those that presented resource use and more limited cost information also had inconsistent results.

Evidence from the 10 qualitative studies (322 participants) that explored views and experiences of hospital-based specialist palliative care by stakeholders suggested that hospital-based specialist palliative care was beneficial as it ensured personalised and holistic care for patients and their families, while also fostering open communication, shared decision-making, respectful and compassionate care and psychosocial support. These areas have been found to be important to patients and their families for end-of-life care in the hospital setting.

The quality of the evidence was judged to be low for patient health-related quality of life, patient satisfaction with care, caregiver grief, caregiver quality of life and achieving patient preferred place of death (measured by number of patients with home death). Evidence on patient symptom burden, patient depression, patient anxiety, patient pain, patient breathlessness, mortality/survival, achieving patient preferred place of care, caregiver satisfaction with care, caregiver burden, caregiver anxiety, caregiver depression, resource use, costs and cost-effectiveness, and adverse events in patients and caregivers was rated to be of very low quality. The quality of the evidence was downgraded for various reasons, for example high risk of bias and differences between studies that made it difficult to analyse the data.

Conclusions

Evidence suggests that, when compared with usual care, hospital-based specialist palliative care may offer benefits for several person-centred outcomes including health-related quality of life, symptom burden, and patient depression and satisfaction with care, while also increasing the chances of patients dying in their preferred place (measured by home death), with little evidence of harm. Although these are only small effect sizes, they may be clinically relevant at an advanced stage of disease with limited prognosis, and are person-centred outcomes important to many patients and families. It is not possible to draw firm conclusions from the limited and inconsistent evidence on survival nor on the most effective models of care. More well-conducted studies are needed of populations with non-malignant diseases and mixed diagnoses; of interventions of different models of hospital-based specialist palliative care; and of outcomes including achieving patient preferred place of care, patient satisfaction with care, unpaid caregiver outcomes (satisfaction with care, burden, depression, anxiety, grief, quality of life) and cost-effectiveness of hospital-based specialist palliative care.

Study registration

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Chapter 1 Introduction and background

Rationale

The global burden of disease has increased because of a number of factors such as increased longevity, reduced childhood and infant infectious disease mortality and global demography of lowered fertility. This increase has taken its toll on health-care systems worldwide.[1] Most adults develop chronic morbidities with which they may live for many years before they die. As well as increased clinical complexity, an ageing population has further led to increasing health-care costs internationally. This has occurred in spite of measures aimed at reducing health-care resource use and cost in many developed countries, including the UK[2] and the USA.[3]

Arguably, the introduction or expansion of new services in hospitals, such as specialist palliative care, and rising staff costs contribute to this increased expenditure. Specialist palliative care in hospital is likely to keep growing because most older people (i.e. aged $\geq$ 65 years) still die in hospitals (71% of all hospital deaths in the USA),[4] with most deaths resulting from terminal illnesses,[5] and also because deaths in institutional care persist into older stages of life, with one in five centenarians dying in hospital.[6] By 2040, it is estimated that, in the UK, roughly 160,000 more people will have palliative care needs, including pain control and end-of-life care in hospitals, hospices and at home.[7] Cost-effective commissioning of end-of-life resources is now a priority globally and also in the UK.[8] Available evidence suggests that hospital-based specialist palliative care (HSPC) may improve clinical outcomes and quality of care and may potentially reduce hospital care expenditure.[9] In addition, specialist palliative care, which includes bereavement care and preparatory grief work, could assist unpaid caregivers to access the care they need following the death of a loved one.[10]

Generally, inpatient hospital palliative care teams are increasing.[11,12] From 2000 to 2016, palliative care prevalence in hospitals with $\geq$ 50 beds in the USA increased by 178%,[13] yet there is a lack of clarity on the effective components of HSPC. This review will provide clarity regarding the effectiveness and cost-effectiveness of HSPC. Five different models of HSPC were specified because it is an evolving area and also to make this review more relevant to clinical practice. The models of HSPC that were eligible were ward-based models, inpatient consulting models, outpatient models, hospital at home or hospital outreach models (hereafter outreach model), and service provision across multiple settings that included hospital.

The rationale for undertaking this systematic review is as follows: first, there is increasing evidence that aggressive, and sometimes futile, treatments are being used with patients in acute hospitals at the end of life.[14] These treatments may lead to negative clinical, financial and utilisation outcomes,[15] and may not be what the patient wants.[16] Consequently, this review is important in order to determine how to improve care and also reduce costs. Second, given that the number of HSPC teams is increasing without a robust evidence base, this review addresses the gap by providing clarity on the effectiveness, and optimal components and models of HSPC.

A previous systematic review[9] showed that HSPC improved clinical outcomes and quality of care and can reduce hospital costs. However, this review was small (nine studies) and included only cancer patients. A 2017 review[17] in hospital, hospice or community settings found that specialist palliative care led to an improvement in quality of life with significant benefits for patients with cancer receiving specialist palliative care early. Results for pain and other outcomes were inconclusive. The 2017 Cochrane review[18] found that early palliative care interventions led to significantly better quality of life and reduced symptom intensity, compared with the control group. Depression levels and survival were not significantly different between the early palliative care group and the control group.

To our knowledge, no review had been carried out on specialist palliative care provided in hospital inpatient, outpatient and outreach settings, as well as multiple settings that include hospital.

The UK government[10] and commissioning guidance[19] have recommended that 24/7 palliative care service should be provided. However, the recent End of Life Care Audit 2016[20] showed that, of the 142 acute NHS trusts in England that participated, only 37% had provision for out-of-hours specialist palliative care services, and that there was variation in the health professionals involved and the level of contact (telephone or on-site visiting). The James Lind Alliance further highlighted the need for research into identifying the core palliative care services needed and the best way of providing out-of-hours palliative care.[21] This systematic review addressed these important priorities.

Description of the condition

Population-based estimates of specialist palliative care have highlighted the types of patients who require this service.[22] They include those with malignant neoplasms and non-malignant and other health-related conditions, specifically heart disease, including cerebrovascular disease; liver disease; renal disease; respiratory disease; neurodegenerative disease (Huntington's disease, Parkinson's disease, multiple sclerosis, motor neurone disease, multisystem degeneration, progressive supranuclear ophthalmoplegia, dementia due to Alzheimer's disease, and senility); and human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS).

Description of the intervention

The intervention in this systematic review is HSPC. HSPC refers to care that is provided with the input of specialist palliative care providers to patients while they are admitted as inpatients to acute care hospitals, outpatients or patients receiving care from hospital outreach teams at home. It includes interventions delivered to patients with advanced,[23] life-limiting[24] or life-threatening illness,[25] which is likely to affect their quality of life adversely.[26] The intervention aims to prevent or alleviate physical, social, psychological and spiritual problems. Patients receiving the intervention may have malignant and/or non-malignant conditions and they may or may not be at the end of their life.[27]

In this review, HSPC has the following important features:

- care co-ordinated by a multiprofessional or multidisciplinary team (MDT)
- collaboration between specialist palliative care providers and generalist providers
- holistic care.[25]

Specialist palliative care is not the same as generalist palliative care. Specialists are likely to have specialist training in palliative care, and the services they provide are mainly for those with palliative care needs; conversely, generalists provide palliative care as part of wider services.[28] Recipients of specialist care are mostly patients with advanced, life-limiting or life-threatening illness who present with complex needs.[24] Complex needs encompasses clinical complexity and its interaction with the confidence or ability of the lead clinical team (generalists) to address the presenting need. Complexity could be as a result of the disease, ethical complexity or both. Complexity usually involves multiple factors, related to the serious nature of illness, age, social or familial backgrounds, and/or the nature of a symptom (e.g. the usualness or intractable nature of the symptom).[24,29] The way in which specialist palliative care is defined differs between countries and there is sometimes little or no detail on the training of the palliative care team. Consequently, this review included studies for which training/clinical experience in specialist palliative care was clearly stated, as well as those that simply stated the involvement of a palliative care team with eligibility informed by activity of delivering specialist palliative care, rather than level of specialist training.[30] Specialist training in palliative care was

accepted if the authors stated that the professionals were palliative care experts or specialists (e.g. palliative care physician or nurse) or if they had obtained clinical competencies and professional characteristics required for the delivery of specialist palliative care through clinical experience.[19] The intervention should be delivered to patients receiving hospital inpatient, outpatient, outreach or HSPC as part of wider services, and their caregivers/families. Recognising the importance of the informal caregiver, palliative care also aims to meet the psychological, social and spiritual needs of caregivers.[31]

Specialist palliative care provided to unpaid caregivers in any of the previously mentioned settings was also included in this review. Unpaid caregivers may be seen by hospital staff to address their pre-bereavement needs. Pre-bereavement interventions are specialist palliative care interventions provided to address bereavement-related physical, psychosocial and spiritual problems experienced by unpaid caregivers before a patient's death. However, not all services provide pre-bereavement interventions.[32–34] Specialist palliative care interventions involving pre-bereavement interventions delivered to the unpaid caregiver alone or together with the patient were included.

Models of hospital-based specialist palliative care

Five different models of HSPC were specified because of their varied nature and also to cover different types of services. They were as follows:

1. ward-based models comprising care provision to patients and their caregivers on a palliative care ward in hospital
2. inpatient consulting models comprising care provision by an inpatient consult team to patients and their caregivers when admitted as inpatients to hospitals
3. outpatient models comprising care provision to hospital outpatients and their caregivers
4. hospital at home or hospital outreach into the community comprising care provision by hospital outreach teams in a patient's home
5. models involving multiple settings including hospital.

How the intervention might work

Although HSPC can lead to benefits, such as improved quality of care, symptom control and care co-ordination, and to a reduction in hospital expenditure, qualitative methods such as interviews and empirical testing have yet to clarify how HSPC might work. Consequently, proposed mechanisms by which HSPC may work are only speculative. HSPC may work with patients through the following means:

- directly improving symptoms through specialist interventions and holistic care[35]
- improving care quality and the tenor of care through assisting patients, unpaid caregivers and staff by delivering or facilitating improved care co-ordination and person-centred holistic care[36,37]
- reducing futile medical interventions and enabling patient dignity and autonomy[38]
- reducing unnecessary hospital costs by decreasing medication, laboratory and intensive care unit (ICU) costs[39]
- addressing holistic needs, including multimorbidity.[40]

The results from a systematic review[41] and randomised controlled trials (RCTs)[42,43] further highlighted that the intervention may support caregivers prior to a patient's death through emphasising the positive aspects of caregiving by providing information and guidance, increasing caregiving competencies and knowledge, helping caregivers to understand their circumstances and supporting their emotional reactions to the demands of caregiving, and improving involvement in care planning.[43,44] Involving both patients and caregivers in life review in consultations may help to decrease the stress caregivers experience.[42]

The intervention may also help caregivers to see problems in a new light, improving coping and planning, and providing them with access to expert information. This has been shown to improve their quality of life overall, while also decreasing caregiver burden and tasks.[45]

Objective

The objective was to assess the effectiveness and cost-effectiveness of HSPC for adults with advanced illness and their unpaid caregivers.

Research question

What is the evidence for the effectiveness and cost-effectiveness of HSPC in adults with advanced illness and their unpaid caregivers?

Changes from the protocol

There were some changes from the published protocol[46] in the review.

Study design

In the published protocol,[46] we stated that we would include a number of study designs including randomised trials, non-randomised trials, controlled before-and-after studies, interrupted time series studies and repeated-measures studies. Owing to the expansion of our review and given that RCTs are the most rigorous study design, we refrained from analysing studies that were not RCTs to reduce heterogeneity and allow meta-analyses when possible. We initially wanted to minimise cross-contamination by including only cluster-unit randomised studies. However, our project advisory group suggested that both cluster and non-cluster RCTs should be included to capture the breadth of evidence from RCTs that met our eligibility criteria. These changes were carried out before data extraction and analysis.

Intervention

The aim of the published protocol[46] was to assess the effectiveness and cost-effectiveness of inpatient specialist palliative care in acute hospitals for adults with advanced illness and their unpaid caregivers. The scope of the review was broadened to include other models of HSPC, such as outpatient models, hospital at home or hospital outreach models into the community and models involving multiple settings including hospital. This review was expanded because how HSPC is defined varies between countries and also to make this review more relevant to clinical practice and policy-makers, with the potential to aid the future development, funding and implementation of evidence-based HSPC. As a result of expanding the scope of our review to cover different models of HSPC, we also expanded the scope of usual care to 'inpatient or outpatient hospital care without specialist palliative care input at the point of entry to the study, community care or hospice care provided outside the hospital setting'.

In the protocol,[46] we stated that the intervention should be administered by hospital staff who have completed specialist training in palliative care or who had obtained clinical competencies and professional characteristics required for the delivery of inpatient specialist palliative care through clinical experience. Experts in our project advisory group recommended that we include studies for which the training of the palliative care team was unclear, with eligibility informed by activity of delivering specialist palliative care, rather than level of specialist training. To capture this difference, we included studies for which the training/clinical competence of the palliative care team was described, as well as studies that simply stated the involvement of a palliative care team. These changes were carried out before data extraction and analysis.

Outcomes

We changed the single primary outcome of pain in the published protocol[46] to two primary outcomes: patient health-related quality of life (HRQoL) and patient symptom burden assessed using a composite measure of two or more symptoms. The clinical experts on our project advisory group suggested that pain may not be an appropriate primary outcome measure for studies about non-malignant conditions, for which pain may be less prevalent than for cancer. Furthermore, the aim of palliative care is to improve quality of life, while also ensuring effective symptom management. We therefore decided to have patient HRQoL and patient symptom burden as our primary outcomes. These changes were carried out before data extraction and analysis.

We have provided further clarity around the outcomes in the protocol:[46]

- We included number of home deaths in the review as a proxy for achieving patient preferred place of death, as people's preference is usually to die at home.[47]
- In the protocol, one of the secondary outcomes was patients' other symptoms (e.g. physical, psychological, social or spiritual domains). We specifically presented data on patient anxiety and patient depression for this outcome.
- Another secondary outcome in the protocol was satisfaction with care, which we present as patient satisfaction with care and caregiver satisfaction with care in this review.
- We had unpaid caregiver symptom control (e.g. physical, psychological, social or spiritual domains) as an outcome in the protocol. In this review, we reported caregiver anxiety and caregiver depression for caregiver symptom control.
- For the unpaid caregiver pre- and post-bereavement outcome that we reported in the protocol, we presented caregiver grief and caregiver quality of life.
- Although we presented achieving preferred place of care or death as one outcome in the protocol, we report it as two outcomes in the review: achieving patient preferred place of death and achieving patient preferred place of care.
- We added a new secondary outcome, breathlessness, to this review because of the recommendations received from clinical experts in the Project Advisory Group on its relevance as an appropriate outcome in non-malignant conditions. Given the expansion of these outcomes, there has been a change in the order of the outcomes reported in this review, compared with the protocol.[46]

Data analysis and assessments

We added early versus late palliative care as a subgroup analysis. This was recommended for inclusion in the review by clinical experts because of its relevance to practice. Although we had initially specified in the published protocol that pain and other outcomes presented as binary data would be treated as binary outcomes, this was not possible, as most studies presented their outcomes as continuous data. The only outcome for which we were able to calculate odds ratios and 95% confidence intervals (CIs), in addition to standardised mean differences (SMDs), was patient depression. These changes were carried out before data extraction and analysis.

We expanded the risk-of-bias methods by carrying out separate assessments for all subjective outcomes (e.g. HRQoL) and all objective outcomes (e.g. mortality). When studies did not include either subjective or objective outcomes, we left the domain that was not included blank. We added the domain 'other' in the full review.

We had planned to use either a fixed-effects or a random-effects model for meta-analysis. Owing to the different models of HSPC in our review, we presented only random-effects models, as we are estimating the average effect across HSPC, rather than any single true effect. We had planned to

estimate an intracluster correlation coefficient (ICC) when the authors of cluster RCTs did not carry out adjustment or provide an ICC. However, we decided to use an estimate of ICC that we obtained from a previous study in adjusting for clustering in McCorkle *et al.*[48] We contacted the authors of McCorkle *et al.*[48] for their ICC, but, at the time of writing, they had not responded. In the protocol,[46] we stated that we will contact the original investigators for missing data and that we will describe any strategy used for imputing missing data. We decided to contact authors for missing data only without carrying out imputations, as this is the preferred method for dealing with missing data.[49] We initially wanted to explore reasons for heterogeneity in sensitivity analyses. However, Cochrane editors recommended the use of subgroup analysis for assessing heterogeneity. Consequently, we explored heterogeneity using subgroup analysis, whereas we used sensitivity analysis to test the estimate we used in adjusting for clustering in the cluster RCT. As we did not include non-randomised studies, we did not have to pay particular attention to selection bias and reporting bias in such studies. We did not carry out a subgroup analysis assessing provision of single or few components of HSPC because very few studies provided a single component of HSPC.

In the published protocol,[46] we stated that we were going to search two health economic databases to identify additional studies. However, we could search the NHS Economic Evaluation Database (NHS EED) only, because it was not possible for us to access the European Network of Health Economic Evaluation Databases (EURONHEED). We contacted the authors of the EURONHEED project, but did not receive any response.

Given that combining end-point scores and change scores is not recommended when using SMDs, and also that Cochrane does not recommend pooling adjusted and unadjusted estimates together, we pooled studies presenting adjusted end-point scores as our main meta-analysis, and we carried out sensitivity analyses with studies reporting unadjusted end-point scores, adjusted change scores and unadjusted change scores. This was a change from the protocol, based on advice from Cochrane editors.

We decided to present only one summary of findings table, rather than three, for the comparison of HSPC versus usual care, as experts in the project advisory group advised that this comparison alone would be the most informative for decision-makers. Compared with the protocol, which included only cost-effectiveness in the summary of findings table, we report the results for both cost and cost-effectiveness in the summary of findings table in this review (see *Table 2*).

Chapter 2 Methods

This systematic review of RCTs assessed the effectiveness and cost-effectiveness of HSPC for adults with advanced illness and their caregivers.

Inclusion and exclusion criteria

Studies were assessed for eligibility based on the criteria described in the subsequent sections.

Population

Studies involving adult patients with advanced illness and their unpaid caregivers were eligible for this review:

- Adult (aged ≥ 18 years) patients receiving HSPC –
    - these patients were diagnosed with advanced, life-limiting or life-threatening illness (malignant or non-malignant), which is likely to affect their quality of life negatively
    - diseases included [and their *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10), codes] were malignant cancers (C00–C97) and non-malignant and other illnesses, in particular heart disease, including cerebrovascular disease (I00–I52, I60–69); respiratory disease (J06–J18, J20–22, J40–47, J96); renal disease (N17, N18, N28, I12, I13); liver disease (K70–K77); neurodegenerative disease [Huntington's disease (G10), motor neuron disease (G12.2), multiple sclerosis (G35), Parkinson's disease (G20)]; progressive supranuclear ophthalmoplegia (G23.1); multisystem degeneration (G90.3); dementia due to Alzheimer's disease, and senility (F01, F03, G20, R54); and HIV/AIDS (B20–B24).
- Unpaid caregivers who have received a pre-bereavement intervention from one or more HSPC staff to manage or alleviate bereavement-related problems prior to the death of the patient. Unpaid caregivers are likely to be family, friends or significant others associated with the patient.[50,51]

Intervention

Hospital-based specialist palliative care differs between settings and countries. As already described in *Chapter 1*, HSPC included five different models of care: ward-based models, inpatient consulting models, outpatient models, hospital at home or hospital outreach models, and models involving multiple settings that included hospital. HSPC was provided to patients with an advanced, life-limiting or life-threatening illness that is likely to compromise a patient's quality of life, with or without pre-bereavement care for unpaid caregivers (provided while the patient is alive to either the unpaid caregiver alone or together with the patient).[11] This included, but was not limited to, interventions that have been labelled as 'palliative care, generic palliative care, hospice care or specialist palliative care'. The intervention was targeted at the primary outcomes of this review or a secondary outcome. It was delivered by a specialist palliative care team or by a 'specialist palliative care', 'palliative care' or 'hospice outreach' staff member (but not a generalist palliative care member, as defined in Shipman *et al.*[28]). We excluded trials that involved only provision of a biomedical component of palliative care (e.g. oxygen) by the HSPC team, as this does not reflect the holistic nature of palliative care.

Comparator

The comparator was usual care. Usual care comprised inpatient or outpatient hospital care without any specialist palliative care input (e.g. oncological care only) at the point of entry to the study, community care (e.g. primary or specialist care services delivered in the usual residence of the patient) or hospice care provided outside the hospital setting. When usual care was compared with HSPC (plus or minus usual care), we extracted descriptive data on what was involved in each intervention.

Outcomes

The primary and secondary outcomes were developed from previous reviews regarding the effectiveness of palliative care.[11,52–54] The outcomes reflect the multicomponent nature of palliative care and the provision of both direct (e.g. face-to-face delivery of patient care) and indirect (e.g. concerning practitioners' prescribing rationale) patient care and care for unpaid caregivers while the patient is still alive. We chose patient HRQoL and patient symptom burden as primary outcomes because a major focus of palliative care is to improve quality of life while also ensuring effective symptom management.[12] All studies assessed effectiveness regarding one of the primary or secondary outcomes.

Primary outcomes

- Patient HRQoL, measured using validated assessment scales, which may be generic or disease-/condition-specific HRQoL measures.
- Patient symptom burden, specifically, a collection of two or more symptoms that could be physical (e.g. pain), psychological (e.g. anxiety, depression), social or spiritual, either patient- or proxy-reported through validated generalised assessment scales.

Secondary outcomes

- Patient satisfaction with care, assessed through validated assessment scales.
- Caregiver satisfaction with care, assessed through validated assessment scales.
- Achieving patient's preferred place of death.
- Achieving patient's preferred place of care.
- Patient mortality/survival.
- Pain measured using validated assessment scales.
- Patient anxiety and depression, measured using validated assessment scales.
- Breathlessness, measured using validated assessment scales.
- Adverse events among participants and unpaid caregivers.
- Unpaid caregiver symptom control, specifically of the physical, psychological (e.g. anxiety and depression), social or spiritual domains, reported through validated assessment scales, and burden, including emotional strain, burden, distress, mastery or positive aspects of caregiving through validated assessment scales.
- Unpaid caregiver pre- and post-bereavement outcomes, reported using validated outcome scales of multidimensional caregiving experiences (strain, distress, positive appraisals and family well-being), caregiver prolonged grief, multidimensional grief responses (despair, panic behaviour, blame and anger, detachment, disorganisation and personal growth) and quality of life.

Economic data

Economic studies eligible were those carried out with the main effectiveness trial. This included full economic evaluations, such as cost-effectiveness analyses, cost–utility analyses and cost–benefit analyses; partial economic evaluations such as cost analyses, cost-description studies and cost-outcome descriptions; and studies that provided minimal information such as resource use or costs associated with the use of services.

Outcomes for the economic studies

This section is reproduced from Bajwah *et al.*[55]

The Bajwah *et al.*[55] review was published in the Cochrane Database of Systematic Reviews 2020, Issue 9. Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Database of Systematic Reviews should be consulted for the most recent version of the Cochrane review.

- Resource use: institutional care services use [e.g. emergency department (ED) or accident and emergency (A&E) use, ICU use, inpatient stay, care in nursing homes (or skilled nursing homes)], outpatient clinic services use (e.g. palliative care visits in outpatient settings, consultation with experts in outpatient settings), community care services use [e.g. contact with general practitioners (GPs), district nurses, home care, hospice care at home], unpaid caregiver's care, and medications and other resources.
- Costs and cost-effectiveness: costs were calculated based on resource use and unit costs of services, whereas cost-effectiveness was measured using incremental cost-effectiveness ratios (ICERs) of costs and condition-specific outcome measures or quality-adjusted life-years (QALYS) or an equivalent.

Study design

We included only RCTs on HSPC because there are rising numbers of RCTs in palliative and end-of-life care. In addition, RCTs are the most rigorous study design[56] and they are more amenable to meta-analysis because there is less heterogeneity among studies. We analysed RCTs by following the *Cochrane Handbook for Systematic Reviews of Interventions*.[49]

When possible, we included qualitative data from nested or embedded qualitative studies whereby qualitative data were used as part of the trial to understand stakeholder views and experiences of the intervention. We analysed these through narrative synthesis methods.

Identification of literature

Search strategy

We searched the databases in the following list in October 2017 and updated our searches in August 2019, using a combination of key terms and medical subject heading terms:

- The Cochrane Library –
  - Cochrane Central Register of Controlled Trials (CENTRAL); Issue 8 of 12, 2019
  - Cochrane Database of Systematic Reviews; Issue 8 of 12, 2019
  - Database of Abstracts of Reviews of Effects (DARE); Issue 2 of 4, 2015
  - Health Technology Assessment (HTA) database; Issue 4 of 4, 2016.
- MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (via Ovid), 1947 to August 2019.
- EMBASE (via Ovid), 1974 to August 2019.
- Cumulative Index to Nursing and Allied Health Literature (via EBSCO*host*), 1982 to August 2019.
- PsycINFO (via Ovid), 1806 to August 2019.
- CareSearch, funded by the Australian government's Department of Health [www.caresearch.com.au/ (accessed 12 September 2019)] (from inception to September 2019).

We also searched the NHS EED, current issue (issue 2 of 4, 2015) to identify further studies. We could not carry out more recent searches in DARE, HTA database or NHS EED because they are no longer updated. We also could not carry out a search of the health economic database EURONHEED as it is no longer available.

Search strategies were refined with the assistance of the information specialist of Cochrane Pain, Palliative and Supportive Care Group. There was no restriction on language as we assessed non-English papers with the assistance of native speakers. See *Appendix 1* for the MEDLINE search strategy in Ovid. This search strategy was modified for use in other databases.

We searched clinicaltrials.gov [www.clinicaltrials.gov (accessed 12 September 2019)] and the World Health Organization's International Clinical Trials Registry Platform [http://apps.who.int/trialsearch/ (accessed 12 September 2019)] for ongoing trials. We screened the reference lists of all included studies and three relevant systematic reviews[17,18,52] for additional studies. We used the 'Citation tracking' option in MEDLINE for lateral searching on the included studies, as recommended for palliative care reviews.[50] We contacted 15 experts in the field for unpublished and ongoing trials.

Details of the search process, the number of studies retrieved and the number included in the review are presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[57] flow diagram in *Figure 1*. The search results were imported into EndNote X8 [Clarivate Analytics (formerly Thomson Reuters), Philadelphia, PA, USA] and de-duplicated.

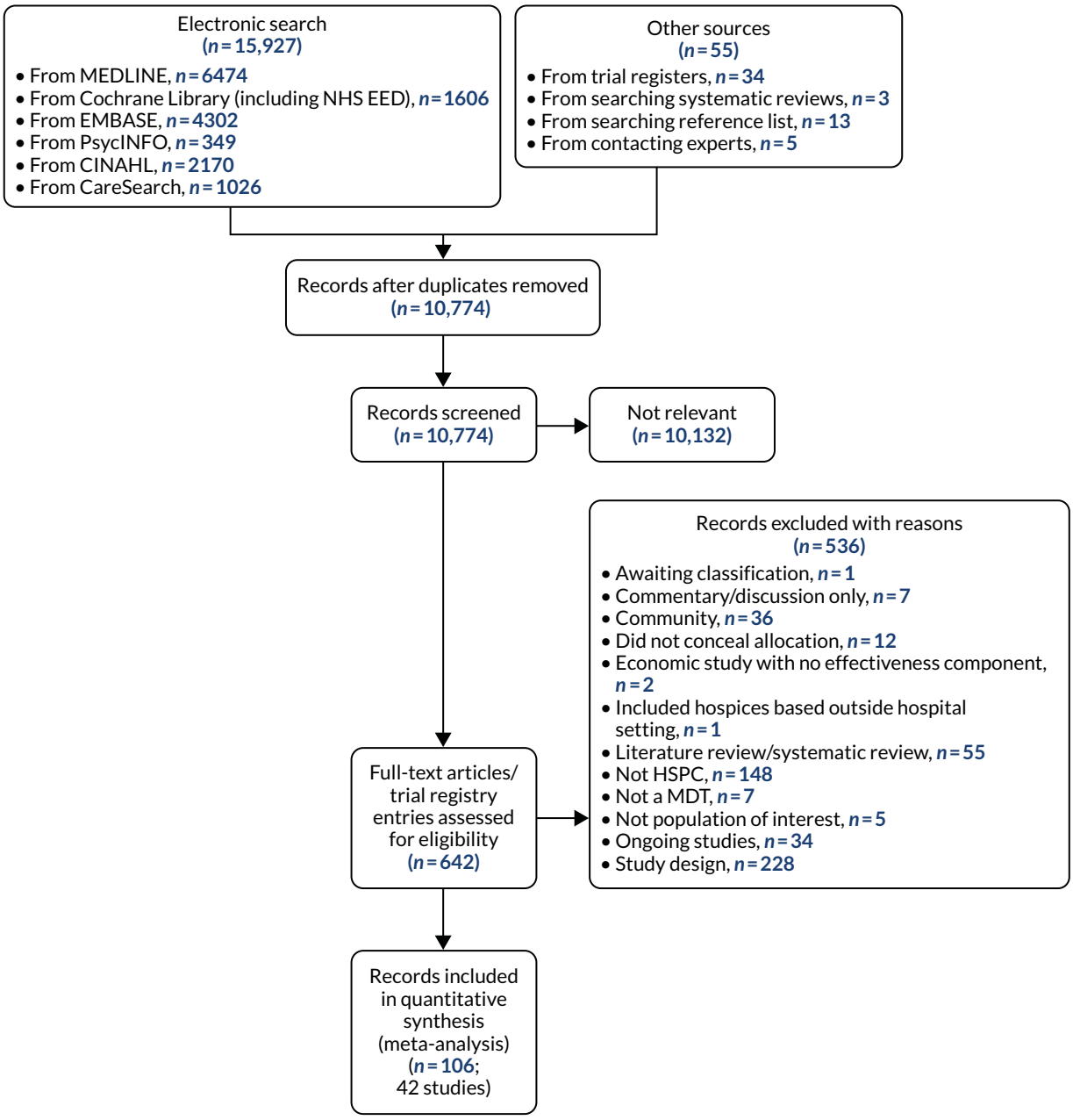

FIGURE 1 The PRISMA flow diagram illustrating the process of study selection. CINAHL, Cumulative Index to Nursing and Allied Health Literature.

Study selection and screening

Records retrieved following searching were uploaded to EndNote X8. Duplicates were removed, and titles and abstracts were first screened by two independent reviewers. If, after reading the abstract, doubt persisted regarding the eligibility of the study, we retrieved the full-text articles for further assessment and again the two reviewers independently assessed these full-text articles (see *Figure 1* for reasons for exclusion of full-text articles). Disagreements were resolved by discussion and consensus.

Data extraction and quality assessment

The data extraction form used in the Cochrane review on home palliative care by Gomes *et al.*[52] was adapted for use in this review. After piloting the form with five studies, two independent reviewers carried out data extraction. When disagreements occurred, they were resolved through discussion and consensus. Given that the review included some studies by the review authors, these review authors were not involved in data extraction or assessments of their studies. Multiple reports of the same study were collated, so that each study, rather than each report, was the unit of interest in the review.

Quality assessment of the studies in a systematic review is an ongoing area of debate, with the calculation of overall scores on quality being discouraged.[58] Highlighting where there is greater strength or confidence in the evidence aids the interpretation of the findings of a systematic review. We assessed the quality of the evidence for each outcome using the recommendations from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. Four levels are specified in the GRADE system for assessing the evidence: very low, low, moderate and high.

Given that this review was a Cochrane review, we carried out quality assessment using the Cochrane Risk of Bias tool.[58] Two independent reviewers assessed the risk of bias for each study. Disagreements were resolved by discussion. The following were assessed for each study:

- Random sequence generation (checking for possible selection bias). We evaluated how the allocation sequence was developed and rated it as having a low risk of bias (any truly random process, e.g. random number table; computer random number generator) or an unclear risk of bias (if the method for developing the sequence was unclear). We excluded studies that used a non-random process (e.g. odd or even date of birth; hospital number).
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment. We assessed the methods as being at low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes) or unclear risk of bias (method not clear). We excluded studies that did not conceal allocation.
- Blinding of participants and personnel (checking for possible performance bias). Guidance from Cochrane suggested that a common assessment of risk may be completed for all subjective outcomes (e.g. quality of life), as compared with objective outcomes (e.g. mortality).[49] Accordingly, we grouped all subjective outcomes (e.g. quality of life) as being at high risk of bias if blinding was unsuccessful. However, objective outcomes (e.g. mortality) are unlikely to be influenced by lack of blinding. Therefore, we treated these outcomes as having a 'low risk of bias', even if blinding was unsuccessful or not carried out. We assessed the methods as being at low risk of bias (e.g. no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken), unclear risk of bias (insufficient information to permit judgement of 'low risk' or 'high risk' or the study did not address this outcome) or high risk of bias (no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but it is probable that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding). When the study did not include either subjective or objective outcomes, we left the domain that was not included blank.

- Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind outcome assessors from knowledge of which intervention a participant received for both subjective and objective outcomes. We grouped all subjective outcomes as being at high risk of bias if blinding was unsuccessful. However, as stated previously, objective outcomes are unlikely to be influenced by lack of blinding; therefore, we rated these outcomes as a having a 'low risk of bias' even when blinding was unsuccessful or not carried out. We assessed the methods as being at low risk of bias (e.g. no blinding of outcome assessment, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken), unclear risk of bias (insufficient information to permit judgement of 'low risk' or 'high risk') or high risk of bias (no blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but it is probable that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding). When the study did not include either subjective or objective outcomes, we left the domain that was not included blank.
- Selective reporting (checking for reporting bias). We assessed whether or not primary and secondary outcome measures were prespecified and whether or not these were consistent with those reported. We assessed the methods as being at low risk of bias (protocol is available and all of the study's prespecified primary and secondary outcomes that are of interest in the review have been reported in the prespecified way), unclear risk of bias (insufficient information to permit judgement of 'low risk' or 'high risk') or high risk of bias [protocol is available and some prespecified outcomes were not reported; one or more primary outcomes were reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified; or one or more reported primary outcomes were not prespecified].
- Incomplete outcome data (checking for possible attrition bias). We judged the methods used to manage incomplete data as being at low risk of bias (< 10% of participants did not complete the study or used 'baseline observation carried forward' analysis), unclear risk of bias (used 'last observation carried forward' analysis) or high risk of bias (used 'completer' analysis).
- Size of study (checking for possible biases confounded by small size). We judged the studies to be at low risk of bias if they had $\geq$ 200 participants per treatment group, to be at unclear risk of bias if they had 50–199 participants per treatment group and to be at high risk of bias if they had $<$ 50 participants per treatment group.
- Other bias (other sources of bias). We also assessed whether or not groups were balanced at baseline and whether or not differences at baseline were controlled for. We assessed the studies as being at low risk of bias (e.g. if there were no baseline differences or if observed differences were controlled for), unclear risk of bias (e.g. if there were baseline differences and it was unclear if the differences were significant and also if they were controlled for) or high risk of bias (e.g. if there were differences that were not controlled for).

Health economics studies were classified according to their design (e.g. full economic evaluation, partial economic evaluation) and the design of the study for the effectiveness component of the health economic study (e.g. a single-study design, a synthesis of several studies). For full economic evaluations, we assessed the risk of bias in results of the single effectiveness study on which the full economic evaluation study was based and methodological quality of the full economic evaluation study. The BMJ checklist for authors and peer reviewers of economic submissions[59] and the Consensus on Health Economic Criteria (CHEC)-list were used for assessing the methodological quality of economic evaluations.[60] For assessment of the quality of relevant economic modelling studies, we planned to use tools such as the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement[61] and the Quality Appraisal Checklist for Economic Evaluations,[62] supplemented by the Philips checklist.[63] We could not apply these planned methods in this review as we did not identify any relevant economic modelling studies for inclusion; we plan to use these tools for future updates of the review, where appropriate.

Synthesis

Meta-analysis

If appropriate, meta-analysis of the primary and secondary outcomes was done using RevMan (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). We used a random-effects model for meta-analysis. Given that included studies were carried out in different years and countries and also with different populations, we incorporated the assumption of heterogeneity in the meta-analysis of our outcomes. When sample sizes and means [standard deviations (SDs)] were missing in studies, we contacted study authors to request additional data. We did not carry out imputations or estimate the missing values for meta-analysis. As recommended by the *Cochrane Handbook for Systematic Reviews of Interventions*,[49] we contacted study authors to request additional data. The potential impact of missing intervention data (e.g. number of staff involved, and skills) is discussed in *Chapter 4*.

Data for the primary outcomes (patient HRQoL and patient symptom burden) were combined using a random-effects model to account for the heterogeneity in patient populations and HSPC services. We used the inverse variance method, which summarises effect sizes from studies by calculating the weighted mean of the effect sizes using the inverse variance of the individual studies as weights.[64] We presented the pooled effect as SMD for HSPC compared with usual care; values of > 0 indicated better patient HRQoL with HSPC, and values of < 0 indicated worse patient HRQoL with HSPC. In contrast, for patient symptom burden, values of > 0 indicated worse symptoms and values of < 0 indicated lessened symptoms. A *p*-value of 0.05 was considered statistically significant and data were presented as effect size with 95% CIs. Where possible, we conducted a similar meta-analysis for other outcomes, with the exception of achieving patient preferred place of death (measured by number of patients with home deaths), whereby the pooled effect was expressed as an odds ratio (OR) for HSPC, compared with usual care; values of > 1 indicated higher odds of achieving patient preferred place of death with HSPC, and values of < 1 indicated decreased odds of achieving patient preferred place of death with HSPC. Even though ORs were used to detect treatment effect, we also presented findings as risk ratios (or relative risk) for easier interpretation by end users. The Mantel–Haenszel method was used in the meta-analysis for achieving patient preferred place of death. A SMD of 0.2 to < 0.5 constituted a small effect, a SMD of 0.5 to < 0.8 constituted a moderate effect and a SMD of ≥ 0.8 constituted a large effect.

Data on resource use and costs could not be combined because of differences in measurements and reporting, such as type of analysis, tools used, assessment time points or time horizon and statistics reported. We therefore carried out a narrative synthesis on the economic studies.

Narrative synthesis

In addition to narrative synthesis of the economic studies, we carried out narrative synthesis when eligible studies were not sufficiently homogenous to permit meta-analysis. We extracted quantitative data (means, SDs, frequencies and proportions, test coefficients, 95% CIs and effects sizes, where available) and applied techniques used in narrative synthesis to analyse the data. When qualitative data were used as part of a trial to explore stakeholders' views and experiences of the intervention, we also carried out narrative synthesis. The techniques employed include the following:

- tabulation, which involved inserting the main elements of extracted data into a table format
- textual descriptions, which involved collating a summary description of each included study
- clustering of group textual descriptions according to attributes
- vote-counting to determine how often certain attributes were reported.[65]

Unit-of-analysis issues

We considered issues in the analysis of studies with particular characteristics, such as cluster randomised trials, in our meta-analysis. We highlighted whether or not cluster randomised trials presented their ICC and if they made adjustment for clustering. If adjustment was made for clustering,

we used the data they presented in the meta-analysis. However, if the authors did not report their ICC or adjust for clustering, we contacted the authors for an estimate of the ICC. If authors did not respond, we obtained this estimate from a previous review. When we estimated an ICC, we carried out a sensitivity analysis to test the estimate we used for clustering.

Assessment of heterogeneity

We examined and assessed heterogeneity through the following three measures:

1. inspecting the studies to examine for plausible areas of heterogeneity based on clinical factors that may influence the findings of our meta-analysis
2. inspecting the forest plots
3. using the I^2 statistics to examine the extent and impact of heterogeneity between included studies.[49]

Assessment of reporting biases

To detect and manage reporting bias, we took the following steps to attend to:

- Multiple (publication) bias by contacting study authors to ascertain whether or not duplication has occurred.
- Location bias by searching relevant national and international trial registries for all relevant studies (e.g. CENTRAL).
- Language bias by including studies published in languages other than English.
- Outcomes reporting (including non-publication of economic evaluation outlined in the protocol) through comparing the findings in eligible studies with published protocols, if available. Where published protocols were unavailable, we asked study authors to supply them.

In addition, when there were > 10 included studies in our meta-analysis, we used funnel plots and visually inspected them for asymmetry/symmetry as a means of exploring whether or not there is evidence that study size (precision) is associated with effect size. Where possible, we also conducted 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.[66] When we observed asymmetry, we considered publication bias as one (of several) plausible explanation.[67]

Quality of the evidence

Two review authors independently rated the quality of the outcomes. We used the GRADE system to rank the quality of the evidence using the GRADEprofiler Guideline Development Tool software (Evidence Prime, Inc., Hamilton, ON, Canada), and the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions*.[49] The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence could be rated as having a high, moderate, low or very low risk of bias based on these considerations.

Summary of findings table

We included a 'summary of findings' table (see *Table 2*) to present the main findings in a transparent and simple tabular format. The table summarises the comparison of HSPC with usual care, which could be inpatient or outpatient hospital care without specialist palliative care input (e.g. oncological care) at the point of entry to the study, community care (e.g. primary or specialist care provided in a patient's place of residence) or hospice care provided outside the hospital setting. The table included key information concerning the quality of the evidence; the magnitude of effect of the interventions examined; and the sum of available data on the outcomes patient HRQoL, patient symptom burden, patient satisfaction with care, achieving patient preferred place of death (measured by the number of patients with a home death), pain, caregiver burden, cost and cost-effectiveness.

Subgroup analysis and investigation of heterogeneity

As part of the primary objective, we identified the effective components and determined the comparative effectiveness of HSPC for adults with advanced illness and their unpaid caregivers/families. We compared the resources and costs associated with these services and determined their cost-effectiveness, we compared effectiveness by disease type (e.g. malignant and non-malignant groups) and country, and we examined other sources of heterogeneity and the applicability of meta-analysis.

Where possible, we performed subgroup analysis using the following components known to influence the effectiveness of specialist palliative care:

- Disease type, including malignant, non-malignant, and mixed malignant and non-malignant disease (mixed diagnoses) to improve the evidence base for different types of palliative care populations.[54] Those with malignant disease were those diagnosed with malignant neoplasms (ICD-10 codes: C00–C97). Those with non-malignant and other health-related conditions included those diagnosed with heart disease, including cerebrovascular disease (ICD-10 codes: I00–I52, I60–69); renal disease (ICD-10 codes: N17, N18, N28, I12, I13); liver disease (ICD-10 codes: K70–K77); respiratory disease (ICD-10 codes: J06–J18, J20–22, J40–47, J96); neurodegenerative disease [Huntington's disease (ICD-10 code: G10), Parkinson's disease (ICD-10 code: G20), multiple sclerosis (ICD-10 code: G35), motor neuron disease (ICD-10 code: G12.2)]; multisystem degeneration (ICD-10 code: G90.3); progressive supranuclear ophthalmoplegia (ICD-10 code: G23.1); dementia due to Alzheimer's disease, and senility (ICD-10 codes: F01, F03, G20, R54); and HIV/AIDS (ICD-10 codes: B20–B24).
- Frailty associated with advanced age. We could not carry out a subgroup analysis with frailty associated with advanced age as planned because none of the included studies assessed frailty.
- Hospital-based specialist palliative care team composition (e.g. physician-led, nurse-led vs. multidisciplinary team-led palliative care services) and organisation [e.g. 24 hours' access (out-of-hours) vs. temporally restricted access] to examine the effectiveness of different models of service provision and to inform service delivery and configuration. Where it was possible to carry out this subgroup analysis, it aided the identification of key components of HSPC models.[54] During this review, we measured what the study authors meant by specialist in palliative care in each instance. We developed a taxonomy of the components. We aimed to fully understand what the intervention was and clearly presented this, allowing clear and transparent conclusions to be reached about the data.
- Models of HSPC (ward-based model, inpatient consult model, outpatient model, outreach model and service provision across multiple settings).
- Early palliative care versus late palliative care to assess the effectiveness of HSPC applied early in the course of a life-threatening disease from palliative care delivered mainly with high symptom burden or in the terminal phase of illness. To be classified as early palliative care, early palliative care intent had to be stated explicitly or be reflected in the sample composition, that is most participants had to be enrolled shortly after diagnosis of advanced disease.[18] Anything besides this was classified as late palliative care.
- Country of origin to explore differences in care structures and the availability of HSPC and any associated impact of this on effectiveness and cost-effectiveness.

Sensitivity analysis

We carried out sensitivity analyses to explore a number of methodological decisions we made:

- A sensitivity analysis was conducted to assess the decision to use an estimate of ICC that we had obtained from a previous study to adjust for clustering in one of the cluster RCTs.[48] The authors did not respond to a request for the ICC for this study.
- Given that combining end-point scores and change scores is not recommended when using SMDs, and also that Cochrane does not recommend pooling adjusted and unadjusted estimates together,[68] we pooled studies presenting adjusted end-point scores as the main meta-analysis, whereas we carried out sensitivity analyses with studies reporting unadjusted end-point scores, adjusted change scores and unadjusted change scores.

Chapter 3 Results

Search results

The number of records identified through searches of databases and other sources was 10,774, excluding duplicates. On screening the titles and abstracts, we excluded 10,132 records and selected 642 for full-text reading (see *Figure 1* for the PRISMA flow diagram). We excluded 536 records for various reasons (see *Figure 1*). We included 42 studies reported in 106 records (91 full papers and 15 abstracts), ranging from one to 10 records per study (see *Figure 1* for the PRISMA flow diagram).

Excluded studies

A total of 536 records assessed for eligibility were excluded for various reasons (see *Figure 1*). See *Appendix 2* for the list of excluded studies. The study awaiting classification is an abstract by Aljohani[69] that had insufficient information on the palliative care team and its setting. The author could not be contacted.

Unit-of-analysis issues

Two studies were cluster randomised trials,[48,70] of which one was a cluster randomised crossover trial.[70] Adjustment was made for clustering by Ma *et al.*[70] In McCorkle *et al.*,[48] the authors did not adjust for clustering. Therefore, we adjusted the data entered into the meta-analysis using 0.02 as the ICC. We obtained this estimate from a previous Cochrane review.[71] We opted to use this estimate because we contacted the authors for an estimate of the ICC, but did not receive it.

Characteristics of included studies

All included studies were RCTs, comprising one cluster RCT,[48] one cluster randomised crossover trial,[70] eight fast-track RCTs[72–79] and 32 RCTs with parallel design. *Table 1* presents the characteristics of included studies (see *Report Supplementary Material 1*, table 1, for more details on the characteristics of included studies). *Appendix 3* provides further descriptions of the intervention and control conditions in each study and the outcomes measured.

Design

All included studies were RCTs. They included one cluster RCT,[48] one cluster randomised crossover trial[70] and eight fast-track RCTs.[72–79] The remaining 32 studies were parallel-designed RCTs. The HSPC models were offered in different ways, namely:

- ward-based services, provided by Jingfen *et al.*[80] only
- inpatient consult or advisory services, provided by 10 studies[70,81,82,84,85,88,89,93,95,96]
- outpatient services, provided by six studies[35,97,101,103,106,116]
- hospital outreach services, provided by five studies[72,79,118,123,126]
- models involving multiple settings including hospital, provided by 20 studies.[48,73–78,129,139,142,147,148,156,160,161,163,165,167,168,170]

TABLE 1 Characteristics of included studies

Type of HSPC model	Study details and design	Disease	Participants randomised (*n*)	Control
Ward-based model	Jingfen *et al.*,[80] China	Lung cancer	Patients: 106	Usual care
Inpatient consulting model	Ahronheim *et al.*,[81] USA	Dementia	Patients: 99	Usual care
Inpatient consulting model	Carson *et al.*,[82] USA Associated report: Nelson *et al.*[83]	Disease not specified, but all patients were adults treated in medical ICUs	• Patients: 256 • Caregivers: 365	Usual care
Inpatient consulting model	Cheung *et al.*,[84] Australia	Actual diseases not stated. However, admission codes were stated. The admission code for those not admitted from the operating theatre include cardiovascular, gastroenterology, neurology, respiratory, sepsis, trauma and others	• Patients: 20 • Families: 9	Usual care
Inpatient consulting model	El-Jawahri *et al.*,[85] USA Associated reports: El-Jawahri *et al.*[86] and VanDusen *et al.*[87]	Adults with haematologic malignancies undergoing autologous/allogeneic HCT	• Patients: 160 • Caregivers: 94	Usual care
Inpatient consulting model	Gade *et al.*,[88] USA	Cancer, CHF, myocardial infarction, other heart disease, COPD, other pulmonary disease, end-stage renal disease, organ failure, stroke and dementia	Patients: 517	Usual care
Inpatient consulting model	Grudzen *et al.*,[89] USA Associated reports: Grudzen *et al.*,[90] Kandarian *et al.*[91] and Kistler *et al.*[92]	Cancer: breast, colorectal, lung and other	Patients: 136	Usual care
Inpatient consulting model	Hopp *et al.*,[93] USA	Heart failure	Patients: 85	Usual care
Inpatient consulting model	Ma *et al.*,[70] USA Associated report: Burnham *et al.*[94]	Patients admitted from skilled nursing facilities/long-term care, end-stage neurological condition, advanced or metastatic cancer, arrest with neurological compromise, multiple organ system failure, end-stage organ disease, shock, acute respiratory failure and prolonged length of stay or ICU re-admission	Patients: 199	Usual care
Inpatient consulting model	Ozcelik *et al.*,[95] Turkey	Cancers: gastrointestinal, genitourinary, breast, sarcoma, lung and unknown primary tumour	Patients: 44	Usual care
Inpatient consulting model	Sidebottom *et al.*,[96] USA	Heart failure	Patients: 232	Usual care
Hospital outpatient model	Lowther *et al.*[97] Kenya Associated reports: Lowther *et al.*[98–100]	People with HIV on antiretroviral therapy	Patients: 120	Usual care
Hospital outpatient model	Mendoza-Galindo *et al.*,[101] Mexico Associated report: Ramirez-Morales *et al.*[102]	Breast cancer	Patients: 53	Usual care

TABLE 1 Characteristics of included studies (*continued*)

Type of HSPC model	Study details and design	Disease	Participants randomised (*n*)	Control
Hospital outpatient model	Nottelmann *et al.*,[103] Denmark Associated reports: Nottelmann *et al.*[104,105]	Cancer: lung, gastrointestinal, prostatic, other	Patients: 281	Usual care
Hospital outpatient model	Tattersall *et al.*,[106] Australia	Cancer: gastrointestinal, lung, gynaecological, breast, prostate and other primary sites	Patients: 120	Usual care
Hospital outpatient model	Temel *et al.*,[35] USA Associated reports: Greer *et al.*,[107,108] Jacobsen *et al.*,[109] Nipp *et al.*,[110,111] Pirl *et al.*,[112] Temel *et al.*[113,114] and Yoong *et al.*[115]	Metastatic non-small cell lung cancer	Patients: 151	Usual care
Hospital outpatient model	Woo *et al.*,[116] Republic of Korea	Pancreatobiliary cancer: pancreatic, biliary	Patients: 288	Usual care
Hospital outreach model	Bajwah *et al.*,[72] UK Associated report: Bajwah *et al.*[117]	Idiopathic fibrotic lung disease	• Patients: 53 • Caregivers: 45	Usual care
Hospital outreach model	Brännström *et al.*,[118] Sweden Associated reports: Brännström *et al.*,[119] Markgren *et al.*,[120] Sahlen *et al.*[121] and Talabani *et al.*[122]	Heart failure	Patients: 72	Usual care
Hospital outreach model	Janssens *et al.*,[123] Switzerland Associated reports: Veron *et al.*[124] and Weber *et al.*[125]	COPD	Patients: 49	Usual care
Hospital outreach model	McWhinney *et al.*,[79] Canada	Cancer	• Patients: 146 • Caregivers: 74	Usual care
Hospital outreach model	Solari *et al.*,[126] Italy Associated reports: Giovannetti *et al.*[127] and Solari *et al.*[128]	Multiple sclerosis	• Patients: 76 • Caregivers: 76	Usual care
Model involving multiple settings	Bakitas *et al.*,[129] USA Associated reports: Bakitas *et al.*,[130,131] Maloney *et al.*[132] and O'Hara *et al.*[133]	Cancer: gastrointestinal tract, lung, genitourinary tract and breast	• Patients: 322 • Caregivers: 198	Usual care
Model involving multiple settings	Bakitas *et al.*,[73] USA Associated reports: Dionne-Odom *et al.*[134–138]	Cancer: lung, breast, gastrointestinal tract, other solid tumour, genitourinary tract and haematological malignancy	• Patients: 207 • Caregivers: 44	Usual care
Model involving multiple settings	Bekelman *et al.*,[139] USA Associated reports: Bekelman *et al.*[140] and Flint *et al.*[141]	Heart failure	Patients: 314	Usual care

continued

TABLE 1 Characteristics of included studies (*continued*)

Type of HSPC model	Study details and design	Disease	Participants randomised (*n*)	Control
Model involving multiple settings	Brumley *et al.*,[142] USA Associated report: Enguidanos *et al.*[143]	Cancers, COPD and CHF	Patients: 297	Usual care
Model involving multiple settings	Edmonds *et al.*,[74] UK Associated report: Higginson *et al.*[144]	Multiple sclerosis	Patients: 52	Usual care
Model involving multiple settings	Farquhar *et al.*,[75] UK Associated reports: Farquhar *et al.*[145] and Javadzadeh *et al.*[146]	Cancer: lung, breast, rectal/bowel, prostate, lymphoma, mesothelioma, gastro-oesophageal junction, renal, endometrial, hepatocellular, bladder and unknown primary	• Patients: 67 • Caregivers: 41	Usual care
Model involving multiple settings	Farquhar *et al.*,[76] UK Associated report: Farquhar *et al.*[145]	COPD and other non-malignant disease	• Patients: 87 • Caregivers: 57	Usual care
Model involving multiple settings	Franciosi *et al.*,[147] Italy	Cancer: lung (non-small cell), pancreatic, gastric and biliary	Patients: 281	Usual care
Model involving multiple settings	Groenvold *et al.*,[148] Denmark Associated reports: Johnsen *et al.*[149,150]	Cancer: lung, digestive system, breast, other	Patients: 297	Usual care
Model involving multiple settings	Higginson *et al.*,[77] UK Associated reports: Higginson *et al.*[144,151–153]	Multiple sclerosis	Patients: 52	Usual care
Model involving multiple settings	Higginson *et al.*,[78] UK Associated reports: Bausewein *et al.*[154] and Dzingina *et al.*[155]	Cancer, COPD, heart failure, interstitial lung disease, other	Patients: 105	Usual care
Model involving multiple settings	Kane *et al.*,[156] USA Associated reports: Kane *et al.*[157,158] and Wales *et al.*[159]	Cancer: lung; prostate; ear, nose and throat; brain; other	• Patients: 247 • Survivors: 96	Usual care
Model involving multiple settings	McCaffrey *et al.*,[160] Australia	Predominantly cancer, non-cancer and not reported	Patients: 31	Usual care
Model involving multiple settings	McCorkle *et al.*,[48] USA	Cancer: gynaecologic, lung, gastrointestinal, and head and neck	Patients: 146	Usual care
Model involving multiple settings	O'Riordan *et al.*,[161] USA Associated report: O'Riordan *et al.*[162]	Heart failure	Patients: 30	Usual care
Model involving multiple settings	Rodin *et al.*,[163] Canada Associated report: Rodin *et al.*[164]	Acute leukaemia	Patient: 42	Usual care
Model involving multiple settings	Rogers *et al.*,[165] USA Associated report: Mentz *et al.*[166]	Heart failure	Patients: 150	Usual care

TABLE 1 Characteristics of included studies (*continued*)

Type of HSPC model	Study details and design	Disease	Participants randomised (*n*)	Control
Model involving multiple settings	Temel *et al.*,[167] USA	Lung: non-small cell, small cell, neuroendocrine, mesothelioma, epidermal growth factor receptor mutation, anaplastic lymphoma kinase translocation. Gastrointestinal: pancreatic, oesophageal/gastro-oesophageal junction, gastric and hepatobiliary	Patients: 350	Usual care
Model involving multiple settings	Vanbutsele *et al.*,[168] Belgium Associated report: Vanbutsele *et al.*[169]	Cancer: gastrointestinal (pancreas, biliary tract, oesophagus, gastro-oesophageal, gastric, colorectal), lung, head and neck, breast, melanoma, genitourinary (prostate, bladder, kidney)	Patients: 186	Usual care
Model involving multiple settings	Wallen *et al.*,[170] USA Associated report: Slota *et al.*[171]	Cancer	Patients: 152	Usual care

CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; HCT, haematopoietic stem cell transplantation.
n = number, T = total sample.

One of the criteria for inclusion of studies in this review is that care should be co-ordinated by a multiprofessional or multidisciplinary team. All included studies either had a MDT as the core team delivering the intervention or included a MDT as needed. HSPC teams were also divided into two based on whether or not the intervention was led by a single professional or by a MDT. Seven studies[72,97,103,106,129,160,168] were led by nurses (nurse-led MDTs); no study was physician led. Thirty-four studies were led by MDTs; in one study,[101] it was unclear. There was provision for out-of-hours care in five studies.[79,88,118,142,160] In McCaffrey *et al.*,[160] services traversed multiple settings including hospital, and there was provision for nursing care for up to 24 hours per day for 5 days. The hospital outreach service by McWhinney *et al.*[79] included 24-hour on-call service, whereas another hospital outreach service, by Brännström *et al.*,[118] involved close co-operation with out-of-hours palliative advanced home care. Brumley *et al.*[142] involved service provision across multiple settings including hospital, and also 24-hour on-call service. Gade *et al.*[88] included a palliative care physician on call after hours in their inpatient consult service.

Sample sizes

Included studies had between 30 and 621 participants. The duration of recruitment was between 10 months and 50 months. A total of 7779 participants (6678 patients and 1101 caregivers) were included. Thirty-three studies had power calculations. Nine studies[35,85,106,139,147,148,165,167,168] were powered only on quality of life. The Ma *et al.*[70] study was powered on the proportion of patients transitioning to 'do not resuscitate' and 'do not intubate'. In addition to quality of life, Bakitas *et al.*[73] also performed calculations on depression, Solari *et al.*[126] performed calculations on symptom burden and O'Riordan *et al.*[161] performed calculations on pain, and Bakitas *et al.*[129] and Sidebottom *et al.*[96] included symptom burden and depression. Both Farquhar *et al.*[75,76] studies were powered on distress due to breathlessness; Brännström *et al.*[118] on symptom burden; Brumley *et al.*[142] on cost; Carson *et al.*[82] on depression and anxiety; Grudzen *et al.*[89] on time to palliative care; Janssens *et al.*[123] on hospital admission; Rodin *et al.*[163] on traumatic stress symptoms; Bajwah *et al.*,[72] Edmonds *et al.*[74] and Higginson *et al.*[77] on the Palliative care Outcome Scale (POS); Lowther *et al.*[97] on the African Palliative care Outcome Scale; Higginson *et al.*[78]

on Chronic Respiratory Disease Questionnaire mastery domain; Hopp *et al.*[93] and Ozcelik *et al.*[95] on palliative outcomes and palliative care service, respectively; McWhinney *et al.*[79] on pain and nausea; and Woo *et al.*[116] on pain and depression.

Eight studies[70,74,76,78,82,95,126,167] were adequately powered at recruitment and also at the primary point of analyses. Fourteen studies were underpowered at recruitment stage (i.e. participants enrolled) by three,[93,142,148] four,[89] eight,[163] 19,[103,104] 25,[161] 30,[106] 50,[165] 74,[79] 78,[129] 111,[123] 153[73] and 268[96] participants. In one of the underpowered studies, by Rogers *et al.*,[165] the Data and Safety Monitoring Board, in consultation with the sponsoring agency, recommended a sample size reduction because of enrolment rates, a mortality rate that was lower than predicted and observed outcome differences at the intermediate time point. Studies were underpowered because of slower than anticipated accrual, resource constraints, early deaths, problems with recruitment and low compliance rate for completion of questionnaires. The remaining 11 studies were able to recruit the numbers that they needed, but dropped below the required numbers by the first time point of analysis (i.e. following baseline assessment and after receiving the intervention or control). The following studies were underpowered by two or more participants: Brännström *et al.*[118] (two participants), El-Jawahri *et al.*[85] (three participants), Bajwah *et al.*[72] and Higginson *et al.*[77] (five participants each), Lowther *et al.*[97] and Farquhar *et al.*[75] (six participants each), Temel *et al.*[35] (13 participants), Vanbutsele *et al.*[168] (22 participants), Franciosi *et al.*[147] (29 participants), Woo *et al.*[116] (60 participants) and Bekelman *et al.*[139] (70 participants). Nine studies did not report any power calculation.[48,80,81,84,88,101,156,160,170] *Figure 2* describes the power of included studies at recruitment and follow-up.

Setting

The studies were carried out in different countries with varying levels of development in palliative care and their health systems,[172] as well as different levels of awareness and attitudes towards palliative and end-of-life care.[173–175]

Nineteen[35,48,70,73,81,82,85,88,89,93,96,129,139,142,156,161,165,167,170] of the included studies were carried out in the USA. One study (Mendoza-Galindo *et al.*[101]) took place in Mexico. Six studies[72,74–78] were conducted in the UK. One was carried out in Belgium,[168] one in China,[80] one in Kenya,[97] one in the Republic of Korea,[116] one in Sweden,[118] one in Switzerland,[123] one in Turkey,[95] two in Canada,[79,163] two in Denmark,[104,148] two in Italy[126,147] and three[84,106,160] in Australia. The first study was a US study by Kane *et al.*[156]

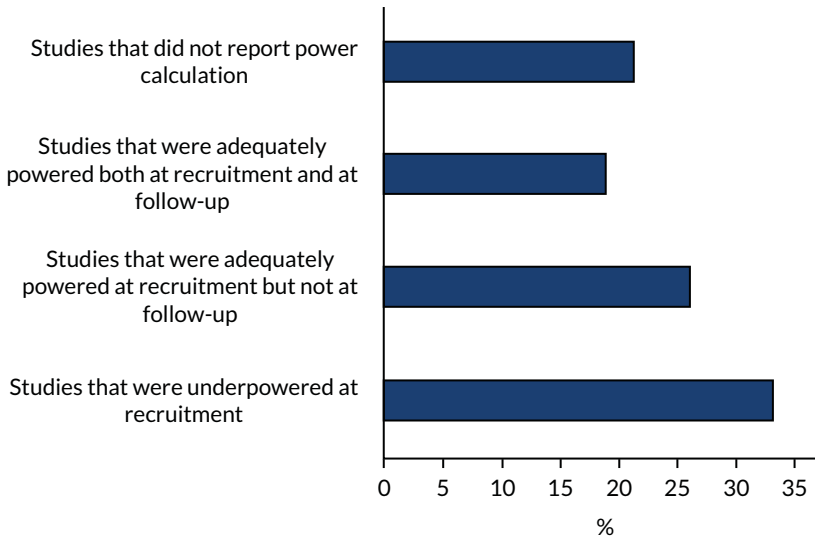

FIGURE 2 The power of included studies at recruitment and follow-up. Fourteen studies[35,70,82,85,88,89,96,97,116,147,148,156,167,168] carried out post-intervention assessments at the primary end point among > 100 participants.

Recruitment occurred in hospital settings in 30 studies (including three studies[70,82,84] that recruited from ICUs). Among the 30 studies, Ahronheim *et al.*[81] recruited patients with advanced dementia from Mount Sinai Hospital in New York; Bajwah *et al.*[72] recruited from a specialist interstitial lung disease centre; Janssens *et al.*[123] recruited from patients followed by Geneva University Hospitals who were on long-term oxygen therapy and/or home non-invasive ventilation, as well as those hospitalised for acute exacerbation of chronic obstructive pulmonary disease (COPD) in the general internal medicine and geriatric wards; Lowther *et al.*[97] recruited from outpatient HIV clinics in a community hospital; McCorkle *et al.*[48] recruited from disease-specific multidisciplinary clinics at a cancer hospital; O'Riordan *et al.*[161] recruited from new inpatient admissions to the medicine and cardiology services; Solari *et al.*[126] recruited from three Italian multiple sclerosis centres; and Franciosi *et al.*[147] recruited from outpatient and inpatient settings at five Italian cancer centres. Seven studies recruited from oncology centres or clinics.[35,106,116,148,163,167,168] Two studies[73,129] recruited from oncology clinics of a cancer centre and affiliated outreach clinics, and the Veterans Affairs Medical Center.

Eleven studies[74–79,88,118,142,160,165] recruited from primary care and/or secondary care. Gade *et al.*[88] recruited from medical services and inpatient units, whereas McWhinney *et al.*[79] recruited through family physicians and home care nurses. Brumley *et al.*[142] received referrals from discharge planners, primary care physicians and other specialty physicians, whereas Rogers *et al.*[165] enrolled both hospitalised patients and recently discharged patients who were at high risk of rehospitalisation. Higginson *et al.*[77] received referrals from local health and social care professionals. Edmonds *et al.*[74] received referrals from health and social care professionals and, in a few instances, through voluntary organisations and self-referral.

Mendoza-Galindo *et al.*[101] did not state the setting where recruitment was carried out.

Participants

Twenty-one studies involved patients with severe/advanced cancer or their caregivers, or both.[35,48,73,75,79,80,85,89,95,101,104,106,116,129,147,148,156,163,167,168,170] Cancers in these studies included solid and non-solid tumours. Seven studies[70,78,82,84,88,142,160] had both cancer and non-cancer populations (mixed diagnoses), whereas the remaining 14 studies had only non-cancer populations. The non-cancer populations included patients with heart failure,[93,96,118,139,161,165] interstitial lung disease,[72] dementia,[81] multiple sclerosis,[74,77,126] HIV,[97] COPD[123] and a combination of COPD (83%) and other non-malignant disease.[76] Two studies involved rural populations;[73,129] Hopp *et al.*[93] included a mainly African American population (92%). Thirty-five (83.3%) studies were conducted or first published from 2010 onwards.

The mean/median ages ranged from 38.3 to 85.6 years. A similar number of male and female participants were included in most studies. However, five studies[74,77,81,95,97] had between 69% and 82% female participants, whereas nine studies[72,76,118,129,139,147,156,163,168] had 60–98% male participants. Ahronheim *et al.*[81] included the most female participants (82%). Kane *et al.*,[156] who recruited at a Veterans Administration hospital, included predominantly male veterans. The sex distribution in Wallen *et al.*[170] was not clear because the authors did not provide this information. Caregivers included in studies tended to be mainly female. Nine of the 16 studies involving caregivers described at least one of their characteristics: they were mostly spouses and women and had a median/mean age ranging from 51 to 65.6 years. In five studies,[48,75–77,168] between 16% and 43% of patients lived alone.

Sixteen studies had survival as an inclusion criterion. Life expectancy in these studies ranged from > 72 hours to 24 months. Eight studies[35,48,73,104,116,147,163,167] stated that they included newly diagnosed patients. Exclusion criteria included palliative care/hospice involvement previously or at present/request for palliative care involvement[35,70,72,82,84,89,96,106,126,147,163,167,168,176] and presence of severe mental illness.[73,80,93,129,167] Three studies[82,84,126] excluded patients without surrogate decision-makers, and Gade *et al.*[88] excluded patients with impaired cognitive status and no surrogate. Two studies[123,163] excluded patients with moderate or severe cognitive impairment.

Intervention

Hospital-based specialist palliative care

Different HSPC models were included in this review. Some were new services assessed through feasibility/pilot studies or early phase trials (e.g. Bajwah *et al.*,[72] Cheung *et al.*,[84] Edmonds *et al.*,[74] Higginson *et al.*,[77] Nottelmann *et al.*[104] and Rodin *et al.*[163]), whereas others existed for some time. Services were based in hospitals, with three studies[70,82,84] in hospital ICUs and three[79,148,177] in palliative care centres/units of hospitals. In Kane *et al.*,[156] the hospice programme was located in a Veterans Administration hospital. Most of the studies served urban and suburban populations; a few, such as Bakitas *et al.*[129] and Bakitas *et al.*,[73] were targeted at rural populations.

Thirty-four teams were multidisciplinary, involving two to eight professionals, comprising mostly nurses, physicians and, sometimes, social workers. Seven studies[72,97,104,106,129,160,168] were nurse led. The nurses who led services included other health professionals as needed. None of the studies was physician led; in Mendoza-Galindo *et al.*,[101] it was unclear who led the service.

Thirty-one studies included either certified experts in palliative care or those described as palliative care clinicians (without being explicit about their training). For example, Bakitas *et al.*[73] included a board-certified palliative care clinician and advanced practice palliative care nurse specialists, and Gade *et al.*[88] included a multiprofessional team consisting of a palliative care physician, nurse, hospital social worker and chaplain. Furthermore, Higginson *et al.*[77] evaluated a new short-term specialist palliative care intervention involving one to three contacts provided by a core team of a part-time consultant in palliative medicine, a part-time palliative care nurse, a psychosocial worker and an administrator. The Bajwah *et al.*,[72] Edmonds *et al.*[74] and Nottelmann *et al.*[104] studies also involved new palliative care services. The service in Bajwah *et al.*[72] was developed for people with interstitial lung disease in which the intervention was a hospital-to-home case conference attended by the palliative care nurse who organised it and different health-care professionals, whereas the service in Edmonds *et al.*[74] comprised a part-time consultant in palliative medicine with a special interest in neurological conditions, a part-time clinical nurse specialist and a full time administrator. The service in Nottelmann *et al.*[104] was a palliative rehabilitation service delivered by a specialised palliative care team consisting of physicians, nurses, physiotherapists, psychologists, a part-time social worker, a dietitian, an occupational therapist and a chaplain.

In 11 studies,[80,81,84,89,93,95,101,116,148,160,161] it was stated that specialist-level interventions were delivered by health-care professionals, but there was no detail on their training or on whether or not they were palliative care clinicians.

The intervention in 19 studies was early palliative care.[35,48,70,73,78,85,89,101,104,106,116,123,129,147,148,163,167,168,170] Early palliative care intent had to be either stated explicitly or reflected in the sample composition, that is most participants had to be enrolled shortly after diagnosis of advanced disease. For instance, McCorkle *et al.*[48] included patients with a late-stage cancer diagnosis within 100 days, and Bakitas *et al.*[73] included advanced cancer patients who were within 30 and 60 days of diagnosis. Five studies[35,104,116,147,167] included patients who were within 8 weeks of diagnosis of advanced cancer. Franciosi *et al.*[147] recruited patients with non-small cell lung cancer or pancreatic, gastric or biliary tract cancer; Nottelmann *et al.*[104] recruited patients diagnosed with non-resectable solid cancer; Temel *et al.*[35] included patients with metastatic lung cancer diagnosed within the previous 8 weeks; Temel *et al.*[167] recruited patients with incurable lung or non-colorectal gastrointestinal cancer; and Woo *et al.*[116] recruited those with a diagnosis of advanced or metastatic pancreatic or biliary tract cancer. Vanbutsele *et al.*[168] included patients who were within the first 12 weeks of a new primary tumour or had a diagnosis progression.

El-Jawahri *et al.*[85] had an early palliative care intention and the intervention was delivered during hospitalisation for haematopoietic stem cell transplantation, and Groenvold *et al.*[148] started their

palliative care intervention earlier than would otherwise have been the case among patients with advanced cancer. Grudzen *et al.*[89] assessed early referral to palliative care for ED patients with advanced cancer. Rodin *et al.*[163] delivered early palliative care interventions to patients newly diagnosed with acute leukaemia, and Wallen *et al.*[170] began early palliative care intervention postoperatively with the intention of providing comfort care for symptom burden earlier in the disease process in order to improve quality of life among patients with advanced cancer. Tattersall *et al.*[106] included ambulatory patients with newly detected incurable metastatic cancer.

Higginson *et al.*[78] evaluated early palliative care integrated with respiratory services for patients with advanced diseases [cancer, COPD (> 50%), heart failure, interstitial lung disease and others] and refractory breathlessness. Janssens *et al.*[123] assessed early palliative care for patients with severe and very severe COPD over a 1-year period, and Mendoza-Galindo *et al.*[101] stated that their intervention was an early palliative care intervention for patients with newly diagnosed or relapsed metastatic breast cancer. The Ma *et al.*[70] study involved early triggered palliative care consultation within 48 hours of ICU admission.

Eleven studies were theoretically grounded: case conference/management,[72,95] chronic care model,[129] person-centred palliative care,[118] palliative care approach,[75,76] hospice,[142,156] knowledge–belief–action model,[80] trauma-focused cognitive behavioural therapy[163] and palliative care and physiotherapy approach.[78] Two studies[142,156] were modelled after hospice programmes.

Five studies[79,88,118,142,160] had provision for 24 hours' access (out-of-hours care). Twenty-three studies[48,70,72–79,82,85,88,95,103,118,126,129,139,147,156,165,170] provided some level of caregiver support.

Taxonomy of the components of hospital-based specialist palliative care

We assessed the components of HSPC using the principles and domains of palliative care described by Zimmermann *et al.*[178] Zimmermann *et al.*[178] developed a conceptual framework that is built on palliative care theory on the domains and principles of team-based outpatient early palliative care. This framework was preferred over others such as the Holistic Common Assessment[179] because the essential elements of the framework are consistent with the need for early provision of palliative care in collaboration with the MDT, and also because it is targeted at the needs of patients and their families, rather than on prognosis.

In the Zimmermann *et al.*[178] framework, the four domains are coping and support, decision-making, symptom control, and future-planning, and the four principles are that care is flexible, attentive, patient led and family centred.

Components of hospital-based specialist palliative care in studies that included either certified experts in palliative care or those described as palliative care clinicians

Thirty-one studies included either certified experts in palliative care or those described as palliative care clinicians. Eight studies[96,106,118,163,165,167,168,170] were patient centred, and one study[82] was family centred. The remaining 22 studies were both patient centred and family centred. For instance, the HSPC intervention in Bajwah *et al.*[72] was individualised to the patient and carer, and, in Vanbutsele *et al.*,[168] semistructured monthly consultations by palliative care nurses allowed for individualised care. Bekelman *et al.*[139] described collaboration between patients and the nurse as they both agreed on the symptom to focus on.

We mapped the 31 studies to the four domains of the Zimmermann *et al.*[178] framework. We included care co-ordination as an additional domain because of its importance among patients with advanced disease, as there is evidence that lack of care co-ordination can lead to increased hospitalisations and suboptimal clinical outcomes.[180] *Figure 3* shows the percentage of studies assessing different domains (*Appendix 4* presents the taxonomy of the components of HSPC in these studies).

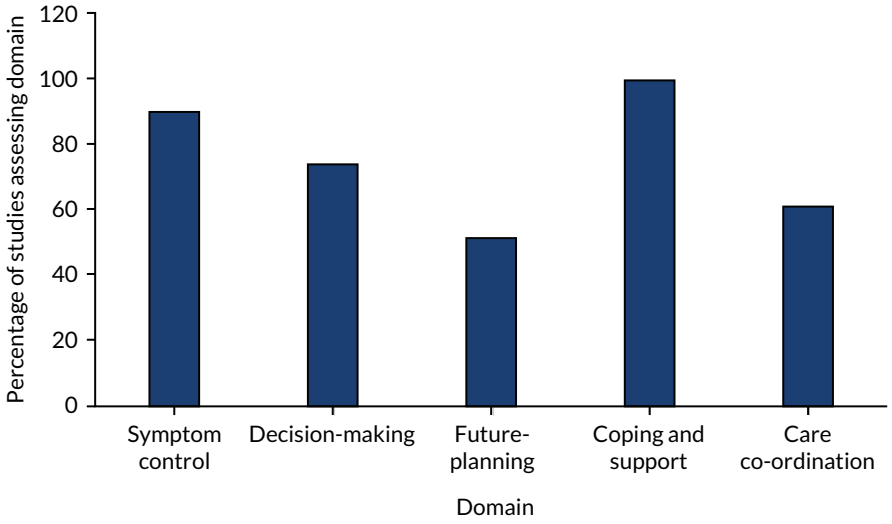

FIGURE 3 The domains of HSPC in the studies that included either certified experts in palliative care or those described as palliative care clinicians.

Symptom control

This involved assessment and management of symptoms. Twenty-eight studies highlighted that the HSPC intervention included symptom or needs assessment and management. In two studies, this was unclear,[79,126] and it appears that Carson *et al.*[82] did not address this domain.

Decision-making

This domain entailed assessing patient and/or their family's understanding of illness, cultural values/beliefs, goals of care and also carrying out regular reviews. Twenty-three studies involved one or more aspects of decision-making. One study stated that it did not focus on decision-making as it was targeted at managing patients' physical and psychological symptoms during hospitalisation;[85] it appeared that five studies did not involve this domain.[77,106,156,163,170] In two studies, it was unclear if the HSPC intervention involved this domain.[79,126]

Future-planning

Future-planning involved discussing concerns and preferences for end-of-life care, making a will, power of attorney and decisions about resuscitation. Half of the studies ($n = 16$) involved planning for the future; in two studies, this was unclear.[79,126] The remaining 13 studies did not include this domain,[35,48,70,82,85,106,118,139,147,163,167,168,170] with El-Jawahri *et al.*[85] explicitly stating that it did not focus on future-planning.

Coping and support

This involved establishing a therapeutic relationship, facilitating coping with advanced illness and spiritual support, providing emotional and practical support, addressing family needs and bereavement care.

All 31 studies involved one or more elements of this domain. In particular, three studies specifically highlighted bereavement care or involved a bereavement co-ordinator as needed.[77,129,142] Bakitas *et al.*[129] provided a bereavement follow-up call to the caregiver as part of the HSPC intervention, and Higginson *et al.*[77] described providing bereavement support when needed. Brumley *et al.*[142] also included a bereavement co-ordinator as needed. Furthermore, Bekelman *et al.*[139] included a topic on grief and loss as part of the counselling session in their HSPC intervention.

We further assessed the provision of spiritual care/support in included studies; 13 studies provided this.[72,78,82,96,97,104,118,123,142,156,165,168,170]

Care co-ordination

We found that more than half of the studies ($n = 19$) involved care co-ordination;[35,48,70,72–74,77,78,96,104,118,123,129,139,142,147,165,167,168] this was unclear in two studies.[79,126] In 10 studies,[75,76,82,85,88,97,106,156,163,170] it appeared that the HSPC intervention did not include this domain.

Symptom control, coping and support, and decision-making were the main domains of care in the HSPC intervention in the 31 studies. At least half of the studies involved care co-ordination and future-planning. All studies addressed at least two domains, with the exception of McWhinney *et al.*[79] and Solari *et al.*[126]

Components of hospital-based specialist palliative care in studies that were unclear about palliative care training

Eleven studies were unclear about the palliative care training of those who delivered the HSPC intervention.[80,81,84,89,93,95,101,116,148,160,161] Four studies were patient centred;[93,116,148,161] only the Ahronheim *et al.*[81] study was family centred. Three studies were both patient- and family-centred;[80,89,95] this was unclear in the remaining three studies.[84,101,160]

In all 11 studies,[80,81,84,89,93,95,101,116,148,160,161] palliative care provision was flexible, with the MDT involved in meeting the needs of patients and/or their families as needed. In 10 studies,[80,81,84,89,93,95,116,148,160,161] the palliative care providers were attentive to the needs of patients and their families, whereas this was unclear in the Mendoza-Galindo *et al.*[101] study. *Figure 4* shows the percentage of studies assessing different domains (see *Appendix 5* for the taxonomy of the components of HSPC in these studies).

We assessed the domains of HSPC included in these studies as follows.

Symptom control

Eight studies[80,81,89,93,95,101,116,161] highlighted that the HSPC intervention included symptom or needs assessment and management. In three studies, this was unclear.[84,148,160]

Decision-making

Three studies involved one or more aspects of decision-making;[80,89,93] this was unclear in three studies.[84,148,160] It appeared that five studies did not involve this domain.[81,95,101,116,161]

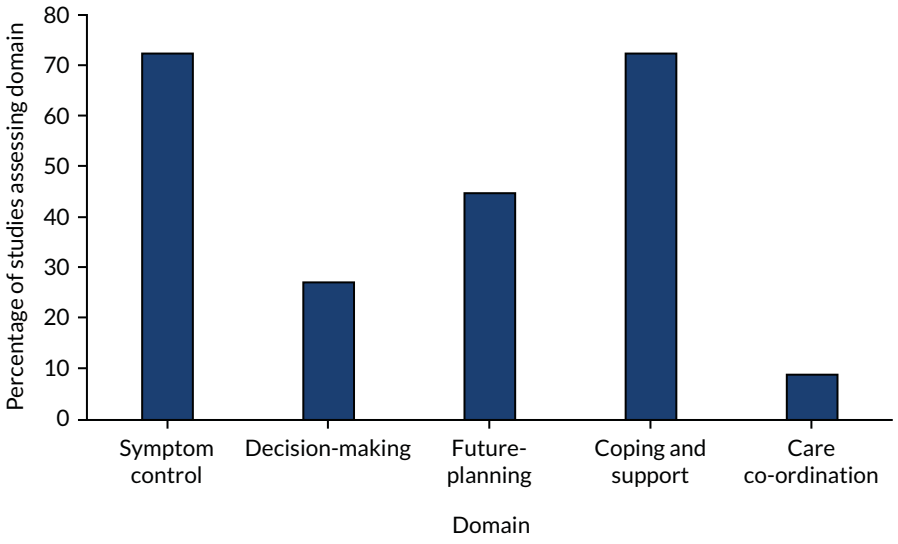

FIGURE 4 The domains of HSPC in the studies that were unclear about palliative care training.

Future-planning

Five studies involved planning for the future;[81,89,93,95,161] this was unclear in three studies.[84,148,160] Three studies did not include this domain.[80,101,116]

Coping and support

Eight studies[80,81,89,93,95,101,116,161] involved one or more elements of this domain, whereas three studies were unclear.[84,148,160] O'Riordan *et al.*[161] further highlighted the provision of spiritual care.

Care co-ordination

McCaffrey *et al.*[160] was the only study that involved care co-ordination; eight studies[80,81,89,93,95,101,116,161] did not. In two studies,[84,148] this was unclear.

Symptom control, coping and support, and future-planning were the main domains of care in the HSPC intervention among studies that were unclear about their training. Very few studies involved decision-making and care co-ordination. Besides three studies[84,148,160] for which the domains were unclear, the remaining eight studies[80,81,89,93,95,101,116,161] addressed at least two domains.

When compared with studies that included experts or those described as palliative care clinicians, studies with unclear palliative care training often did not include decision-making and care co-ordination. There was also reduced focus on symptom control and on coping and support in studies with unclear palliative care training. Both groups were similar with regards to future-planning.

Controls

The control group received usual care. Most studies had a poor description of usual care, with no information or very minimal information provided. For example, Cheung *et al.*[84] stated that the control group received usual ICU care without palliative care consultation, and there was no description of usual ICU care. Ahronheim *et al.*[81] stated that the control group was treated by the primary care team without palliative care input, with no description of the treatment received. Among studies that provided some detail on usual care, usual care was varied, possibly reflecting the local context and differences in health systems. For example, in the Kenyan study by Lowther *et al.*,[97] those in the usual-care group received care from nurses without experience in palliative care from the HIV clinic, consisting of monthly clinical assessments once antiretroviral therapy was established. In Bajwah *et al.*,[72] a UK study, the control group remained under interstitial lung disease specialist care, which involved input from interstitial lung disease physicians, interstitial lung disease clinical nurse specialists, occupational therapists, physiotherapists, and oxygen assessment and treatment services. All patients were also able to access inpatient interstitial lung disease treatment as needed. In Higginson *et al.*,[78] the control group received usual care services according to UK guidance. After 6 weeks, the control group was offered the intervention.

In 20 studies, palliative care professionals provided services to patients in the control group if needed;[35,70,72,73,79,82,85,89,106,116,129,139,147,148,160,163,165,167,168,170] in Brumley *et al.*,[142] usual care incorporated hospice care. Wallen *et al.*[170] allowed the usual-care group to cross over to the intervention group if standard care could not meet their needs.

Outcomes

The primary outcomes were patient HRQoL and patient symptom burden (assessed using generalised measures) reported as adjusted end-point values. Ten studies[35,48,73,85,106,129,161,163,167,168] assessed patient HRQoL and also reported adjusted end-point values; six studies[35,73,85,106,129,163] assessed patient symptom burden and also reported adjusted end-point values. Nine[35,48,73,85,106,129,163,167,168] of the 10 studies assessing patient HRQoL were with cancer populations, and one[161] with non-cancer populations. Nine of the 10 studies were on early palliative care.[35,48,73,85,106,129,163,167,168] All six studies that reported patient symptom burden using a generalised scale were with cancer populations and they involved early palliative care.[35,73,85,106,129,163]

Other patient outcomes assessed by the studies were individual symptoms (anxiety, depression, pain, breathlessness, post-traumatic stress disorder, fatigue, appetite loss, nausea/vomiting, sleep disturbance); traumatic stress symptoms; mortality/survival; achieving preferred place of care or death; advanced care planning; functional independence; satisfaction with care; physical function; psychological, social and spiritual well-being; nutrition; and cognitive status.

The caregiver outcomes assessed included caregiver symptom control (e.g. depression, anxiety), satisfaction with care, HRQoL, coping, burden, distress with patients' symptoms and grief.

Economic data

Thirty-one studies compared the resource use and/or costs between HSPC and usual care, alongside clinical effectiveness. Four[75–77,160] of the 31 studies were full economic evaluations, five[35,78,88,142,156] were partial economic evaluations and 22 studies reported more limited resource use/cost information.

The studies measured the resource use associated with care received in the intervention and the control groups. Resources included were ED or A&E visits, inpatient and outpatient hospital care, home and community care, care in nursing homes (or skilled nursing homes), inpatient stay and day care in hospice, hospice care at home, informal care, drugs and equipment. Thirteen studies calculated the costs associated with resource use.[35,70,75–78,88,95,101,118,142,156,160] Four studies[75–77,160] reported the results of cost-effectiveness analyses using outcome measures relevant to the research questions (palliative outcome, caregiver burden, QALYs) and hospital costs or total costs. Results of cost-effectiveness analyses were reported by ICERs and/or costs per QALY (point estimates or cost-effectiveness planes). The four studies reported ICERs, cost per QALY or cost-effectiveness planes from cost-effectiveness analysis.[75–77,160]

Risk of bias in included studies

Randomised controlled trials

We assessed risk of bias in included studies using the Cochrane Risk of Bias tool[58] (*Figure 5*). We assessed risk of bias in all the domains specified for RCTs in the Cochrane handbook,[58] and also added one additional domain (size of study). The domains in the Cochrane handbook are selection bias (random sequence generation and allocation concealment), performance, detection, attrition and reporting biases.

Allocation (selection bias)

Random sequence generation

Twenty-seven studies were randomised and provided a good description of the process of sequence generation. These 27 studies[48,72–80,82,84,85,88,103,106,118,123,126,129,139,142,147,148,163,167,168] were judged to be at low risk of bias. Fifteen studies[35,70,81,89,93,95–97,101,116,156,160,161,165,170] had an unclear risk-of-bias rating because of insufficient descriptions of the sequence generation process.

Allocation concealment

The authors of 21 studies[35,48,73,80,81,85,88,93,95–97,101,116,118,129,142,156,160,161,165,170] did not provide adequate information on how they concealed the allocation; these studies were judged to be at unclear risk of bias. Twenty-one studies[70,72,74–79,82,84,89,103,106,123,126,139,147,148,163,167,168] were judged as having a low risk of bias.

Blinding (performance bias and detection bias)

Blinding was assessed separately for subjective and objective outcomes.

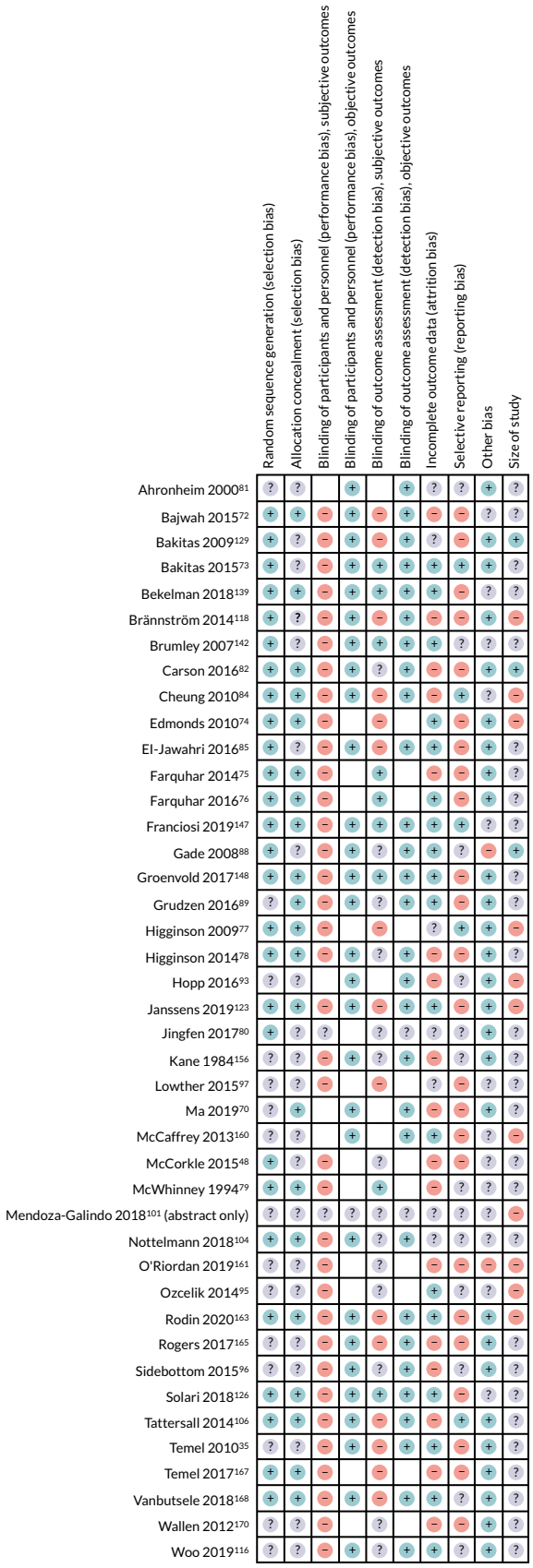

FIGURE 5 Cochrane risk-of-bias assessment. Note that blinding of participants and personnel (performance bias) subjective outcomes focused on subjective outcomes only, whereas blinding of participants and personnel (performance bias) objective outcomes focused only on objective outcomes. Similarly, blinding of outcome assessment (detection bias) subjective outcomes focused on subjective outcomes only, whereas blinding of outcome assessment (detection bias) objective outcomes focused only on objective outcomes.

Blinding of participants and personnel (subjective outcomes)

No study that reported on subjective outcomes blinded participants. Generally, in palliative care research, blinding of participants and personnel is often not possible or feasible.[18] An unclear risk-of-bias rating was given to two studies because they did not state whether or not participants and personnel were blinded;[80,101] 36 studies[35,48,72–79,82,84,85,88,89,95–97,103,106,116,118,123,126,129,139,142,147,148,156,161,163,165,167,168,170] were rated as having a high risk of bias because they did not carry out blinding. The remaining four studies did not include subjective outcomes.[70,81,93,160] Therefore, we did not assess this domain in these studies: we left it blank.

Blinding of participants and personnel (objective outcomes)

Twenty-nine studies[35,70,72,73,78,81,82,84,85,88,89,93,96,103,106,116,118,123,126,129,139,142,147,148,156,160,163,165,168] were rated as having a low risk of bias in this domain because lack of blinding of participants and personnel was judged not to have affected the objective outcomes they assessed. This domain did not apply to 12 studies[48,74–77,79,80,95,97,161,167,170] because they did not include objective outcomes. We therefore left this domain blank in the 12 studies. One study was judged to be at unclear risk of bias because it did not state whether or not blinding of participants and personnel occurred.[101]

Blinding of outcome assessment (subjective outcomes)

Only nine studies[73,75,76,79,126,139,142,147,148] were judged to have a low risk of bias in this domain because they were able to blind outcome assessors. Fourteen studies had an unclear risk-of-bias rating,[48,78,80,82,88,89,95,96,101,104,116,156,161,170] and 15 studies were judged to have a high risk of bias because they did not carry out blinding of outcome assessors. Some authors of studies with a high risk of bias stated that there was no blinding of outcome assessment (e.g. Vanbutsele *et al.*[168]), others stated that they were open-label or non-blinded studies (e.g. Bakitas *et al.*,[129] Janssens *et al.*[123] and Temel *et al.*[167]), and Lowther *et al.*[97] stated that investigators were not blinded. Four studies did not include subjective outcomes; we left this domain blank in these studies.[70,81,93,160]

Blinding of outcome assessment (objective outcomes)

Twenty-nine studies[35,70,72,73,78,81,82,84,85,88,89,93,96,103,106,116,118,123,126,129,139,142,147,148,156,160,163,165,168] were rated as having a low risk of bias in this domain, and two studies[80,101] were rated as having an unclear risk of bias. The remaining 11 studies[48,74–77,79,97,161,167,170,181] did not include objective outcomes; we left this domain blank in these studies.

Incomplete outcome data (attrition bias)

Most of the included studies reported similar attrition rates in the intervention and control groups. Attrition was caused by severe illness, exhaustion/weakness, hospital admission, transfer of care, death, failure to complete questionnaires and lack of interest. Seventeen studies were rated as having a high risk of bias. For example, Brännström *et al.*[118] had a high risk-of-bias rating because attrition was not balanced across the intervention and control groups. In the intervention group, 77.8% of participants were completers, and, in the control group, 88.9% were completers. Missing data were also excluded from the analysis. Furthermore, in McCorkle *et al.*,[48] missing data were not included in the analysis, and 55% of the intervention group were completers and 70% of the control group were completers. Tattersall *et al.*[106] was rated as having a high risk of bias because of high attrition. Only 18.3% of the intervention group and 30% of the control group completed the study, and reasons for non-completion were not stated. In McWhinney *et al.*,[79] a high attrition rate was reported at 1 month (36%), but the attrition rate of each treatment arm (intervention and control) was not stated. Eighteen studies[35,73,74,76,85,88,89,95,116,123,126,139,142,147,148,160,163,168] were judged as having a low risk of bias. In Bekelman *et al.*,[139] 79% of both the intervention and control groups completed the study, with 14 (8.9%) and 12 (7.6%) participants unaccounted for in the intervention and control groups, respectively. Given that missing data were included in the analysis using maximum likelihood estimates, a low risk-of-bias rating was given. The remaining seven studies were rated as having an unclear risk of bias. Examples of reasons for unclear risk-of-bias ratings were differences in numbers analysed despite carrying out imputations;[77] inclusion of missing data in primary outcome analysis, but not secondary outcome analysis;[129] and the study was an abstract and had no information on attrition.[101]

Selective reporting (reporting bias)

Only five studies[73,77,84,106,147] were deemed as having a low risk of bias in this domain. Thirteen studies were rated as having an unclear risk of bias, mainly because their study protocols were not available or study protocols were available, but only an abstract had been published. A total of 24 studies were rated as having a high risk of bias because some prespecified outcomes were not reported (e.g. Bajwah *et al.*,[72] Bekelman *et al.*,[139] Carson *et al.*,[82] Temel *et al.*,[35] Vanbutsele *et al.*[168] and Wallen *et al.*[170]), some outcomes in published papers were not stated a priori in the protocol/trial registry (e.g. Brännström *et al.*[118] and Janssens *et al.*[123]) or because primary outcomes in the protocol/trial registry were reported as secondary outcomes in published papers (e.g. Bakitas *et al.*[129]). Temel *et al.*[167] was given a high risk-of-bias rating because it included a terminal decline joint modelling approach that was not prespecified in the protocol.

Other potential sources of bias

Twenty-seven studies[35,70,73–78,80–82,85,89,93,96,106,116,118,123,129,148,156,163,165,167,168,170] were judged as having a low risk of bias in this domain. Two studies[88,161] were rated as having a high risk of bias because of baseline differences that were not adjusted for. In 13 studies, an unclear risk of bias was rated because there were baseline differences and it was unclear if any adjustment was carried out for them (e.g. Bajwah *et al.*,[72] Bekelman *et al.*,[139] Brumley *et al.*,[142] Cheung *et al.*,[84] McCorkle *et al.*[48] and Franciosi *et al.*[147]). McWhinney *et al.*[79] was judged to have an unclear risk of bias because baseline characteristics were not reported.

Size of study

The size of studies was assessed to check for possible biases confounded by small size. Eleven studies[74,77,84,93,95,101,118,123,160,161,163] were judged as having a high risk of bias because they had < 50 participants in each treatment arm. Three studies[82,88,129] were rated as having a low risk of bias as they had > 200 participants in each treatment arm. The remaining 28 studies were judged to have an unclear risk of bias because they had between 50 and 199 participants in one or both of the treatment groups. For example, Bekelman *et al.*[139] had 157 participants in the intervention group and 157 participants in the control group.

Quality assessment for cost-effectiveness studies

For full economic evaluations,[75–77,160] we assessed the risk of bias in the results of the single effectiveness study on which the full economic evaluation study was based (see *Figure 5* for the risk-of-bias assessment). We judged Farquhar *et al.*[75,76] and Higginson *et al.*[77] to be at low risk of selection bias because there were adequate descriptions of the sequence generation process and allocation concealment. We rated McCaffrey *et al.*[160] as having an unclear risk of bias because there was insufficient information about the random sequence generation process and allocation concealment. Three of the studies reported on subjective outcomes, but did not blind participants.[75–77] Consequently, these three studies were rated as having a high risk of bias under 'blinding of participants and personnel (subjective outcomes)'. McCaffrey *et al.*[160] did not include subjective outcomes; therefore, we left this domain blank. Besides McCaffrey *et al.*,[160] the remaining three studies did not include objective outcomes, so we left the domain 'blinding of participants and personnel (objective outcomes)' blank. We judged the McCaffrey *et al.*[160] study to have a low risk of bias under the domain 'blinding of participants and personnel (objective outcomes)' because lack of blinding was unlikely to lead to bias in objective outcomes such as place of death.

We judged the Farquhar *et al.*[75,76] study to be at a low risk of bias for blinding of outcome assessment (subjective outcomes) because outcome assessors were blinded, whereas we rated the Higginson *et al.*[77] study as having a high risk of bias because of lack of blinding. McCaffrey *et al.*[160] did not include subjective outcomes; therefore, we left this domain blank. McCaffrey *et al.*[160] included objective outcomes; we rated the study as having a low risk of bias for blinding of outcome assessment (objective outcomes) because lack of blinding is unlikely to affect objective outcomes. We left this domain blank for the Farquhar *et al.*[75,76] and Higginson *et al.*[77] studies because they did not include objective outcomes.

We judged Farquhar *et al.*[76] and McCaffrey *et al.*[160] as having a low risk of bias for incomplete outcome data (attrition bias), whereas we assessed Higginson *et al.*[77] as having an unclear risk of bias because the number of patients analysed differed from the number of patients randomly assigned to the intervention and control groups. We assessed Farquhar *et al.*[75] as having a high risk of bias in this domain because of the exclusion of missing data from the analysis. With the exception of Higginson *et al.*,[77] we rated the remaining three studies as having a high risk of bias for selective reporting (reporting bias) because all outcomes in the protocol/trial registry were not reported in the publication.

We gave a low risk-of-bias rating for 'other bias' in all studies except McCaffrey *et al.*[160] In McCaffrey *et al.*,[160] it was unclear whether or not the differences between the intervention and control groups were controlled for. We assessed Farquhar *et al.*[75,76] as having an unclear risk of bias for 'size of study', and Higginson *et al.*[77] and McCaffrey *et al.*[160] as having a high risk of bias because of sample sizes of < 50 participants in the intervention and control groups.

The BMJ checklist for authors and peer reviews of economic submissions

The methodological quality of the 13 studies that examined total costs varied across the different areas assessed (see *Appendix 6*). We assessed methodological quality using the BMJ checklist for authors and peer reviewers of economic submissions.[59] Given that they used different methods and reported on different resources used by patients, we could not pool their data in a meta-analysis. All the studies were clear about their research question. We considered all the studies to have provided the rationale for choosing the alternatives they compared because they all compared HSPC (or HSPC in addition to usual care) with usual care. However, only eight of them stated the economic importance of the research question. Six studies stated the form of economic evaluation used. The viewpoint of the analysis was stated in only three studies [Higginson *et al.*,[77] McCaffrey *et al.*[160] and Sahlen *et al.*[121] (linked to Brännström *et al.*[118])]. All studies were clear about the source of effectiveness estimates used. Besides Mendoza-Galindo *et al.*[101] (abstract only), they all provided details on the design and results of their effectiveness study. The primary outcome for the economic evaluation was clearly stated in seven studies [Farquhar *et al.*,[75,76] Higginson *et al.*,[77,78] Gade *et al.*,[88] McCaffrey *et al.*[160] and Sahlen *et al.*[121] (linked to Brännström *et al.*[118])]. Quantities of resources were not reported separately from their unit costs in four studies [Ma *et al.*,[70] Mendoza-Galindo *et al.*[101] (abstract only), Ozcelik *et al.*[95] and Sahlen *et al.*[121] (linked to Brännström *et al.*[118])]. In Brumley *et al.*,[142] this was unclear because the authors described how the costs were derived, but did not present the unit costs. Details of currency of price adjustments for inflation or currency conversion were not provided in any of the studies. The relevance of productivity changes to the study question was also not discussed in any of the studies. All studies except Mendoza-Galindo *et al.*[101] (abstract only) stated the time horizon of costs and benefits. They all addressed the research question with conclusions following from their findings. Higginson *et al.*,[77,78] Gade *et al.*,[88] McCaffrey *et al.*[160] and Sahlen *et al.*[121] (linked to Brännström *et al.*[118]) provided details of statistical tests and CIs.

Consensus on Health Economic Criteria list

We also used the CHEC list to assess the methodological quality of economic evaluations (see *Appendix 7*). Overall, 13 studies met 7–16 (out of 19) quality items on the list. Five items were considered to have been met by all studies: clear description of study population, a well-defined research question in answerable form, identification of important and relevant outcomes for each alternative, appropriate measurement of outcomes, and conclusion following the reported data. All studies but Mendoza-Galindo *et al.*[101] (abstract only) discussed the generalisation of results to other settings or patient groups and chose the appropriate time horizon to include relevant costs and outcomes. Eleven out of the 13 studies used the appropriate economic study design to answer the stated objective; Brumley *et al.*[142] and Sahlen *et al.*[121] (linked to Brännström *et al.*[118]) did not. All studies except McCaffrey *et al.*[160] and Mendoza-Galindo *et al.*[101] (abstract only) discussed the ethical and distributional issues appropriately. Only two studies[78,95] clearly described the competing alternatives, and three studies[35,78,160] were considered to have appropriately chosen a perspective for the study. Valuing outcomes appropriately was achieved in only five studies.[35,75,76,156,160] No study needed, or clearly stated, the discounting methods.

Effects of hospital-based specialist palliative care

Table 2 provides the summary of findings of the intervention on the key outcomes in this review.

TABLE 2 Summary of findings for comparison of HSPC with usual care on key outcomes

Hospital-based specialist palliative care, compared with usual care, for adults with advanced illness and their unpaid caregivers/families

Patient or population: adults with advanced illness and their unpaid caregivers/families

Setting: hospital and home

Intervention: HSPC

Comparison: usual care

Outcome	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	*n* participants (*n* studies)	Certainty of the evidence (GRADE)
	Risk with usual care	Risk with HSPC			
Patient HRQoL.[b] SD units (higher scores indicate better quality of life). Follow-up range: 2 weeks after hospitalisation to 13 months	Mean ranging from −45.4 (SD 26.83) to 131.14 (SD 26.62)	SMD 0.26 SDs higher (0.15 higher to 0.37 higher)	–	1344 (10 RCTs)	⊕⊕⊖⊖ Low[c]
Patient symptom burden. Assessed with generalised measures,[d] SD units (lower scores indicate lower symptom burden). Follow-up range: 2 weeks after hospitalisation to 13 months	Mean ranging from −19.3 (SD 4.2) to 268.59 (SD 201.65)	SMD 0.26 SDs lower (0.41 lower to 0.12 lower)	–	761 (6 RCTs)	⊕⊖⊖⊖ Very low[c,e]
Patient satisfaction with care.[f] SD units (higher scores indicate better patient satisfaction) Follow-up range: 3–6 months	Mean ranging from 6.4 (SD 1.1) to 68.37 (SD 9.03)	SMD 0.36 SDs higher (0.14 higher to 0.57 higher)	–	337 (2 RCTs)	⊕⊕⊖⊖ Low[c]
Achieving patient preferred place of death (measured by number of patients with home death). Follow-up: range 1 month to 13 months	462 per 1000	583 per 1000 (513 to 649)	OR 1.63 higher (1.23 higher to 2.16 higher)	861 (7 RCTs)	⊕⊕⊖⊖ Low[c]
Pain.[g] SD units (lower scores indicate less pain) Follow-up range: 8 weeks to 6 months	Mean ranging from 2.2 (SD 3.7) to 28.19 (SD 32.81)	SMD 0.16 SDs lower (0.33 lower to 0.01 higher)	–	525 (4 RCTs)	⊕⊖⊖⊖ Very low[c,e]
Unpaid caregiver burden.[h] Follow-up: 6 months	Only two studies reported adjusted end-point values, but we could not pool them in a meta-analysis. They both found no between-group difference between HSPC and usual care		–	170 (2 RCTs)	⊕⊖⊖⊖ Very low[c,i]

TABLE 2 Summary of findings for comparison of HSPC with usual care on key outcomes (*continued*)

Outcome	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	*n* participants (*n* studies)	Certainty of the evidence (GRADE)
	Risk with usual care	Risk with HSPC			
Cost and cost-effectiveness	Of 13 studies reporting costs of HSPC, nine studies found no difference between HSPC and usual care, and two studies favoured HSPC over usual care. The difference in cost was unclear in one study, and another study reported mixed findings, with lower cost of hospitalisation in favour of HSPC, but no difference in the cost of emergency room visit Four studies with full economic analysis were inconclusive on the cost-effectiveness of HSPC		–	2103 (13 RCTs)	⊕⊖⊖⊖ Very low[c,j]

EORTC QLQ-C30, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACIT, Functional Assessment of Chronic Illness Therapy; FACT, Functional Assessment of Cancer Therapy.

a The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
b Assessed with the EORTC QLQ-C30, the FACT-Bone Marrow Transplant, the FACT-General, the FACT-Lung, the FACIT for Palliative Care, the FACIT-Spiritual Well-being Scale, the McGill Quality of Life Questionnaire and the Minnesota Living with Heart Failure Questionnaire.
c We downgraded by two levels for very serious study limitations because of a high risk of bias in studies.
d Assessed with the Edmonton Symptom Assessment Scale or a modified form of it, the severity subscale of the Memorial Symptom Assessment Scale, the symptom impact subscale of the Quality of Life at the End of Life, the Rotterdam Symptom Checklist (Physical Symptoms Score) and the lung cancer subscale of the FACT-Lung.
e We downgraded by one level because of inconsistency between our main meta-analysis and sensitivity analyses.
f Assessed with the 16-item Family Satisfaction with Care-Patient Version and the Modified City of Hope Patient Questionnaire-Place of Care Environment Scale.
g Assessed with the pain item of EORTC QLQ-C30 and Brief Pain Inventory.
h Assessed with the Montgomery–Borgatta Caregiver Burden Scale and the Zarit Burden Interview.
i We downgraded by one level for imprecision because of the small number of participants.
j We downgraded by one level for inconsistency because the results were inconsistent across studies.

Note

GRADE Working Group grades of evidence:

- High quality – we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate quality – we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low quality – our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low quality – we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Primary outcomes

Patient health-related quality of life

As our main meta-analysis, we pooled data from 10 studies that reported adjusted end-point values.[35,48,73,85,106,129,161,163,167,168] We found that significantly better patient HRQoL was achieved with HSPC than with usual care ($n = 10$ studies, 1344 participants, SMD 0.26, 95% CI 0.15 to 0.37; $I^2 = 3\%$, random effects) (*Figure 6*). Positive SMDs indicate better patient HRQoL with HSPC, whereas negative SMDs indicate lower patient HRQoL with HSPC. The effect size obtained (0.26) is small, based on conventional standards.

We carried out sensitivity analyses with studies reporting unadjusted end-point values,[48,72,78,80,85,88,118,147,165] unadjusted change values[35,72,85,89,95,96,139,165,167] and also assessed the impact of using an ICC of 0.02 in adjusting for clustering in the cluster RCT by McCorkle *et al.*[48] We could not carry out a sensitivity analysis with adjusted change values because only one study reported them.[126]

In a sensitivity analysis in which McCorkle *et al.*[48] was removed from the studies that reported adjusted end-point values, HSPC was still better than usual care in improving patient HRQoL ($n = 9$ studies, 1280 participants, SMD 0.29, 95% CI 0.18 to 0.40; $I^2 = 0\%$) (*Figure 7*).

A sensitivity analysis using unadjusted end-point values led to a larger difference between HSPC and usual care, but the CIs were wider and there was greater heterogeneity ($n = 9$ studies, 1201 participants, SMD 0.41, 95% CI 0.11 to 0.70; $I^2 = 83\%$) (*Figure 8*).

When we removed McCorkle *et al.*[48] from the studies that reported unadjusted end-point values, HSPC was still better than usual care at improving patient HRQoL ($n = 8$ studies, 1137 participants, SMD 0.46, 95% CI 0.13 to 0.78; $I^2 = 85\%$) (*Figure 9*).

When we pooled unadjusted change values, we also found better patient HRQoL with HSPC ($n = 9$ studies, 1278 participants, SMD 0.67, 95% CI 0.16 to 1.18; $I^2 = 95\%$) (*Figure 10*).

The results from the sensitivity analyses supported those from the main analysis. Solari *et al.*[126] was the only study that presented adjusted change values; it assessed patient HRQoL using the Schedule for the Evaluation of Individual Quality of Life-Direct Weighting (SEIQoL-DW) (range 0–100, 100 = best HRQoL). It found no between-group difference between the HSPC and usual-care groups at either 3 or 6 months. At 3 months, the mean change was −0.9 (95% CI −6.8 to 5.1) in the HSPC group and −3.7 (95% CI −17.6 to 10.3) in the usual-care group, with a difference of 2.8 (95% CI −12.2 to 17.8) between the groups. At 6 months, the mean change was 0.8 (95% CI −5.3 to 6.9) in the HSPC group and −4.0 (95% CI −21.1 to 13.1) in the usual-care group, with a difference of 4.8 (95% CI −13.2 to 22.7) between the groups.

Across the studies in the meta-analyses, we combined different scales assessing patient HRQoL by calculating SMDs. *Appendix 8* describes the HRQoL scales and the dimensions they covered. The scales used included the Functional Assessment of Chronic Illness Therapy for Palliative Care (FACIT-Pal),[73,129,165] the King's Brief Interstitial Lung Disease Questionnaire,[72] the Kansas City Cardiomyopathy Questionnaire (KCCQ),[139] the EuroQol-5 Dimensions (EQ-5D),[118] the Functional Assessment of Cancer Therapy-Bone Marrow Transplant,[85] the Modified City of Hope Patient Questionnaire (MCOHPQ),[88] the Functional Assessment of Cancer Therapy-General,[48,89,147,167] the Functional Assessment of Chronic Illness Therapy-Spiritual Well-being Scale,[163] the Chronic Respiratory Disease Questionnaire (CRQ),[78] the European Organisation for the Research and Treatment of Cancer-Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) (Chinese version),[80] the EORTC QLQ-C30,[95,168] the Minnesota Living with Heart Failure Questionnaire,[96,161] the McGill Quality of Life Questionnaire,[106] the Functional Assessment of Cancer Therapy-Lung (FACT-L)[35] and the SEIQoL-DW.[126]

Four studies[72,78,118,165] used more than one scale to measure patient HRQoL. In particular, Brännström *et al.*[118] showed data obtained using only the EQ-5D, and not those from the KCCQ. Consequently, data from the EQ-5D were used in the meta-analysis. Higginson *et al.*[78] assessed patient HRQoL using the CRQ and the EQ-5D. Only data from the CRQ[182] were used in the meta-analysis because, unlike the EQ-5D[183] (a generic HRQoL measure), it is more specific to chronic respiratory disease. Rogers *et al.*[165] assessed patient HRQoL using the FACIT-Pal and the KCCQ; both were presented as primary outcomes. Given that the FACIT-Pal has more extensive validation in palliative populations, it was used in the meta-analysis.

Of the remaining 19 studies that were not in any of the meta-analyses, 10 did not report on patient HRQoL;[70,77,81,82,84,101,142,156,160,170] six presented data on different domains of patient HRQoL;[74,75,97,123,146,148] one assessed patient HRQoL at baseline, but not at follow-up;[93] and McWhinney *et al.*[79] only reported that there was 'no significant difference', without presenting data. Nottelmann *et al.*[104] assessed patient HRQoL, but did not present analysable data.

Study or subgroup	HSPC Mean	HSPC SD	HSPC Total	Control Mean	Control SD	Control Total	Weight (%)	SMD IV, random, 95% CI
Bakitas 2009[129]	141.27	26.25	145	131.14	26.62	134	20.3	0.38 (0.15 to 0.62)
Bakitas 2015[73]	129.9	14.04	72	127.2	14.2	83	11.7	0.19 (−0.13 to 0.51)
El-Jawahri 2016[85]	94.33	20.31	80	86.6	20.27	77	11.8	0.38 (0.06 to 0.69)
McCorkle 2015[48]	78.33	12.47	25	81.34	12.81	39	4.7	−0.23 (−0.74 to 0.27)
O'Riordan 2019[161]	−40	26.24	16	−45.4	26.83	14	2.3	0.20 (−0.52 to 0.92)
Rodin 2020[163]	114.37	32.69	22	100.61	33.54	20	3.2	0.41 (−0.20 to 1.02)
Tattersall 2014[106]	4.8	0.83	13	5.1	0.72	13	2.0	−0.37 (−1.15 to 0.40)
Temel 2010[35]	98	15.1	60	91.5	15.8	47	8.0	0.42 (0.03 to 0.80)
Temel 2017[167]	80.1	12.12	145	77.7	12.08	153	21.9	0.20 (−0.03 to 0.43)
Vanbutsele 2018[168]	61.98	23.95	92	54.39	25.19	94	14.0	0.31 (0.02 to 0.60)
Total number of participants (95% CI)			670			674	100.0%	0.26 (0.15 to 0.37)

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 9.30$, df = 9 ($p = 0.41$); $I^2 = 3\%$

Test for overall effect: $z = 4.67$ ($p < 0.00001$)

FIGURE 6 Effect of HSPC vs. usual care on patient HRQoL: adjusted end-point values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

Study or subgroup	HSPC Mean	HSPC SD	HSPC Total	Control Mean	Control SD	Control Total	Weight (%)	SMD IV, random, 95% CI
Bakitas 2009[129]	141.27	26.25	145	131.14	26.62	134	21.7	0.38 (0.15 to 0.62)
Bakitas 2015[73]	129.9	14.04	72	127.2	14.2	83	12.2	0.19 (−0.13 to 0.51)
El-Jawahri 2016[85]	94.33	20.31	80	86.6	20.27	77	12.2	0.38 (0.06 to 0.69)
O'Riordan 2019[161]	−40	26.24	16	−45.4	26.83	14	2.4	0.20 (−0.52 to 0.92)
Rodin 2020[163]	114.37	32.69	22	100.61	33.54	20	3.3	0.41 (−0.20 to 1.02)
Tattersall 2014[106]	4.8	0.83	13	5.1	0.72	13	2.0	−0.37 (−1.15 to 0.40)
Temel 2010[35]	98	15.1	60	91.5	15.8	47	8.2	0.42 (0.03 to 0.80)
Temel 2017[167]	80.1	12.12	145	77.7	12.08	153	23.5	0.20 (−0.03 to 0.43)
Vanbutsele 2018[168]	61.98	23.95	92	54.39	25.19	94	14.6	0.31 (0.02 to 0.60)
Total number of participants (95% CI)			645			635	100.0%	0.29 (0.18 to 0.40)

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 5.35$, df = 8 ($p = 0.72$); $I^2 = 0\%$

Test for overall effect: $z = 5.12$ ($p < 0.00001$)

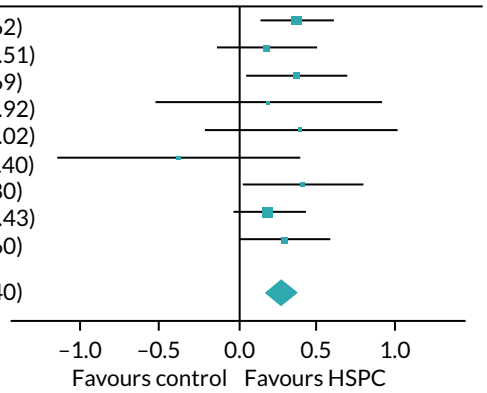

FIGURE 7 Effect of HSPC vs. usual care on patient HRQoL: adjusted end-point values (excluding McCorkle *et al.*[48]). df, degrees of freedom; IV, inverse variance; random, random-effects model.

Study or subgroup	HSPC Mean	HSPC SD	HSPC Total	Control Mean	Control SD	Control Total	Weight (%)	SMD IV, random, 95% CI
Bajwah 2015[72]	40	16.2	23	30.3	16.2	24	9.2	0.59 (0.00 to 1.17)
Brännström 2014[118]	57.6	19.2	28	48.5	24.4	32	10.0	0.41 (−0.11 to 0.92)
El-Jawahri 2016[85]	95.46	13.3	80	85.42	15.07	77	12.1	0.70 (0.38 to 1.03)
Franciosi 2019[147]	70.1	15.5	111	69.6	15.5	103	12.7	0.03 (−0.24 to 0.30)
Gade 2008[88]	6.4	2.3	199	6.3	2.1	191	13.3	0.05 (−0.15 to 0.24)
Higginson 2014[78]	71	19	42	67	20	40	10.9	0.20 (−0.23 to 0.64)
Jingfen 2017[80]	59.42	4.27	53	53.23	4.18	53	10.9	1.45 (1.02 to 1.88)
McCorkle 2015[48]	82.07	18.13	25	82.71	14.47	39	10.1	−0.04 (−0.54 to 0.46)
Rogers 2017[165]	136.5	28.6	41	125.8	30.7	40	10.8	0.36 (−0.08 to 0.80)
Total number of participants (95% CI)			602			599	100.0%	0.41 (0.11 to 0.70)

Heterogeneity: $\tau^2 = 0.16$; $\chi^2 = 46.98$, df = 8 ($p < 0.00001$); $I^2 = 83\%$

Test for overall effect: $z = 2.66$ ($p = 0.008$)

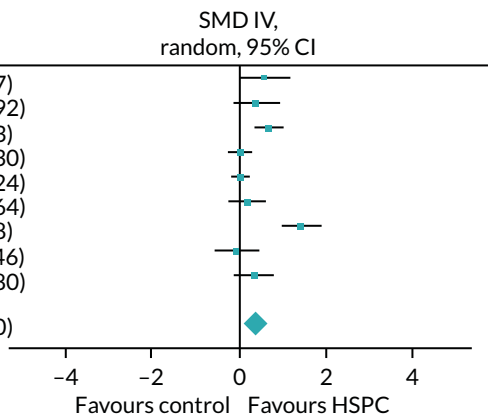

FIGURE 8 Effect of HSPC vs. usual care on patient HRQoL: unadjusted end-point values. a, 95% CIs were estimated from the graph. df, degrees of freedom; IV, inverse variance; random, random-effects model.

Study or subgroup	HSPC Mean	HSPC SD	HSPC Total	Control Mean	Control SD	Control Total	Weight (%)	SMD IV, random, 95% CI
Bajwah 2015[72]	40	16.2	23	30.3	16.2	24	10.3	0.59 (0.00 to 1.17)
Brännström 2014[118]	57.6	19.2	28	48.5	24.4	32	11.2	0.41 (0.11 to 0.92)
[a]El-Jawahri 2016[85]	95.46	13.3	80	85.42	15.07	77	13.5	0.70 (0.38 to 1.03)
Franciosi 2019[147]	70.1	15.5	111	69.6	15.5	103	14.0	0.03 (−0.24 to 0.30)
Gade 2008[88]	6.4	2.3	199	6.3	2.1	191	14.7	0.05 (−0.15 to 0.24)
Higginson 2014[78]	71	19	42	67	20	40	12.1	0.20 (−0.23 to 0.64)
Jingfen 2017[80]	59.42	4.27	53	53.23	4.18	53	12.2	1.45 (1.02 to 1.88)
Rogers 2017[165]	136.5	28.6	41	125.8	30.7	40	12.1	0.36 (−0.08 to 0.80)
Total number of participants (95% CI)	577					560	100.0%	0.46 (0.13 to 0.78)

Heterogeneity: $\tau^2 = 0.17$; $\chi^2 = 45.18$, df = 7 ($p < 0.00001$); $I^2 = 85\%$

Test for overall effect: $z = 2.77$ ($p = 0.006$)

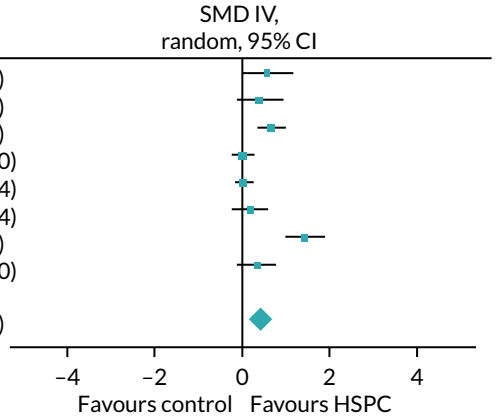

FIGURE 9 Effect of HSPC vs. usual care on patient HRQoL: unadjusted end-point values (excluding McCorkle *et al.*[48]). a, 95% CIs were estimated from the graph. df, degrees of freedom; IV, inverse variance; random, random-effects model.

Study or subgroup	HSPC Mean	HSPC SD	HSPC Total	Control Mean	Control SD	Control Total	Weight (%)	SMD IV, random, 95% CI
Bajwah 2015[72]	3.5	11	23	−2.6	21.3	24	10.4	0.35 (−0.23 to 0.93)
Bekelman 2018[139]	5.5	15.71	121	2.9	15.71	121	11.7	0.16 (−0.09 to 0.42)
El-Jawahri 2016[85]	−14.72	21.28	80	−21.54	21.28	77	11.5	0.32 (0.00 to 0.63)
Grudzen 2016[89]	5.91	16.65	69	1.08	16	67	11.4	0.29 (−0.04 to 0.63)
Ozcelik 2014[95]	30.3	18.2	22	9.09	15.4	22	10.0	1.24 (0.59 to 1.89)
Rogers 2017[165]	16.7	21.1	41	8.3	29.1	39	11.0	0.33 (−0.11 to 0.77)
Sidebottom 2015[96]	14.86	1.02	79	11.8	1.02	88	11.0	2.99 (2.54 to 3.43)
Temel 2010[35]	2.3	11.2	60	−2.3	11.4	47	11.2	0.40 (0.02 to 0.79)
Temel 2017[167]	0.39	13.72	145	−1.13	13.72	153	11.7	0.11 (−0.12 to 0.34)
Total number of participants (95% CI)	640					638	100.0%	0.67 (0.16 to 1.18)

Heterogeneity: $\tau^2 = 0.56$; $\chi^2 = 146.25$, df = 8 ($p < 0.00001$); $I^2 = 95\%$

Test for overall effect: $z = 2.60$ ($p = 0.009$)

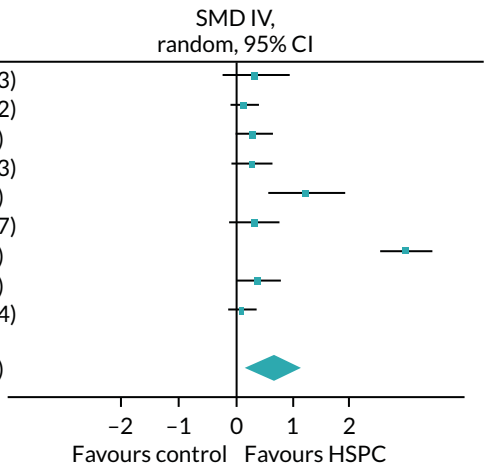

FIGURE 10 Effect of HSPC vs. usual care on patient HRQoL: unadjusted change values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

The funnel plot suggested some asymmetry (*Figure 11*). Egger's test for asymmetry resulted in a *p*-value of 0.02. However, given evidence of publication of negative studies in the funnel plot, this asymmetry is not necessarily indicative of publication bias.

We did not carry out a subgroup analysis because of the low heterogeneity ($I^2 = 3\%$) in the main meta-analysis.

Quality of the evidence

In the GRADE approach, we downgraded the quality of the evidence on patient HRQoL to low because of a high risk of bias across studies (–2 levels as a result of very serious study limitations: high risk of bias for selection, performance, detection, attrition and reporting bias) (see *Table 2*).

Patient symptom burden (as a collection of two or more symptoms)

As our main meta-analysis, we pooled data from six studies that presented adjusted end-point values. We found significant improvement in patient symptom burden with HSPC, compared with usual care (six studies, 761 participants, SMD –0.26, 95% CI –0.41 to –0.12; $I^2 = 0\%$, random effects) (*Figure 12*). Negative SMDs indicate benefit (lower symptom burden) and positive SMDs reflect greater symptom burden.

We carried out sensitivity analyses with unadjusted end-point values, adjusted change values and unadjusted change values, and also assessed the impact of using an ICC of 0.02 in adjusting for clustering in McCorkle *et al.*[48]

A sensitivity analysis using unadjusted end-point values showed a pooled effect of SMD –0.17 (six studies, 833 participants, 95% CI –0.54 to 0.20; $I^2 = 83\%$) (*Figure 13*).

When we excluded McCorkle *et al.*,[48] we had similar results (five studies, 769 participants, SMD –0.19, 95% CI –0.62 to 0.24; $I^2 = 87\%$) (*Figure 14*).

When we considered adjusted change values, the pooled effect was a SMD of –1.31 (four studies, 353 participants, 95% CI –3.27 to 0.64; $I^2 = 98\%$) (*Figure 15*).

When we excluded McCorkle *et al.*,[48] we found a pooled effect of SMD –1.79 (three studies, 289 participants, 95% CI –4.29 to 0.70; $I^2 = 98\%$) (*Figure 16*).

When we pooled unadjusted change values, we had a SMD of –0.44 (six studies, 641 participants, 95% CI –0.94 to 0.06; $I^2 = 88\%$) (*Figure 17*).

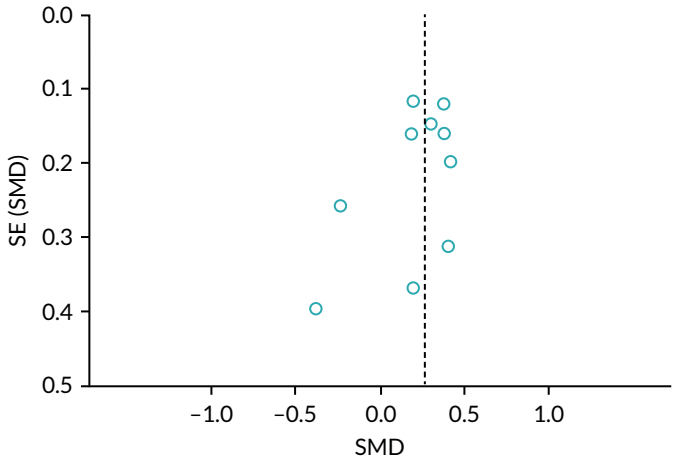

FIGURE 11 Funnel plot of comparison of HSPC vs. usual care on patient HRQoL. SE, standard error.

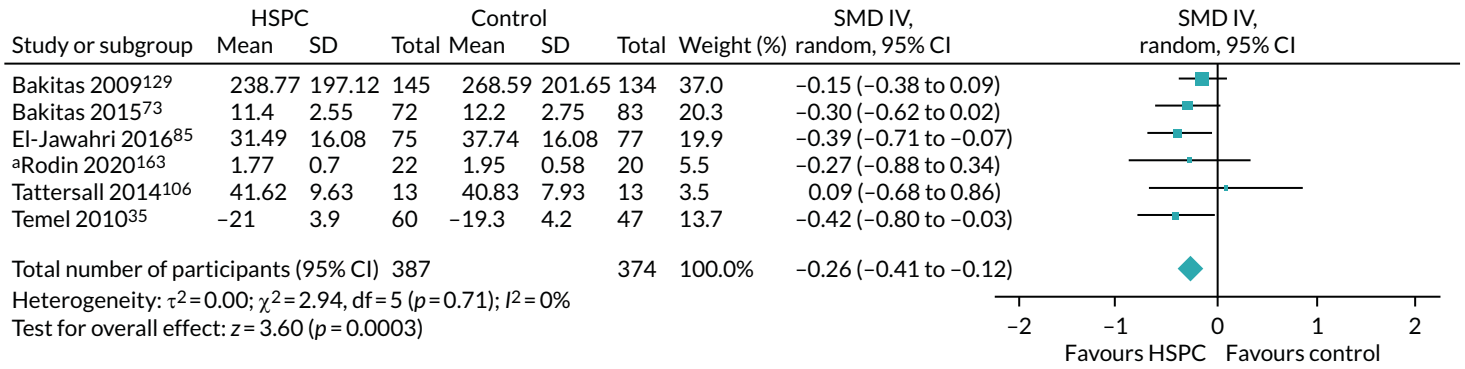

FIGURE 12 Effect of HSPC on patient symptom burden: adjusted end-point values. a, Data from the severity subscale of the Memorial Symptom Assessment Scale was used in meta-analysis. df, degrees of freedom; IV, inverse variance; random, random-effects model.

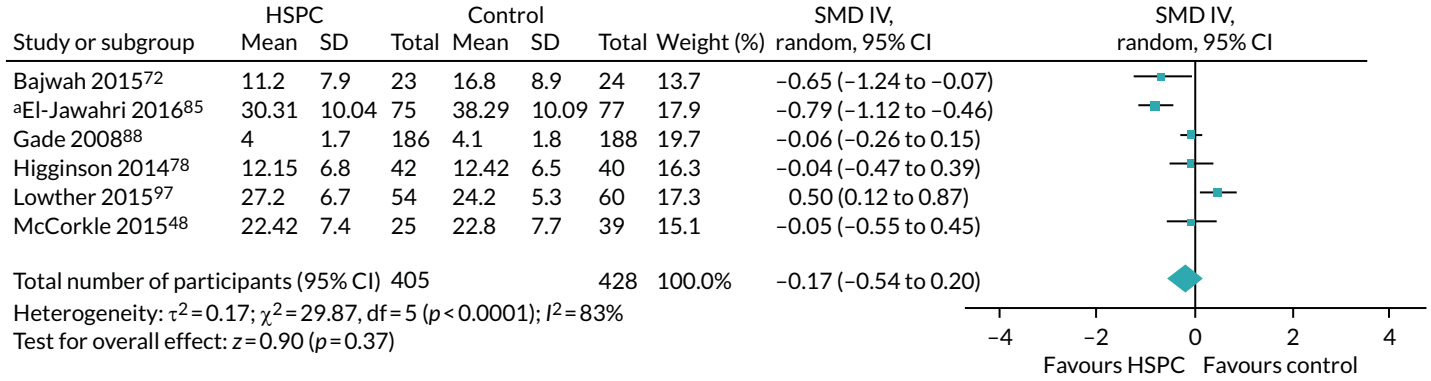

FIGURE 13 Effect of HSPC on patient symptom burden: unadjusted end-point values. a, 95% CI estimated from graph. df, degrees of freedom; IV, inverse variance; random, random-effects model.

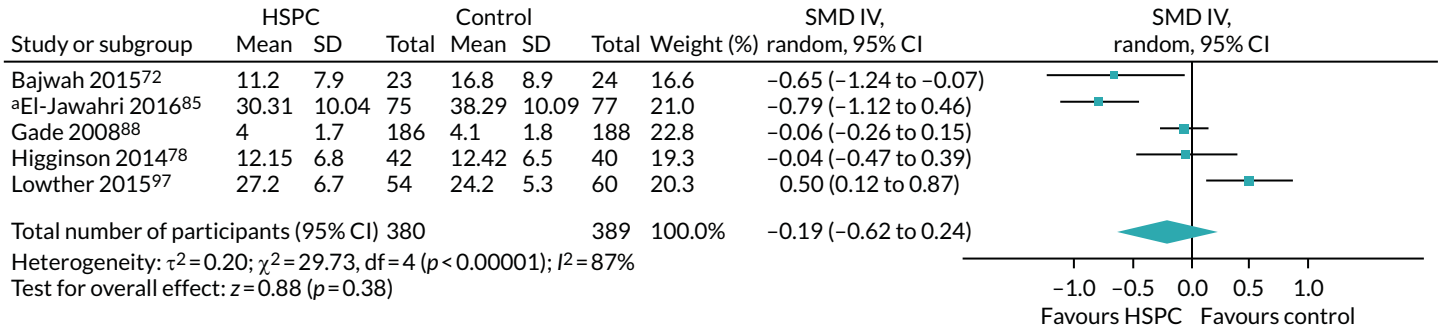

FIGURE 14 Effect of HSPC on patient symptom burden: unadjusted end-point values (excluding McCorkle *et al.*[48]). a, 95% CIs were estimated from graph. df, degrees of freedom; IV, inverse variance; random, random-effects model.

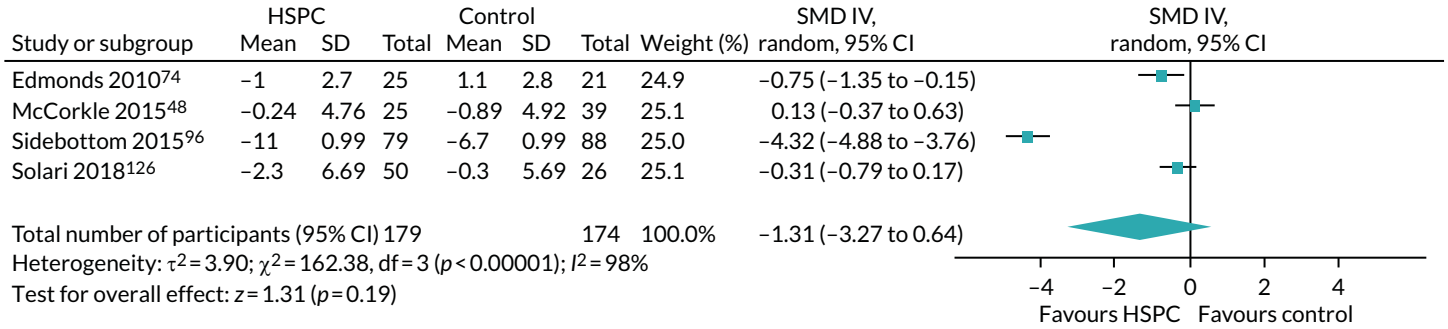

FIGURE 15 Effect of HSPC on patient symptom burden: adjusted change values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

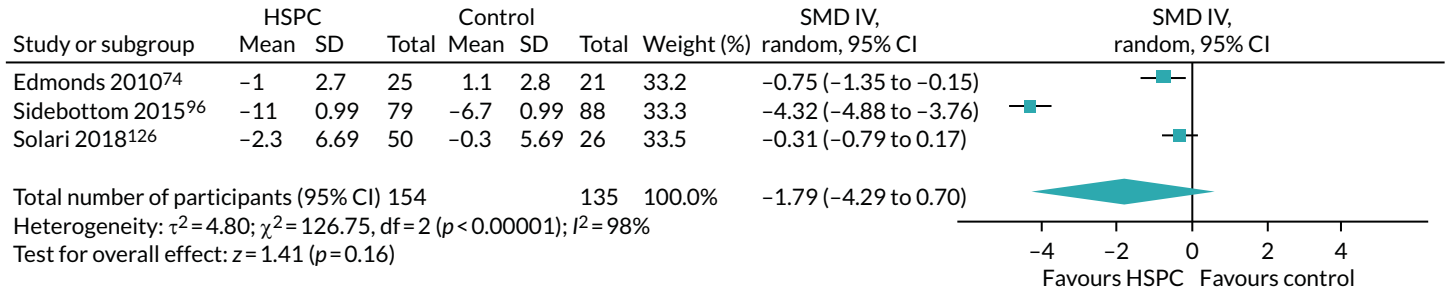

FIGURE 16 Effect of HSPC on patient symptom burden: adjusted change values (excluding McCorkle *et al.*[48]). df, degrees of freedom; IV, inverse variance; random, random-effects model.

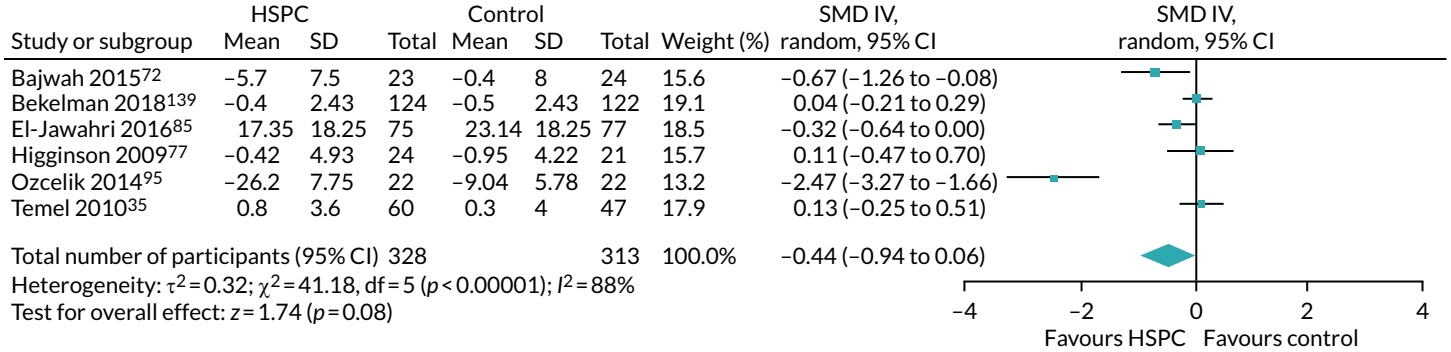

FIGURE 17 Effect of HSPC on patient symptom burden: unadjusted change values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

Across the studies in the meta-analyses, we combined different generalised measures of patient symptom burden using SMDs. Studies assessed patient symptom burden using the following scales: POS, or a modified form of it;[72,74,77,78,126] African POS;[97] Edmonton Symptom Assessment Scale (ESAS), or a modified form of it;[85,95,96,129] symptom impact subscale of the Quality of Life at End of life;[73] General Symptom Distress Scale;[139] physical area scale of the MCOHPQ;[88] Symptom Distress Scale;[48,170] Rotterdam Symptom Checklist (Physical Symptoms Score);[106] lung cancer subscale of the FACT-L;[35] and Memorial Symptom Assessment Scale.[163] Only the severity subscale of the Memorial Symptom Assessment Scale, reported by Rodin *et al.*,[163] was used in the meta-analysis.

Of the remaining 25 studies that were not in any of the meta-analyses, 20 did not report on patient symptom burden;[70,75,76,79–82,84,89,93,101,104,116,142,147,148,160,165,167,168] two studies reported that there were 'no significant differences' between the intervention and control groups, but they did not present data;[118,156] and O'Riordan *et al.*[161] did not present data from the ESAS. Wallen *et al.*[170] did not present analysable data, and Janssens *et al.*[123] assessed symptom burden using the ESAS in the intervention group only.

Given that there were fewer than 10 included studies in the main meta-analysis of studies that presented adjusted end-point values, we did not use funnel plots or carry out tests for funnel plot asymmetry. We also did not carry out subgroup analysis because of a lack of heterogeneity ($I^2 = 0\%$) in the main meta-analysis.

Quality of the evidence

In the GRADE approach, we downgraded the quality of the evidence for patient symptom burden to very low because of a high risk of bias across studies (–2 levels as a result of very serious study limitations: high risk of bias for selection, performance, detection, attrition and reporting) and inconsistency (–1 level because of differences between the main meta-analysis and sensitivity analyses) (see *Table 2*).

Secondary outcomes

Patient satisfaction with care

Eight studies assessed the effect of HSPC on patient satisfaction with care.[80,88,95,142,156,161,163,170] We excluded Jingfen *et al.*,[80] O'Riordan *et al.*[161] and Ozcelik *et al.*[95] from the synthesis because they used measures that had not been validated, and we excluded Wallen *et al.*[170] because they did not present analysable data. We excluded Janssens *et al.*[123] because the authors did not state what scale was used in assessing satisfaction with the intervention.

Four studies with 733 participants used validated measures.[88,142,156,163] However, we could not include Brumley *et al.*[142] or Kane *et al.*[156] in our meta-analysis because Brumley *et al.*[142] presented OR, whereas Kane *et al.*[156] presented only *p*-values.

We pooled data from the two studies[88,163] that reported adjusted end-point values as our main meta-analysis. These studies found a significant improvement in patient satisfaction with care with HSPC, compared with usual care (two studies, 337 participants, SMD 0.36, 95% CI 0.14 to 0.57; $I^2 = 0\%$) (*Figure 18*). Positive SMDs indicate higher levels of patient satisfaction, whereas negative SMDs indicate lower levels of patient satisfaction.

Gade *et al.*[88] used the MCOHPQ-Place of Care Environment Scale and the Doctors, Nurses/Other Care Providers Communication Scale for assessing patient satisfaction with care. The MCOHPQ-Place of Care Environment Scale addressed experiences with pain management and symptom relief, psychological and social support, discharge planning, and end-of-life planning, whereas the Doctors, Nurses/Other Care Providers Communication scale addressed the level of caring and respect a patient felt from their providers, as well as the opportunity, ease and level of understanding a patient had with their providers. Only data from the MCOHPQ-Place of Care Environment Scale were used in the meta-analysis. Rodin *et al.*[163] assessed patient satisfaction with care using the 16-item Family Satisfaction with Care-Patient Version.

Study or subgroup	HSPC Mean	HSPC SD	HSPC Total	Control Mean	Control SD	Control Total	Weight (%)	SMD IV, random, 95% CI
Gade 2008[88]	6.8	1	156	6.4	1.1	139	87.4	0.38 (0.15 to 0.61)
Rodin 2020[163]	70.38	11.35	22	68.37	9.03	20	12.6	0.19 (–0.42 to 0.80)
Total number of participants (95% CI)			178			159	100.0%	0.36 (0.14 to 0.57)

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.33$, df = 1 ($p = 0.57$); $I^2 = 0\%$

Test for overall effect: $z = 3.24$ ($p = 0.001$)

FIGURE 18 Effect of HSPC on patient satisfaction with care: adjusted end-point values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

Brumley *et al.*[142] reported a 3.37-times higher odds of satisfaction in the HSPC group than in the control group ($p = 0.03$). Brumley *et al.*[142] assessed patient satisfaction with care using the Reid–Gundlach Satisfaction with Services instrument. Kane *et al.*[156] found differences in satisfaction scores ($p < 0.01$), with HSPC patients expressing more satisfaction than control patients in two of the three areas examined. The two areas were interpersonal care and involvement in care. Kane *et al.*[156] used the interpersonal care scale adapted from the Ware scale,[184] a physical environment scale from McCaffree and Harkins[185] and involvement-in-care questions adapted from the National Cancer Institute's hospice study.[186] Kane *et al.*[156] reported that these measures have been shown to be reliable and valid for patients with terminal cancer.

As a result of the small number of studies in the main meta-analysis with adjusted end-point values, we could not carry out subgroup analysis and we did not use funnel plots or carry out tests for funnel plot asymmetry.

Quality of the evidence

In the GRADE approach, we downgraded the quality of the evidence for patient satisfaction with care to low because of a high risk of bias in some domains in the two studies (–2 levels as a result of very serious study limitations: high risk of performance, detection, reporting, attrition, size of study and other biases) (see *Table 2*).

Caregiver satisfaction with care

Four studies assessed the effect of HSPC on family satisfaction with care.[82,84,95,156] We excluded Cheung *et al.*[84] and Ozcelik *et al.*[95] from the meta-analysis because they used non-validated family satisfaction measures.

Two studies[82,156] used validated measures with a total of 408 participants. Carson *et al.*[82] was the only study that presented adjusted end-point values, with family satisfaction assessed using the Family Satisfaction in the Intensive Care Unit (FS-ICU) survey (range 0–100, 100 = best caregiver satisfaction). They found no between-group difference between the HSPC and usual-care groups. The mean satisfaction was 81.1 (95% CI 78.3 to 83.9) in the HSPC group and 84.3 (95% CI 81.3 to 87.3) in the usual-care group, with a difference of −3.1 (95% CI −7.3 to 1.0) between groups ($p = 0.13$).

Kane *et al.*[156] did not present their data. They reported only *p*-values in favour of the HSPC group in two of the five cohorts they assessed. Kane *et al.*[156] assessed caregiver satisfaction with care using the interpersonal care scale adapted from the Ware scale,[184] a physical environment scale based on that of McCaffree and Harkins[185] and involvement-in-care questions adapted from the National Cancer Institute's hospice study.[186]

Quality of the evidence

In the GRADE approach, we downgraded the quality of the evidence for caregiver satisfaction with care to very low because of a high risk of bias across studies (–2 levels as a result of very serious study quality limitations: high risk of bias for performance, attrition and reporting) and inconsistency (–1 level because of heterogeneity in study findings).

Achieving patient preferred place of death (measured by number of patients with home death)

We decided to use number of home deaths as a proxy measure for achieving preferred place of death, because most people in developed countries prefer to die at home.[47]

Effect of hospital-based specialist palliative care on achieving patient preferred place of death

We pooled data from seven studies and found that those receiving HSPC had higher odds of achieving their preferred place of death than those receiving usual care (861 participants, OR 1.63, 95% CI 1.23 to 2.16; $I^2 = 0\%$) (*Figure 19*). The OR of 1.63 translates to a risk ratio of 1.22 (95% CI 1.08 to 1.39). This implies an increase in the relative risk of home deaths of 22% (95% CI 8% to 39%), when compared with usual care.

Kane *et al.*[156] reported that, in the intervention group, only 3% of deaths occurred at home, with almost 60% dying in the inpatient hospice; by contrast, in the control group, 7% of deaths occurred at home, with almost 80% dying in hospital. The authors did not provide the actual number of deaths, but they stated that the difference between the intervention and control groups was not 'statistically significant'. One study by Janssens *et al.*[123] reported two home deaths, but it was unclear if the deaths occurred in the HSPC group or the control group. The remaining 33 studies did not report on home death.

Given that there were fewer than 10 included studies in the meta-analysis, we did not use funnel plots or carry out tests for funnel plot asymmetry. In addition, we could not carry out subgroup analysis because of lack of heterogeneity ($I^2 = 0\%$) in the meta-analysis.

Quality of the evidence

In the GRADE approach, we downgraded the quality of the evidence for achieving patient preferred place of death to low because of a high risk of bias across studies (–2 levels as a result of very serious study limitations: high risk of bias for selection, performance, detection, attrition and reporting) (see *Table 2*).

Achieving patient preferred place of care

Only Bajwah *et al.*[72] (47 participants) reported on this outcome. Bajwah *et al.*[72] was a fast-track RCT. Patients in the intervention group received HSPC immediately after randomisation, whereas the control group received HSPC 4 weeks after randomisation. Consequently, both the intervention and control groups received HSPC. Results at the end of the study showed that all eight patients (100%) who died in the intervention group achieved their preferred place of care, and 11 patients (84%) in the control group who received HSPC after 4 weeks achieved this.

Quality of the evidence

In the GRADE approach, we downgraded the quality of the evidence for achieving patient preferred place of care to very low because of a high risk of bias in different domains (–2 levels as a result of very serious study limitations: high risk of bias for performance, detection, attrition and reporting) and imprecision (–1 level because of the limited numbers of studies and participants).

Mortality/survival

Thirty six studies, with 7103 participants, reported on mortality/survival[35,48,70,72–79,81,82,84,85,88,89,93,96,97,106,116,118,123,126,129,139,142,147,148,156,160,161,165,167,168] (see *Appendix 9*). We decided against pooling their hazard ratios (HRs) in a meta-analysis because of methodological limitations in the included studies.

Three studies did not report on the number of deaths,[95,101,170] and Nottelmann *et al.*[104] reported the number of deaths in the HSPC group only. There were no deaths in the study by Rodin *et al.*,[163] and this was unclear in the foreign language study by Jingfen *et al.*[80] because it was not stated in the study.

Study or subgroup	HSPC Events	HSPC Total	Control Events	Control Total	Weight (%)	OR M–H, random, 95% CI
Bajwah 2015[72]	5	8	5	13	2.4	2.67 (0.43 to 16.39)
Bakitas 2009[129]	67	112	62	119	29.4	1.37 (0.81 to 2.31)
Bakitas 2015[73]	27	50	28	59	14.0	1.30 (0.61 to 2.77)
Brumley 2007[142]	81	118	54	113	27.8	2.39 (1.40 to 4.09)
McCaffrey 2013[160]	13	23	6	8	2.5	0.43 (0.07 to 2.62)
Tattersall 2014[106]	13	58	8	53	8.4	1.63 (0.61 to 4.30)
Temel 2010[35]	40	61	36	66	15.5	1.59 (0.78 to 3.25)
Total number of participants (95% CI)	430		431		100.0%	1.63 (1.23 to 2.16)
Total events	246		199			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 5.11$, df = 6 ($p = 0.53$); $I^2 = 0\%$

Test for overall effect: $z = 3.38$ ($p = 0.0007$)

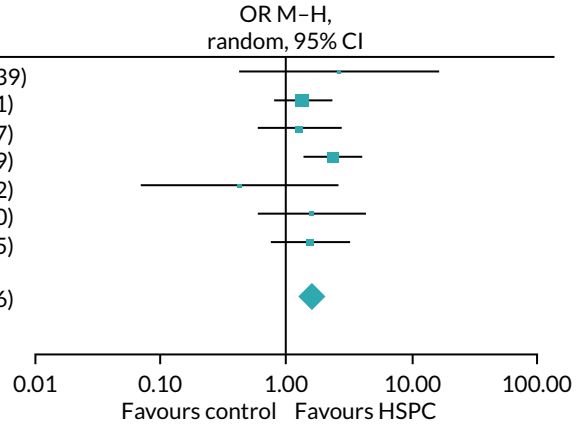

FIGURE 19 Effect of HSPC on achieving preferred place of death. df, degrees of freedom; M–H, Mantel–Haenszel; random, random-effects model.

Ten studies reported on deaths in the HSPC and control groups without presenting survival time, and they found no between-group difference in the number of deaths.[70,77,81,84,93,118,139,147,160,165] Sidebottom *et al.*[96] found no association between study group assignment and death within 6 months, after adjustment for age, sex and marital status (HR 1.90, 95% CI 0.88 to 4.09; $p = 0.101$). Sidebottom *et al.*[96] reported 14 deaths (12.1%) in the HSPC group and five deaths (4.3%) in the control group.

In 11 studies, it was unclear if there was any significant difference in mortality because the *p*-values were not presented.[48,72,74–76,79,85,97,126,161,167] McWhinney *et al.*[79] presented the total number of deaths at 1 month only [$n = 36$ (24.7%)], but did not report the numbers in the HSPC and control groups.

In the studies that reported survival time, there was no significant difference between HSPC and usual care on survival.[73,82,88,89,116,123,129,148,156,168] In Bakitas *et al.*,[129] the median survival time was 14 months (95% CI 10.6 to 18.4 months) in the HSPC group and 8.5 months (95% CI 7 to 11.1 months) in the control group, with a *p*-value of 0.14. There were 112 deaths (69.6%) in the HSPC group and 119 deaths (73.9%) in the control group. The Cox proportional hazards model estimate demonstrated a reduced relative risk of death (HR 0.67, 95% CI 0.496 to 0.906; $p = 0.009$) in the HSPC group during the first year of the study and a greater relative risk after 1 year (HR 1.56, 95% CI 0.908 to 2.655). In Bakitas *et al.*,[73] a fast-track RCT in which the intervention group was offered HSPC immediately, whereas the control group received HSPC after 3 months, the median survival time by the end of data collection in the intervention group was 18.3 months, and it was 11.8 months in the control group, which began HSPC 3 months later. Kaplan–Meier curves illustrate a 15% difference in survival at 1 year (HSPC, 63% vs. control, 48%; $p = 0.038$). However, the overall log-rank test *p*-value was 0.18, suggesting a convergence in overall survival after 12 months. At 1 year, there were 109 deaths (52.7%), but numbers in intervention and control groups were not stated. Carson *et al.*[82] reported a median survival time of 19 days (95% CI 12 to 37 days) in the HSPC group and 23 days (95% CI 12 to 39 days) in the control group ($p = 0.51$). There was no difference in 90-day survival (HR 0.95, 95% CI 0.65 to 1.38; $p = 0.96$). Post hoc adjustment for baseline activities of daily living and study site did not alter the outcome (HR 1.01, 95% CI 0.69 to 1.47; $p = 0.96$). In Grudzen *et al.*,[89] the median survival time was 289 days (95% CI 128 to 453 days) in the HSPC group and 132 days (95% CI 80 to 302 days) in the control group, with a *p*-value of 0.2. At 1 year, 41 participants (59.4%) had died in the HSPC group and 44 (65.7%) had died in the control group. However, there was no difference between the groups ($p = 0.20$). Janssens *et al.*[123] was not clear about whether they were reporting mean or median survival. Survival was 454 days (95% CI 382 to 525 days) in the HSPC group and 425 days (95% CI 339 to 509 days) in the control group (log-rank test, *p*-value of 0.91). In the follow-up period in Janssens *et al.*,[123] there were four deaths (15.4%) in the HSPC group and four deaths (17.4%) in the control group. Kane *et al.*[156] reported no difference in survival time between the HSPC and control groups, as the survival curves were similar. In Gade *et al.*,[88] the median survival was 30 days [interquartile range (IQR) 6–104 days] in the HSPC group and 36 days (IQR 13–106 days) in control group ($p = 0.08$). There were 173 deaths (63%) in the HSPC group and 132 deaths (56%) in control group during the study period. Groenvold *et al.*[148] reported that survival time did not differ between the HSPC and control groups. The median survival time was 323 days in the HSPC group and 364 days in the control group ($p = 0.16$, but in the adjusted analysis $p = 0.39$). There were 25 deaths (27%) in the HSPC group and 22 deaths (23%) in the control group. Woo *et al.*[116] reported that there was no difference in survival between the HSPC and usual-care groups, but did not present any data. Vanbutsele *et al.*[168] found the median survival time to be 312 days (95% CI 190 to 434 days) in the HSPC group and 343 days (95% CI 253 to 433 days) in the control group ($p = 0.97$). Sidebottom *et al.*[96] reported no association between study group assignment and death within 6 months after adjusting for age, sex and marital status ($p = 0.10$).

Two studies[35,78] found significantly longer survival in the HSPC group than in the usual-care group. Higginson *et al.*[78] was a fast-track RCT in which the intervention group received HSPC immediately, whereas those in control group were offered HSPC after 6 weeks. Survival was calculated from the time of randomisation to the time of death, if death occurred during the study period, or to

the time of censoring. The median survival time from randomisation to the time of censoring was 745 days (range 338–1075) days in the intervention group and 711 days (range 345–1045 days) in the control group, which received HSPC after 6 weeks ($p = 0.048$). In a subgroup analysis, this pattern was not recorded for patients with cancer ($p = 0.97$), but it became more marked for patients with diseases other than cancer ($p = 0.01$). Temel *et al.*[35] reported that median survival time was 11.6 months (95% CI 6.4 to 16.9 months) in the HSPC group and 8.9 months (95% CI 6.3 to 11.4 months) in the control group (log rank $p = 0.02$). After adjustment for age, sex and baseline Eastern Cooperative Oncology Group performance status, the group assignment remained a predictor of survival (HR for death in the standard care group 1.70, 95% CI 1.14 to 2.54; $p = 0.01$).

On the other hand, Brumley *et al.*[142] and Tattersall *et al.*[106] reported greater survival in the control group than in the HSPC group. Brumley *et al.*[142] reported a mean survival of 242 days (SD 200 days) in the control group, compared with 196 days (SD 164 days) in the HSPC group ($p = 0.03$). However, results of the Kaplan–Meier survival analysis did not show differences in survival time between study groups ($p = 0.08$). The authors also highlighted 75% death among participants, but the percentages in the HSPC and control groups were not stated. In Tattersall *et al.*,[106] there were 39 (65%) deaths in the HSPC group and 31 (51.7%) in control group at 12 months. Tattersall *et al.*[106] found the median survival time in the HSPC group to be 7 months (95% CI 5.2 to 9.8 months), compared with 11.7 months (95% CI 9.8 to 18.8 months) in control group (log rank $p = 0.014$). The estimated HR was 1.6 (95% CI 1.1 to 2.3; $p = 0.015$). This estimate changed to 1.5 (95% CI 0.99 to 2.2; $p = 0.06$) when adjusted for the oncologist's baseline estimate of likely survival, diagnosis, months since diagnosis and sex.

Quality of the evidence

In the GRADE approach, we downgraded the quality of the evidence for mortality/survival to very low because of a high risk of bias across studies (–2 levels as a result of very serious study limitations: high risk of bias for selection, performance, detection, attrition, reporting and other biases) and inconsistency (–1 level because of variability in study findings).

Pain

We pooled data from four studies that reported adjusted end-point values as our main meta-analysis and found no significant difference between HSPC and usual care (four studies, 525 participants, SMD –0.16, 95% CI –0.33 to 0.01; $I^2 = 0\%$) (*Figure 20*). Positive SMDs indicate more pain; negative SMDs indicate less pain (benefit).

We carried out sensitivity analyses with studies that reported adjusted change values and unadjusted change values. Only Woo *et al.*[116] presented unadjusted end-point values and they found no difference in mean pain scores on the Brief Pain Inventory (BPI) between the HSPC and usual-care groups ($p = 0.22$).

A sensitivity analysis using adjusted change values showed a significant improvement in pain with HSPC (two studies, 218 participants, SMD –0.47, 95% CI –0.74 to –0.20, $I^2 = 0\%$) (*Figure 21*).

When we pooled unadjusted change values, we found no significant difference between HSPC and usual care (two studies, 291 participants, SMD –0.93, 95% CI –3.05 to 1.19; $I^2 = 97\%$) (*Figure 22*).

In the protocol,[46] we had initially specified that we would treat pain as a binary outcome. However, this was not possible because most studies presented pain as a continuous outcome. Studies such as Tattersall *et al.*[106] reported on the percentage of patients with pain, whereas Lowther *et al.*[97] presented pain data as median values. Kane *et al.*[156] reported that there was no difference in pain between the intervention and control groups over time, but did not present data. Furthermore, McWhinney *et al.*[79] stated that there were 'no clinically or statistically significant differences' between the intervention and control groups, but did not report their data.

Study or subgroup	HSPC Mean	HSPC SD	HSPC Total	Control Mean	Control SD	Control Total	Weight (%)	SMD IV, random, 95% CI
Groenvold 2017[148]	31.4	30	130	35	30.8	137	51.1	−0.12 (−0.36 to 0.12)
O'Riordan 2019[161]	2.5	4.2	16	2.2	3.7	14	5.7	0.07 (−0.64 to 0.79)
Rodin 2020[163]	2.23	12.48	22	9.66	9.35	20	7.6	−0.66 (−1.28 to −0.03)
Vanbutsele 2018[168]	23.18	31.82	92	28.19	32.81	94	35.6	−0.15 (−0.44 to 0.13)
Total number of participants (95% CI)			260			265	100.0%	−0.16 (−0.33 to 0.01)

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.96$, df = 3 ($p = 0.40$); $I^2 = 0\%$
Test for overall effect: $z = 1.84$ ($p = 0.07$)

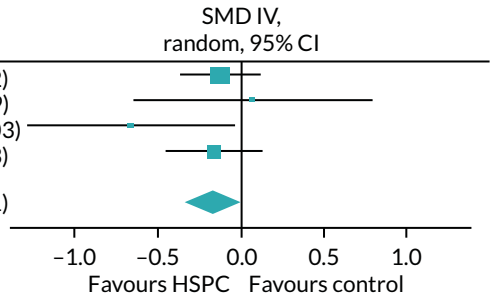

FIGURE 20 Effect of HSPC on pain: adjusted end-point values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

Study or subgroup	HSPC Mean	HSPC SD	HSPC Total	Control Mean	Control SD	Control Total	Weight (%)	SMD IV, random, 95% CI
Higginson 2009[77]	−0.46	1.29	26	0.3	1.11	25	22.9	−0.62 (−1.18 to −0.06)
Sidebottom 2015[96]	−0.93	1.02	79	−0.49	1.02	88	77.1	−0.43 (−0.74 to −0.12)
Total number of participants (95% CI)			105			113	100.0%	−0.47 (−0.74 to −0.20)

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.34$, df = 1 ($p = 0.56$); $I^2 = 0\%$
Test for overall effect: $z = 3.44$ ($p = 0.0006$)

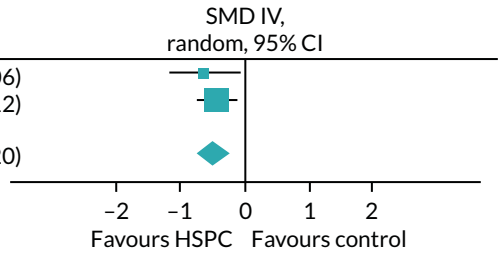

FIGURE 21 Effect of HSPC on pain: adjusted change values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

Study or subgroup	HSPC Mean	HSPC SD	HSPC Total	Control Mean	Control SD	Control Total	Weight (%)	SMD IV, random, 95% CI
Bekelman 2018[139]	−0.5	2.44	123	−0.8	2.44	124	51.4	0.12 (−0.13 to 0.37)
Ozcelik 2014[95]	−4.2	1.3	22	−1.7	1.1	22	48.6	−2.04 (−2.78 to −1.30)
Total number of participants (95% CI)			145			146	100.0%	−0.93 (−3.05 to 1.19)

Heterogeneity: $\tau^2 = 2.26$; $\chi^2 = 29.38$, df = 1 ($p < 0.00001$); $I^2 = 97\%$
Test for overall effect: $z = 0.86$ ($p = 0.39$)

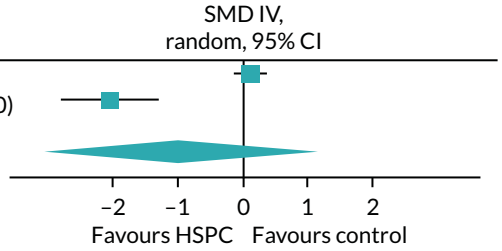

FIGURE 22 Effect of HSPC on pain: unadjusted change values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

The remaining 30 studies did not report on pain. We combined different scales assessing pain by calculating SMDs. Across the studies in these meta-analyses, we combined different measures for assessing pain [the Pain, Enjoyment of Life and General Activity (PEG) scale, derived from the BPI, in Bekelman *et al.*;[139] pain item of the EORTC QLQ-C30 in Groenvold *et al.*[148] and Vanbutsele *et al.*;[168] pain item of the POS in Higginson *et al.*;[77] pain severity on the BPI in O'Riordan *et al.*,[161] Rodin *et al.*[163] and Woo *et al.*;[116] and pain item of the ESAS in Ozcelik *et al.*[95] and Sidebottom *et al.*[96]].

Given that there were fewer than 10 included studies in the main meta-analysis on pain using adjusted end-point values, we did not use funnel plots or carry out tests for funnel plot asymmetry. In addition, we could not carry out subgroup analysis because of a lack of heterogeneity ($I^2 = 0\%$) in the main meta-analysis with adjusted end-point values.

Quality of the evidence

In the GRADE approach, we downgraded the quality of the evidence for pain to very low because of a high risk of bias across studies (–2 levels as a result of very serious study limitations: high risk of bias for performance, attrition and other bias) and inconsistency (–1 level because of differences between the main meta-analysis and sensitivity analyses) (see *Table 2*).

Patient anxiety

We pooled data from five studies that reported adjusted end-point values as the main meta-analysis and found no significant difference between HSPC and usual care [five studies, 384 participants, mean difference (MD) –0.63, 95% CI –2.22 to 0.96; $I^2 = 76\%$] (*Figure 23*). All five studies assessed anxiety using the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS), the Hospital Anxiety and Depression Scale-Anxiety (HADS-A) (seven items; 0–21 scale, 21 = maximum distress). Negative MD indicates benefit (lower levels of patient anxiety) and positive MD reflects harm (higher levels of patient anxiety).

We carried out sensitivity analyses with studies that presented unadjusted end-point values and unadjusted change values, and also assessed the impact of using an estimate of 0.02 in adjusting for clustering in the cluster RCT by McCorkle *et al.*[48] Only Sidebottom *et al.*[96] (167 participants) reported adjusted change values; they found that anxiety scores improved by a mean of 1.27 points in the HSPC group and by 0.89 points in the control group on the anxiety subscale of the ESAS (using a visual scale line, 0–10, 10 = worst possible) at 3 months (difference 0.38; $p = 0.017$) after adjusting for age, sex and marital status differences between trial groups. This difference was already evident at 1 month ($p = 0.007$).

When we removed McCorkle *et al.*[48] in the sensitivity analysis with adjusted end-point values, we found significant improvement in patient anxiety with HSPC (four studies, 320 participants, MD –1.60, 95% CI –2.56 to –0.65; $I^2 = 17\%$) (*Figure 24*).

A sensitivity analysis with unadjusted end-point values showed no significant difference between HSPC and usual care (four studies, 273 participants, MD –0.90, 95% CI –2.52 to 0.71; $I^2 = 67\%$) (*Figure 25*). All the studies measured anxiety using the HADS-A.

When we removed McCorkle *et al.*,[48] the MD was –1.48 (three studies, 209 participants, 95% CI –3.52 to 0.56; $I^2 = 71\%$) (*Figure 26*).

Studies that presented unadjusted change values showed an effect in favour of HSPC (four studies, 496 participants, SMD –0.62, 95% CI –1.02 to –0.21; $I^2 = 74\%$) (*Figure 27*).

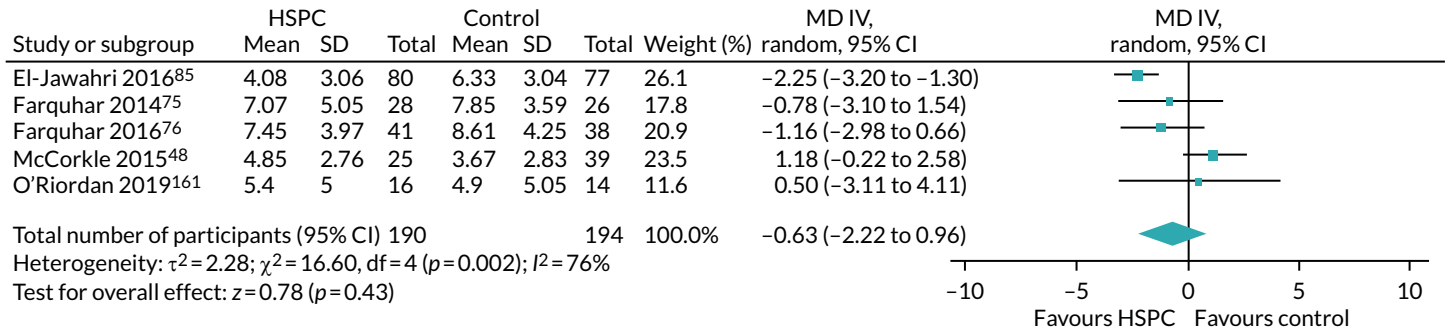

FIGURE 23 Effect of HSPC on patient anxiety: adjusted end-point values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

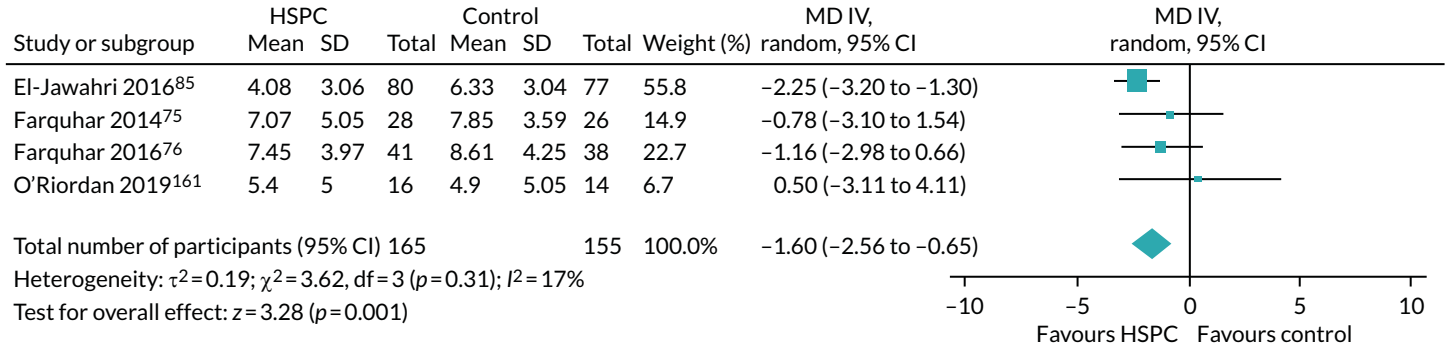

FIGURE 24 Effect of HSPC on patient anxiety: adjusted end-point values (excluding McCorkle *et al.*[48]). df, degrees of freedom; IV, inverse variance; random, random-effects model.

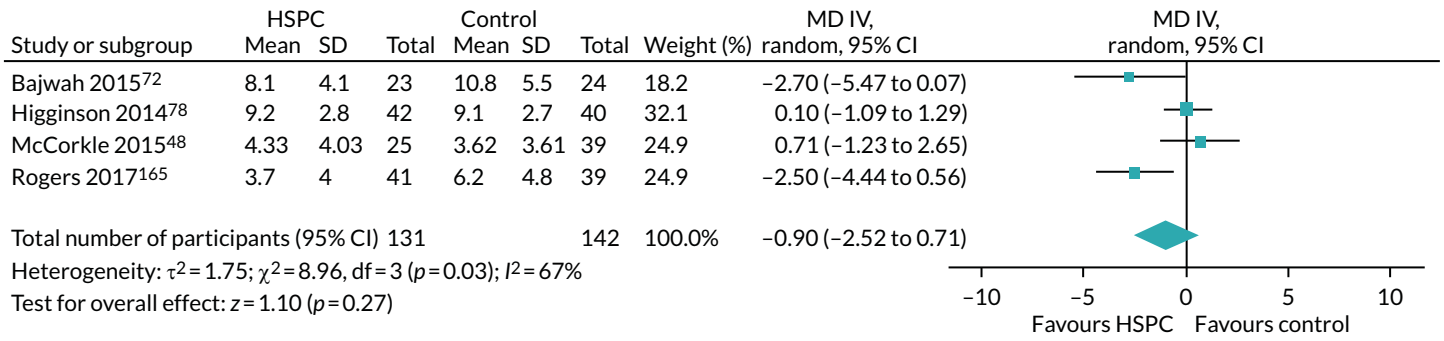

FIGURE 25 Effect of HSPC on patient anxiety: unadjusted end-point values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

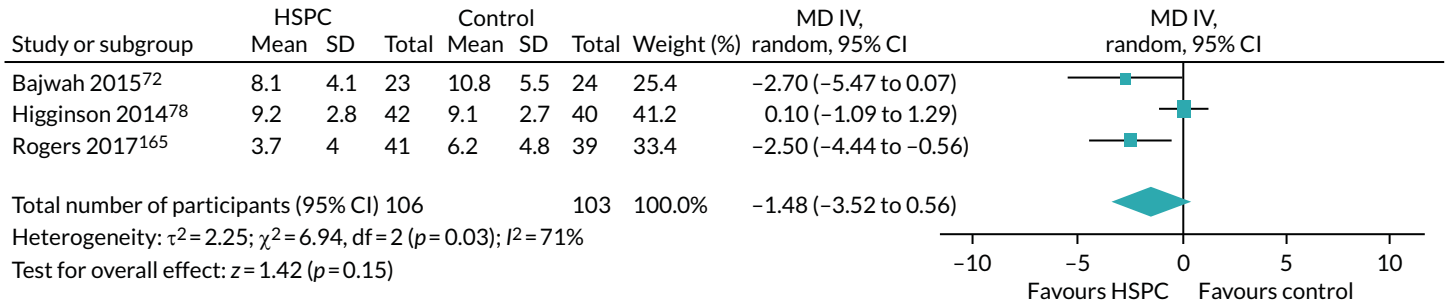

FIGURE 26 Effect of HSPC on patient anxiety: unadjusted end-point values (excluding McCorkle *et al.*[48]). df, degrees of freedom; IV, inverse variance; random, random-effects model.

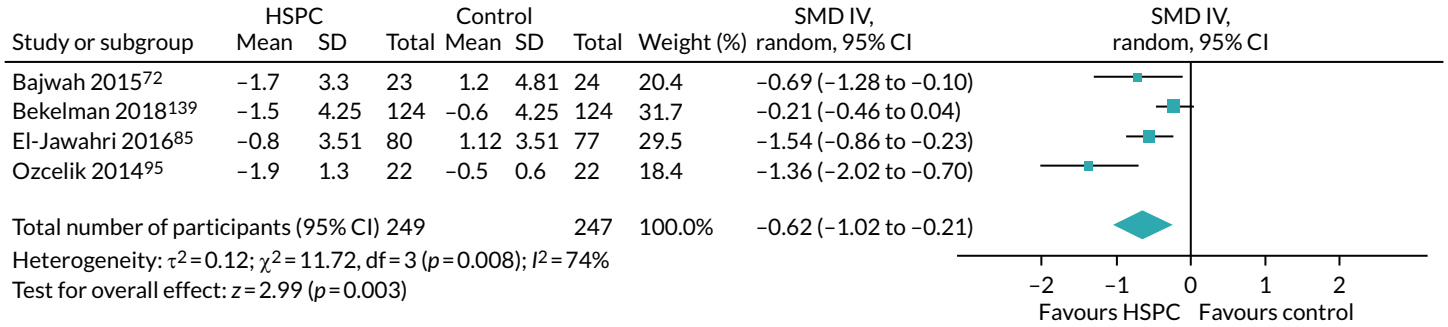

FIGURE 27 Effect of HSPC on patient anxiety: unadjusted change values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

Standardised MD was used in pooling the estimates because the four studies that reported unadjusted change values used different scales for measuring anxiety: Bajwah *et al.*[72] and El-Jawahri *et al.*[85] used the HADS-A, Bekelman *et al.*[139] used the Generalised Anxiety Disorder-7 and Ozcelik *et al.*[95] used the anxiety subscale of the ESAS.

Five studies also assessed patient anxiety, but we could not include them in the meta-analysis for a number of reasons: Kane *et al.*[156] stated the *p*-values for the difference between the intervention and control groups only; Temel *et al.*[35] presented the percentage of patients with anxiety at the primary point of analysis only; Temel *et al.*[167] did not provide data, but stated that scores did not differ between the intervention and control groups at 12 or 24 weeks; Solari *et al.*[126] reported no difference between groups for change at 3 or 6 months, but did not present usable data; and Vanbutsele *et al.*[168] presented ORs at 12, 18 and 24 weeks. This study[168] did not find any difference between groups at these different time points.

The remaining 26 studies did not report on patient anxiety. Given that there were fewer than 10 included studies in the main meta-analysis on patient anxiety using adjusted end-point values, we did not use funnel plots or carry out tests for funnel plot asymmetry.

Subgroup analysis on patient anxiety

We carried out the following subgroup analyses on patient anxiety with studies that reported adjusted end-point values.

Effect of hospital-based specialist palliative care on patient anxiety in different populations

Among studies that reported adjusted end-point values, we assessed the effect of HSPC on patient anxiety in different populations. Three studies[48,75,85] with 275 participants were with cancer populations, and two[76,161] were with non-cancer populations (109 participants). Subgrouping according to patient population explained heterogeneity in the non-cancer population subgroup ($I^2 = 0\%$), but not the cancer population subgroup ($I^2 = 87\%$) (*Figure 28*). There was no evidence of a subgroup effect ($p = 0.90$; $I^2 = 0\%$).

This finding may be spurious because of the small number of studies and participants in the subgroups. When McCorkle *et al.*[48] was excluded from the cancer population subgroup, heterogeneity (I^2) reduced to 24% (*Figure 29*). No subgroup difference was observed ($p = 0.29$; $I^2 = 10\%$).

Effect of different models of hospital-based specialist palliative care on patient anxiety

Four studies[48,75,76,161] (227 participants) that involved service provision across multiple settings, and one study by El-Jawahri *et al.*[85] with an inpatient consult model (157 participants), reported adjusted end-point values. We could not carry out subgroup analysis because of the limited number of studies in the inpatient consult model subgroup.

Effect of 24 hours' access (out-of-hours care) on patient anxiety

None of the studies had provision for 24 hours' access.

Effect of early palliative care versus late palliative care on patient anxiety: adjusted end-point values

Among studies that reported adjusted end-point data, two studies[48,85] with 221 participants provided HSPC early, and three studies[75,76,161] with 163 participants provided HSPC late. Subgrouping explained heterogeneity in the late palliative care subgroup only ($I^2 = 0\%$), not the early palliative care subgroup ($I^2 = 94\%$) (*Figure 30*). There was no evidence of a subgroup effect ($p = 0.90$; $I^2 = 0\%$).

When McCorkle *et al.*[48] was removed from the early palliative care subgroup, only El-Jawahri *et al.*[85] was remaining in the subgroup, so we could not carry out any further analysis.

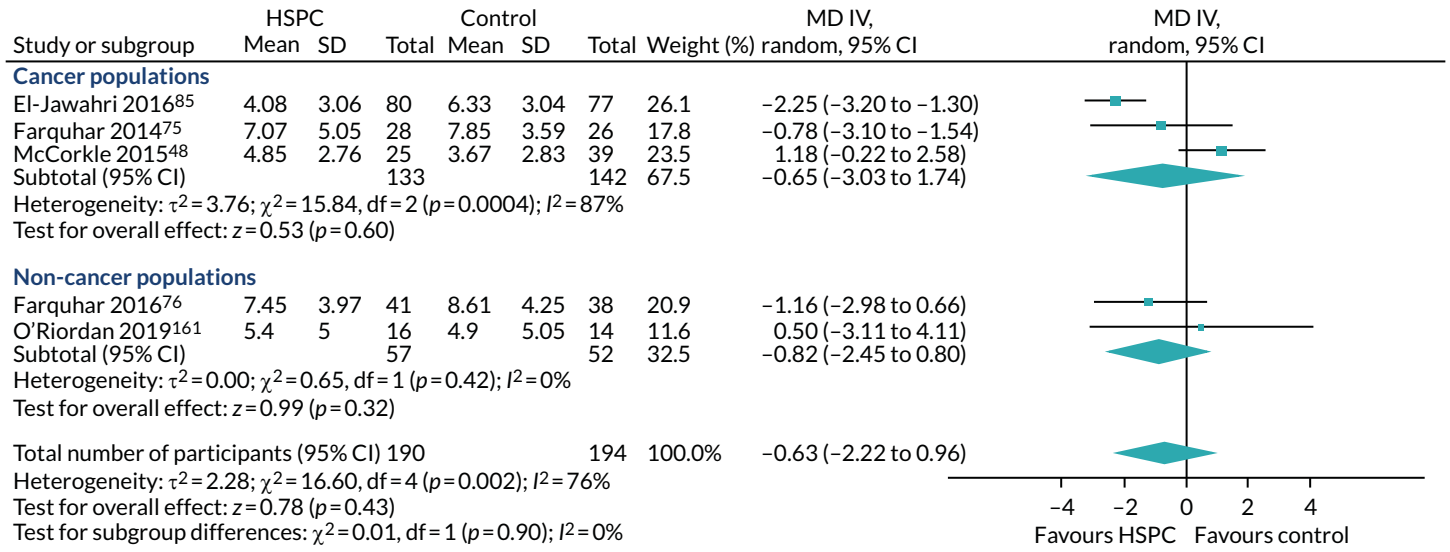

FIGURE 28 Effect of HSPC on patient anxiety in different populations: adjusted end-point values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

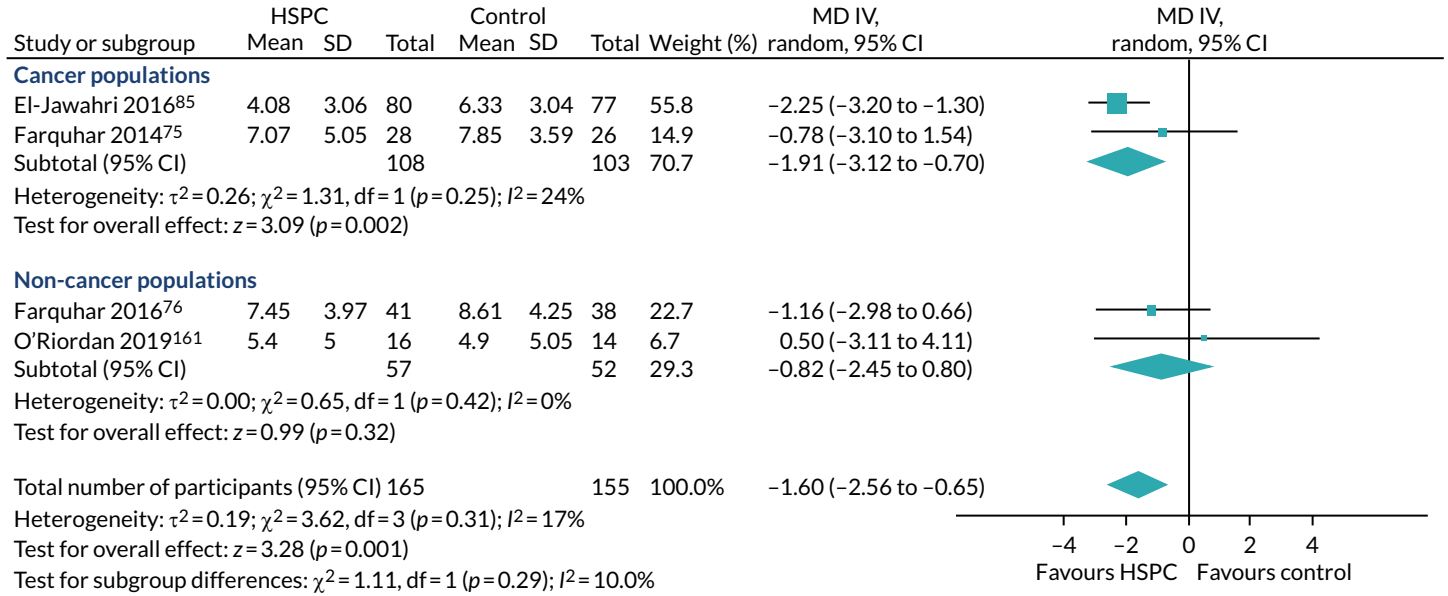

FIGURE 29 Effect of HSPC on patient anxiety in different populations: adjusted end-point values (excluding McCorkle *et al.*[48]). df, degrees of freedom; IV, inverse variance; random, random-effects model.

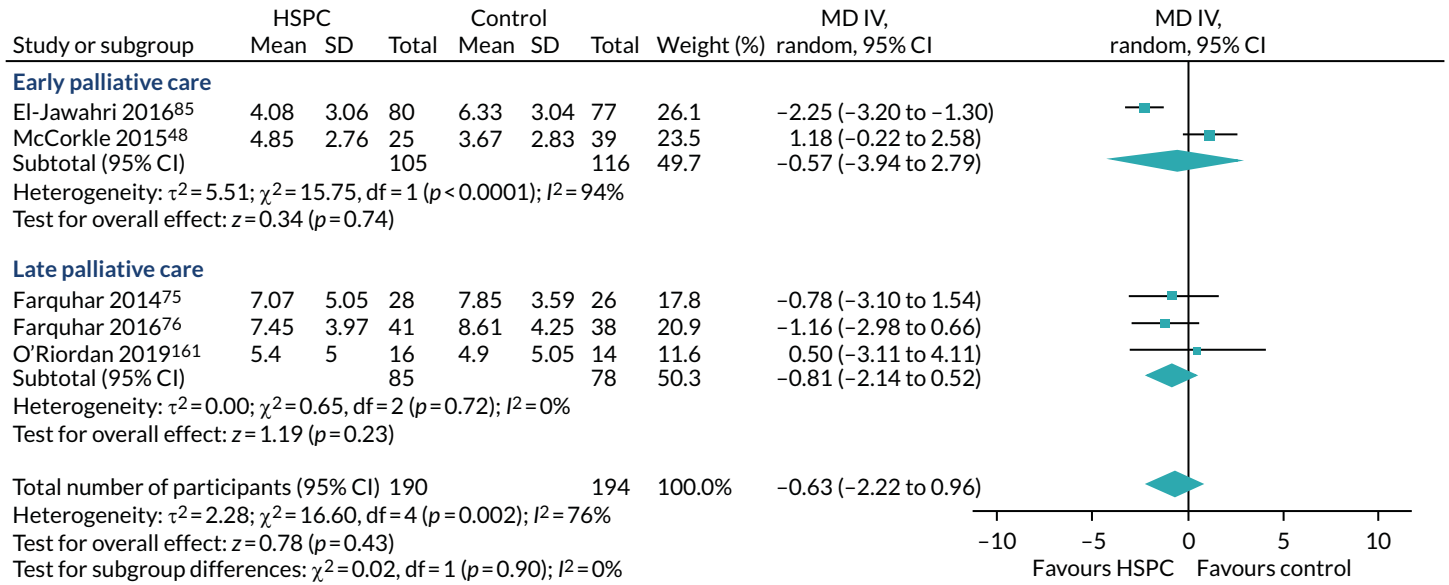

FIGURE 30 Effect of early palliative care vs. late palliative care on patient anxiety: adjusted end-point values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

Effect of nurse-led versus multidisciplinary team-led services on patient anxiety

All five studies (384 participants) that reported adjusted end-point values were MDT-led services, with a pooled MD of −0.63 between HSPC and usual care (95% CI −2.22 to 0.96; $I^2 = 76\%$) (*Figure 31*).

After removal of McCorkle *et al.*,[48] there was evidence in favour of HSPC, when compared with usual care (four studies, 320 participants, MD −1.60, 95% CI −2.56 to −0.65; $I^2 = 17\%$) (*Figure 32*).

Effect of hospital-based specialist palliative care on patient anxiety in different countries

Among studies that reported adjusted end-point values, three[48,85,161] (251 participants) were carried out in USA, and two[75,76] (133 participants) were carried out in the UK. Subgrouping by country only explained heterogeneity in the UK studies ($I^2 = 0\%$), but not in the US studies ($I^2 = 88\%$) (*Figure 33*). A subgroup analysis showed no difference between the two countries ($p = 0.66$; $I^2 = 0\%$).

This subgroup analysis is unlikely to detect a subgroup difference because of the small number of studies and participants in the subgroups. When the McCorkle *et al.*[48] study was removed from the US subgroup, I^2 was 52% in the subgroup, and there was no evidence of a subgroup effect or heterogeneity ($p = 0.77$; $I^2 = 0\%$) (*Figure 34*).

Quality of the evidence

In the GRADE approach, we downgraded the quality of the evidence for patient anxiety to very low because of a high risk of bias across studies (−2 levels as a result of very serious study limitations: high risk of bias for selection, performance, detection, attrition and reporting) and inconsistency (−1 level as a result of unexplained heterogeneity).

Caregiver anxiety

The Carson *et al.*[82] study (312 participants) was the only study that presented adjusted end-point values. Carson *et al.*[82] assessed caregiver anxiety using the HADS-A (seven items; 0–21 scale, 21 = maximum distress). Carson *et al.*[82] reported higher mean levels of caregiver anxiety in the HSPC group than in the control group at 3 months on adjusting for baseline and multiple respondents: mean 7.2 (95% CI 6.6 to 7.9) vs. 6.4 (95% CI 5.7 to 7.1) in the HSPC and control groups, respectively; the MD was 0.8 (95% CI −0.1 to 1.8; $p = 0.09$). Adjustments for three variables (baseline, multiple respondents and study sites) and six variables (baseline, multiple respondents, study sites, race, sex and primary/additional surrogate) also produced similar results, with *p*-values of 0.11 and 0.12, respectively.

Two studies[72,82] with 351 participants reported unadjusted end-point data with a pooled estimate of MD of −0.71 (95% CI −4.27 to 2.85; $I^2 = 77\%$) (*Figure 35*). Both studies used the HADS-A in assessing caregiver anxiety. Negative MDs indicate benefit (lower levels of caregiver anxiety) and positive MDs reflect harm (higher levels of caregiver anxiety).

Four studies recorded this outcome, but did not present analysable data.[75,76,85,156] El-Jawahri *et al.*[85] and Farquhar *et al.*[76] did not present the numbers of participants in the intervention and control groups at the primary point of analysis. Farquhar *et al.*[75] reported that there was little change in carer outcomes, but did not present data, and Kane *et al.*[156] found differences in favour of HSPC in three of the five cohorts examined, but did not present usable data.

The remaining 37 studies did not report on caregiver anxiety. Given that we had only one study that presented adjusted end-point values, we could not carry out any further analysis.

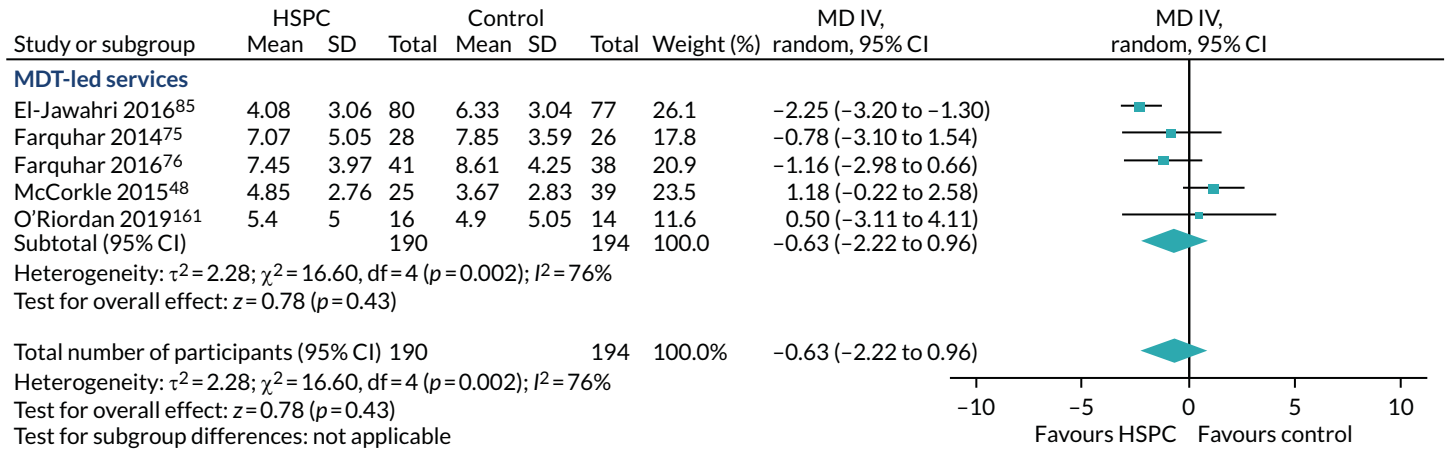

FIGURE 31 Effect of MDT-led services on patient anxiety: adjusted end-point values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

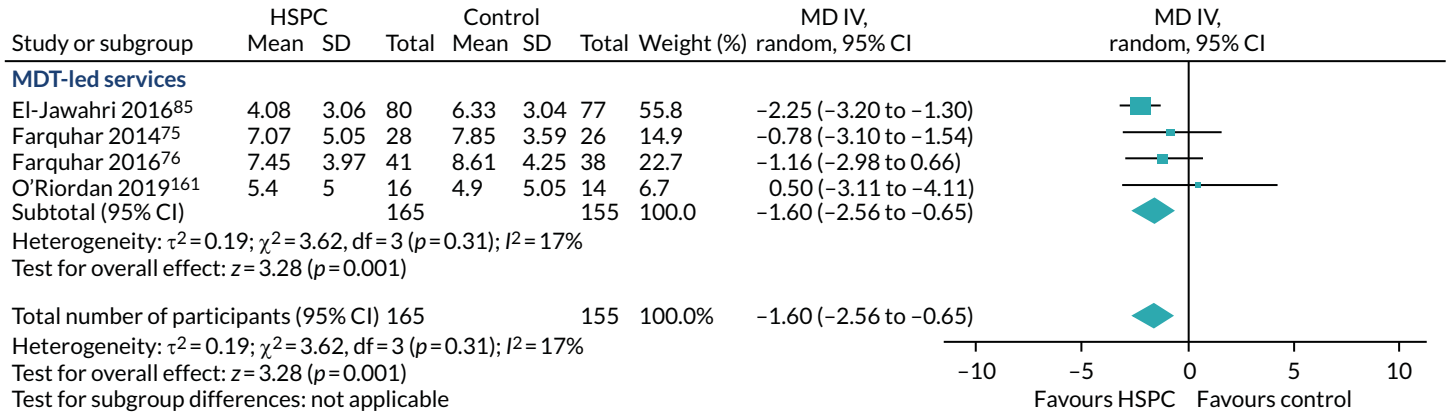

FIGURE 32 Effect of MDT-led services on patient anxiety: adjusted end-point values (excluding McCorkle *et al.*[48]). df, degrees of freedom; IV, inverse variance; random, random-effects model.

Study or subgroup	HSPC Mean	HSPC SD	HSPC Total	Control Mean	Control SD	Control Total	Weight (%)	MD IV, random, 95% CI
Studies from the USA								
El-Jawahri 2016[85]	4.08	3.06	80	6.33	3.04	77	26.1	−2.25 (−3.20 to −1.30)
McCorkle 2015[48]	4.85	2.76	25	3.67	2.83	39	23.5	1.18 (−0.22 to 2.58)
O'Riordan 2019[161]	5.4	5	16	4.9	5.05	14	11.6	0.50 (−3.11 to 4.11)
Subtotal (95% CI)			121			130	61.3	−0.32 (−3.04 to 2.39)
Heterogeneity: $\tau^2 = 4.66$; $\chi^2 = 16.53$, df = 2 ($p = 0.0003$); $I^2 = 88\%$								
Test for overall effect: $z = 0.23$ ($p = 0.81$)								
Studies from the UK								
Farquhar 2014[75]	7.07	5.05	28	7.85	3.59	26	17.8	−0.78 (−3.10 to 1.54)
Farquhar 2016[76]	7.45	3.97	41	8.61	4.25	38	20.9	−1.16 (−2.98 to 0.66)
Subtotal (95% CI)			69			64	38.7	−1.02 (−2.45 to 0.42)
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.06$, df = 1 ($p = 0.80$); $I^2 = 0\%$								
Test for overall effect: $z = 1.39$ ($p = 0.16$)								
Total number of participants (95% CI)			190			194	100.0%	−0.63 (−2.22 to 0.96)
Heterogeneity: $\tau^2 = 2.28$; $\chi^2 = 16.60$, df = 4 ($p = 0.002$); $I^2 = 76\%$								
Test for overall effect: $z = 0.78$ ($p = 0.43$)								
Test for subgroup differences: $\chi^2 = 0.20$, df = 1 ($p = 0.66$); $I^2 = 0\%$								

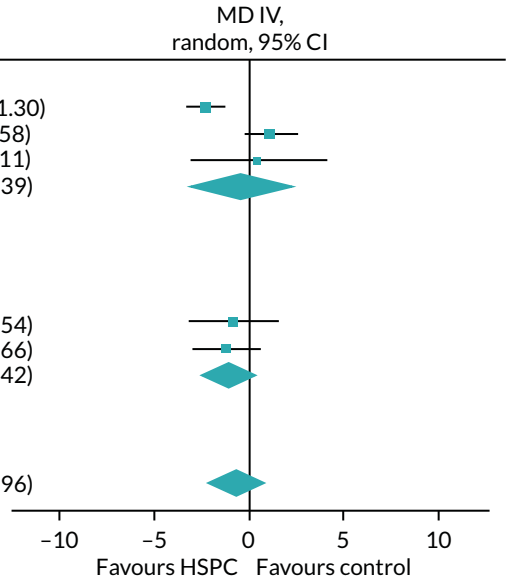

FIGURE 33 Effect of HSPC on patient anxiety in different countries: adjusted end-point values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

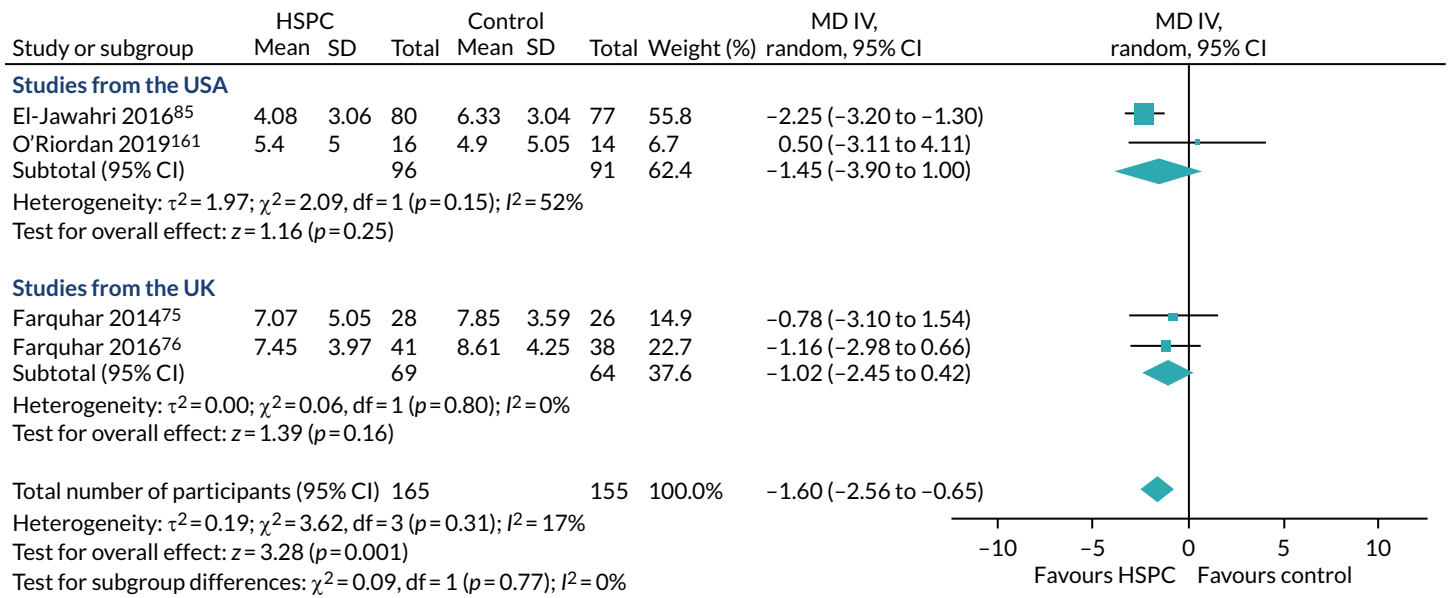

FIGURE 34 Effect of HSPC on patient anxiety in different countries: adjusted end-point values (excluding McCorkle *et al.*[48]). df, degrees of freedom; IV, inverse variance; random, random-effects model.

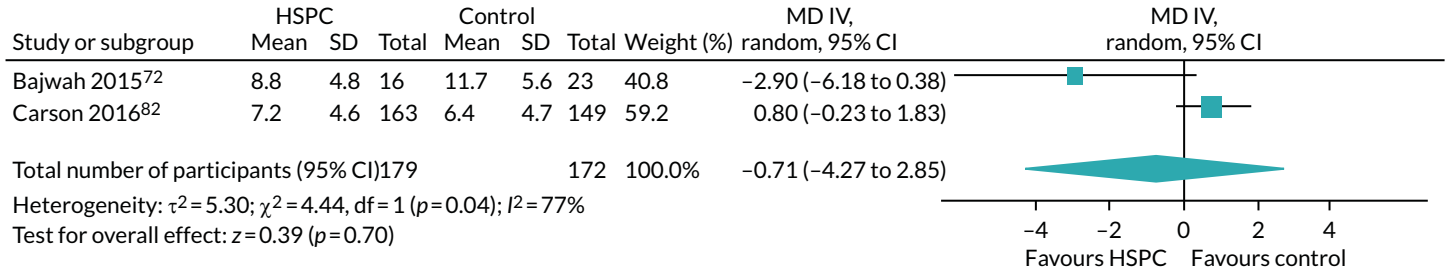

FIGURE 35 Effect of HSPC on caregiver anxiety: unadjusted end-point values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

Quality of the evidence

In the GRADE approach, we downgraded the quality of the evidence for caregiver anxiety to very low because of a high risk of bias (–2 levels as a result of very serious study limitations: high risk of bias for performance, attrition and reporting), and imprecision (–1 level as a result of the small number of participants).

Patient depression

For the main meta-analysis on patient depression, we pooled data from eight studies (1096 participants) that presented adjusted end-point values. The results showed that HSPC led to improvement in depression, compared with usual care (eight studies, 1096 participants, SMD –0.22, 95% CI –0.34 to –0.10; $I^2 = 0\%$) (*Figure 36*). Negative SMDs indicate benefit (lower levels of depression) and positive SMDs reflect higher levels of depression.

We carried out sensitivity analyses with unadjusted end-point values, adjusted change values and unadjusted change values, and also assessed the impact of adjusting for clustering using an ICC of 0.02 in the cluster RCT by McCorkle *et al.*[48]

Five studies (350 participants) presented unadjusted end-point values and found a pooled estimate of SMD of –0.25 (95% CI –0.55 to 0.04; $I^2 = 47\%$) (*Figure 37*).

We carried out a sensitivity analysis to assess the impact of using an estimate of 0.02 in adjusting for clustering in McCorkle *et al.*,[48] and found evidence in favour of HSPC (four studies, 286 participants, SMD –0.34, 95% CI –0.65 to –0.03; $I^2 = 42\%$) (*Figure 38*).

Two studies[48,96] with 231 participants contributed data to the sensitivity analysis using adjusted change values with a pooled estimate of MD –0.32 (95% CI –1.10 to 0.45; $I^2 = 92\%$) (*Figure 39*).

The sensitivity analysis using unadjusted change values showed evidence in favour of HSPC (four studies, 488 participants, SMD –0.38, 95% CI –0.58 to –0.18; $I^2 = 12\%$) (*Figure 40*).

Three studies also presented binary data and were pooled using ORs.[35,85,116] We found evidence of lower odds of patient depression with HSPC than with usual care (three studies, 338 participants, OR 0.38, 95% CI 0.21 to 0.68; $I^2 = 32\%$) (*Figure 41*). The OR of 0.38 translates to a risk ratio of 0.55, implying that the risk of patient depression was 0.55 times lower with HSPC than with usual care.

Four studies assessed patient depression but we excluded them from the main meta-analysis because they did not present analysable data.[126,156,168,170] Kane *et al.*[156] determined that there was no between-group difference between the intervention and control groups, but did not provide the data. Solari *et al.*[126] reported that they found no difference between groups at 3 and 6 months, but did not present analysable data; Vanbutsele *et al.*[168] presented only ORs and their corresponding 95% CIs for the two measures they used in assessing depression [Hospital Anxiety and Depression Scale-Depression (HADS-D) and Patient Health Questionnaire-9 items (PHQ-9)]. There was no difference between the intervention and control groups at 12, 18 and 24 weeks in Vanbutsele *et al.*[168] Wallen *et al.*[170] assessed depression, but did not present data on it at baseline and follow up. The remaining 21 studies did not report on patient depression.

Studies included in the meta-analyses used different scales in assessing depression: Beck Depression Inventory, version 2;[163] depression subscale of the HADS (HADS-D);[72,75,76,78,85,161,165,167] PHQ-9;[48,85,89,96,139,167] depression subscale of the ESAS;[95] and Center for Epidemiologic Studies Depression Scale (CES-D).[73,116,129]

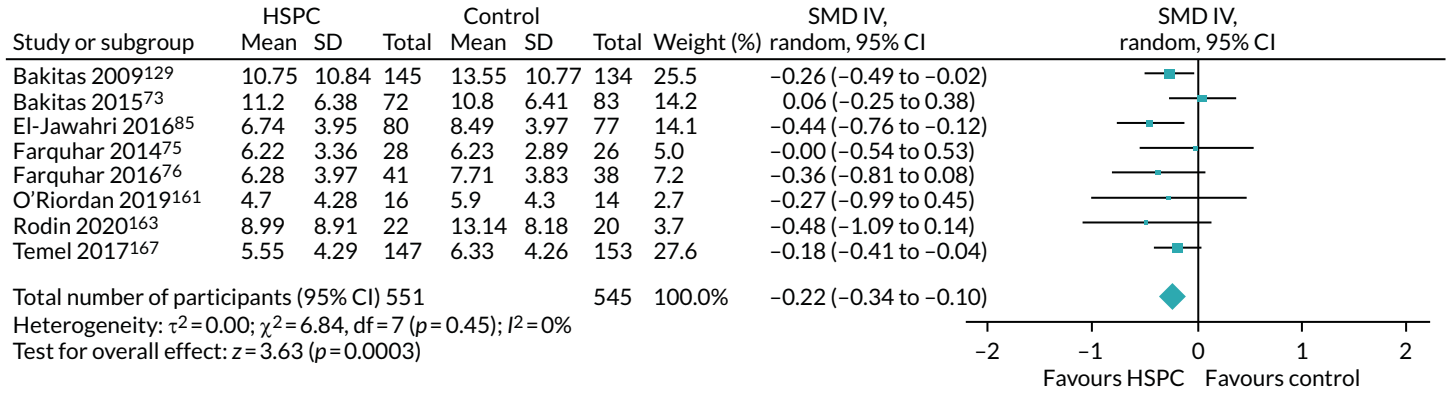

FIGURE 36 Effect of HSPC on patient depression: adjusted end-point values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

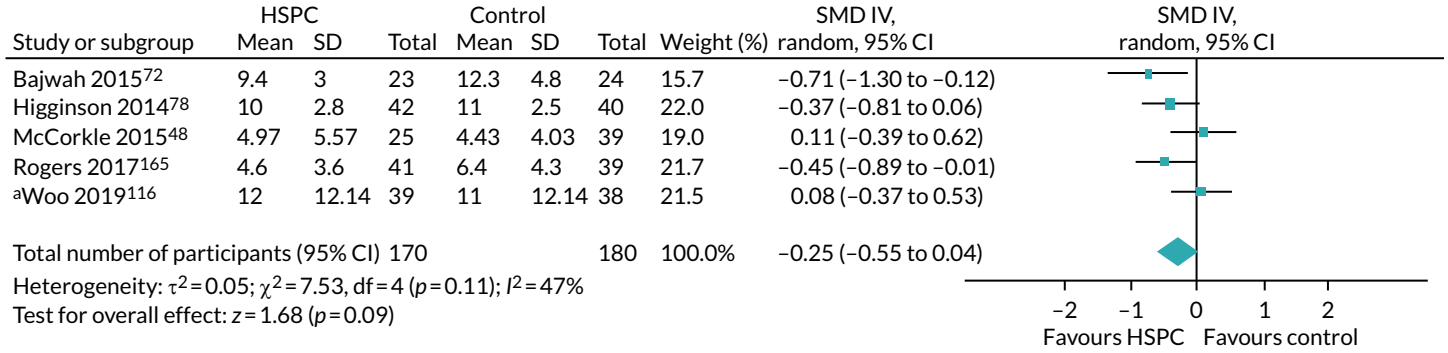

FIGURE 37 Effect of HSPC on patient depression: unadjusted end-point values. a, Data approximated from graph. df, degrees of freedom; IV, inverse variance; random, random-effects model.

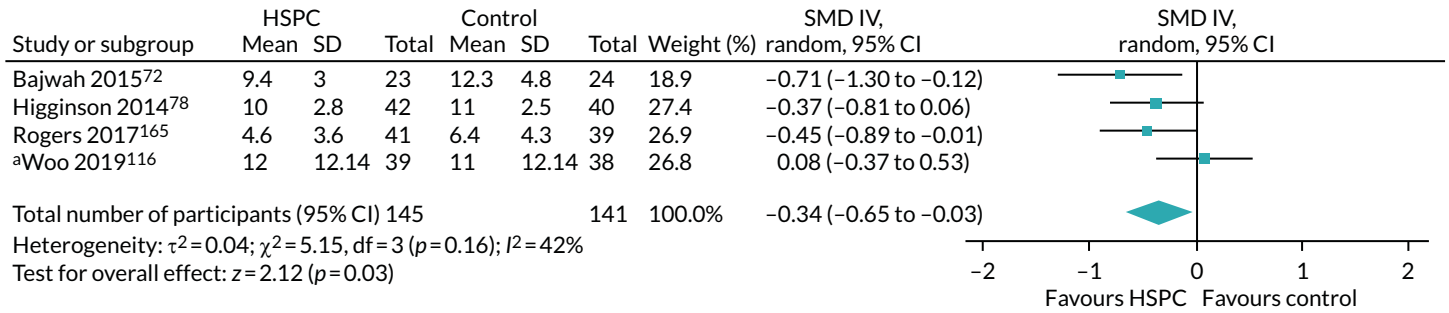

FIGURE 38 Effect of HSPC on patient depression: unadjusted end-point values (excluding McCorkle *et al.*[48]). a, Data approximated from graph. df, degrees of freedom; IV, inverse variance; random, random-effects model.

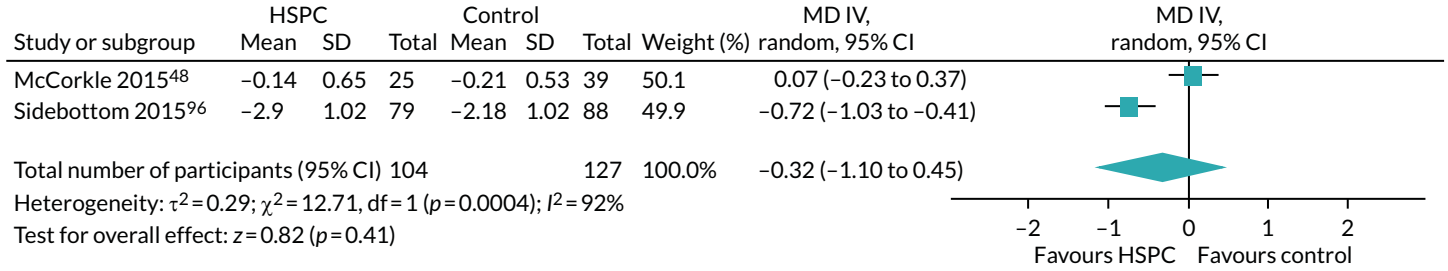

FIGURE 39 Effect of HSPC on patient depression: adjusted change values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

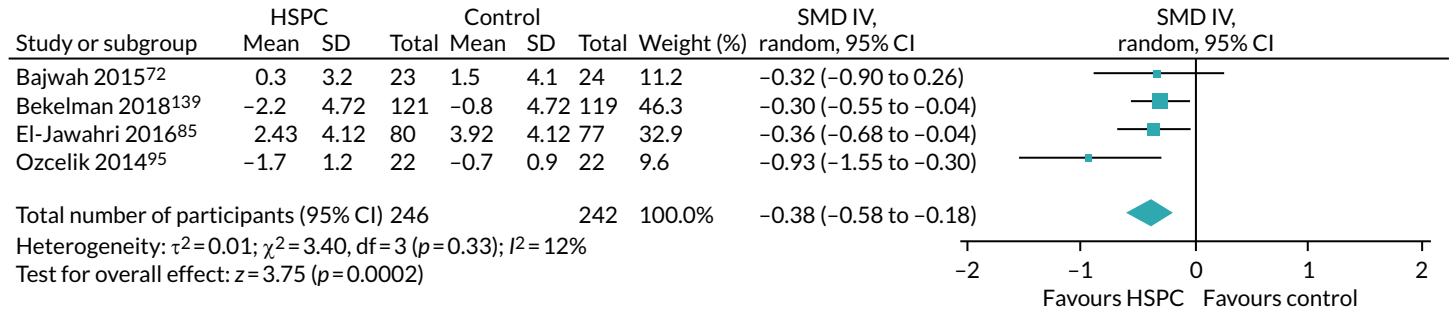

FIGURE 40 Effect of HSPC on patient depression: unadjusted change values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

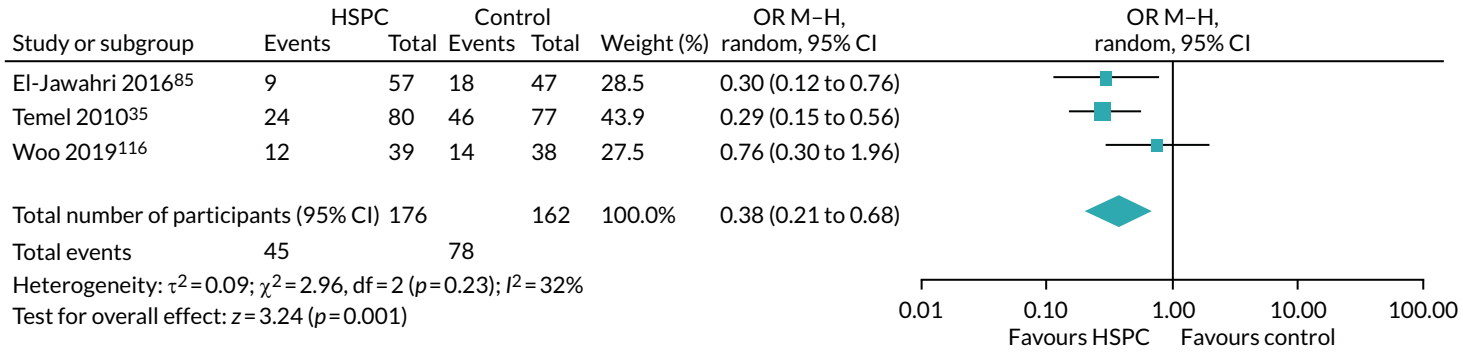

FIGURE 41 Effect of HSPC on patient depression as a binary outcome. M–H, Mantel–Haenszel; random, random-effects model.

Given that there was no heterogeneity in the main meta-analysis ($I^2 = 0\%$), we did not carry out any subgroup analyses. There were fewer than 10 studies that reported adjusted end-point values in the main meta-analysis, and we did not use funnel plots or carry out tests for funnel plot asymmetry.

Quality of the evidence

In the GRADE approach, we downgraded the quality of the evidence for patient depression to very low because of a high risk of bias across studies (–2 levels as a result of very serious study limitations: high risk of bias for selection, performance, detection, attrition and reporting) and inconsistency (–1 level because of differences between the main meta-analysis and sensitivity analyses).

Caregiver depression

As the main meta-analysis on caregiver depression, we pooled data from two studies[82,139] that presented adjusted end-point values. We found that HSPC had little or no effect on caregiver depression (two studies, 413 participants, SMD –0.02, 95% CI –0.21 to 0.18; $I^2 = 0\%$) (*Figure 42*). Negative SMDs indicate benefit (lower levels of depression) and positive SMDs reflect harm (higher levels of depression).

We carried out sensitivity analyses with unadjusted end-point values and found a SMD of –0.29 (three studies, 420 participants, 95% CI –0.70 to 0.12; $I^2 = 63\%$) (*Figure 43*).

Bajwah *et al.*[72] (35 caregiver participants) was the only study that presented unadjusted change values on the HADS-D (seven items; 0–21 scale, 21 = maximum distress). It found a 0.3-point mean decrease in caregiver depression scores from baseline at 4 weeks for the HSPC group, whereas, for controls, caregiver depression increased by 1 point. The effect size at 4 weeks was –0.7 (95% CI –1.3 to 0.0). Between the period when the control group received HSPC (4 weeks) and 8 weeks, mean depression improved in the control group from 9.6 (SD 4.9) to 7.2 (SD 3.9) points.

Four studies reported on caregiver depression, but did not present usable data.[75,76,85,156] In the El-Jawahri *et al.*[85] study, the numbers of participants in the intervention and control groups at the primary point of analysis were not stated. Farquhar *et al.*[75,76] and Kane *et al.*[156] did not present their data. The remaining 34 studies did not report on caregiver depression.

Studies included in the meta-analyses used different scales in assessing caregiver depression: Bajwah *et al.*[72] and Carson *et al.*[82] used the depression subscale of the HADS (HADS-D), Bakitas *et al.*[73] used the CES-D and Bekelman *et al.*[139] used the Patient Health Questionnaire-8 items.

We could not carry out a subgroup analysis because of the lack of heterogeneity in the main meta-analysis ($I^2 = 0\%$). Given that there were fewer than 10 included studies in the meta-analysis on caregiver depression, we did not use funnel plots or carry out tests for funnel plot asymmetry.

Quality of the evidence

In the GRADE approach, we downgraded the quality of evidence for caregiver depression to very low because of a high risk of bias in the two studies that presented adjusted end-point data (–2 levels as a result of very serious study limitations: high risk of bias for performance, attrition and reporting) and imprecision (–1 level as a result of wide 95% CIs around the effect estimates that included both benefit and harm).

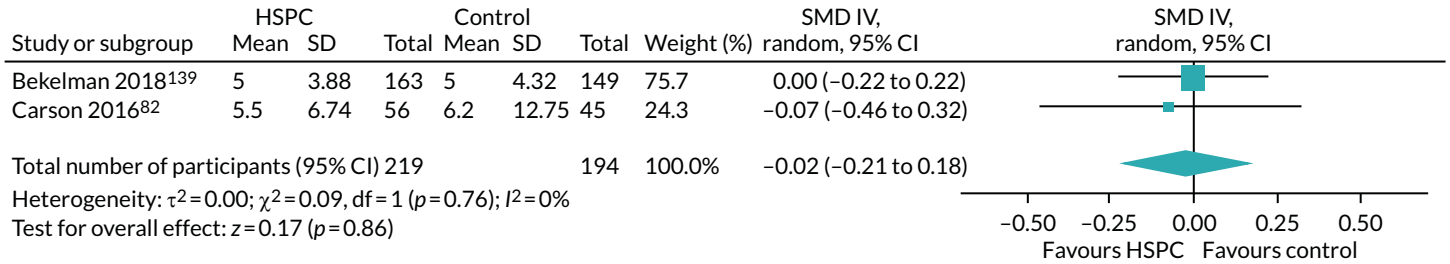

FIGURE 42 Effect of HSPC on caregiver depression: adjusted end-point values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

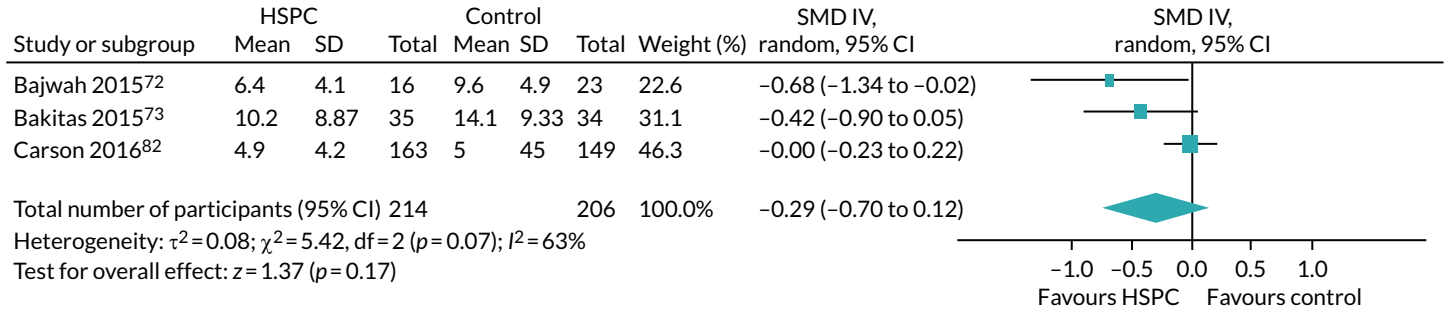

FIGURE 43 Effect of HSPC on caregiver depression: unadjusted end-point values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

Patient breathlessness

We combined data from five studies[75,76,148,161,168] (616 participants) reporting adjusted end-point values for our main meta-analysis on breathlessness, with a pooled estimate of SMD of −0.04 (95% CI −0.19 to 0.12; $I^2 = 0\%$) (*Figure 44*). Negative SMDs indicate benefit (reduced breathlessness) and positive SMDs reflect harm (worsened breathlessness).

The five studies used different instruments and reported on different breathlessness domains. For instance, both Farquhar *et al.*[75,76] studies assessed distress due to breathlessness and breathlessness mastery using a Numeric Rating Scale (NRS) and the mastery domain of the CRQ, respectively; Groenvold *et al.*[148] and Vanbutsele *et al.*[168] assessed breathlessness intensity using the dyspnoea item of the EORTC QLQ-C30; and O'Riordan *et al.*[161] assessed breathlessness intensity using the Borg scale. For both Farquhar *et al.*[75,76] studies, we used only data for distress due to breathlessness assessed with the NRS in the meta-analysis because it was the primary outcome. We did not differentiate between different breathlessness domains in the meta-analysis because of small numbers.

We carried out sensitivity analyses with unadjusted end-point values and unadjusted change values.

A sensitivity analysis carried out with the two studies[72,78] (128 participants) presenting unadjusted end-point values showed a pooled estimate in favour of HSPC (SMD −0.35, 95% CI −0.70 to −0.00; $I^2 = 0\%$) (*Figure 45*).

A sensitivity analysis with the two studies[95,139] (292 participants) that reported unadjusted change values showed a pooled estimate of SMD of −0.47 (95% CI −1.55 to 0.61; $I^2 = 90\%$) (*Figure 46*).

Only Sidebottom *et al.*[96] presented adjusted change values. They assessed breathlessness using the dyspnoea item of the ESAS (using a visual scale line, 0–10, 10 = worst possible), and found that breathlessness scores improved by a mean of 2.8 points in the HSPC group and by 1.7 points in the control group at 3 months (difference 1.08 points; $p < 0.001$) after adjusting for age, sex and marital status differences between trial groups. This difference was evident at 1 month, with a MD of 1.10 points ($p < 0.001$).

A study by Tattersall *et al.*[106] also recorded this outcome, but did not present analysable data. The remaining 31 studies did not report on breathlessness.

Studies included in the meta-analyses used different scales in assessing breathlessness: Dyspnoea-12 questionnaire;[72] Memorial Symptom Assessment Scale;[139] NRS for distress due to breathlessness;[75,76] dyspnoea item of the EORTC QLQ-C30;[148,168] breathlessness mastery domain of the CRQ (CRQ mastery);[78] Borg scale;[161] and dyspnoea item of the ESAS.[95,96]

Owing to lack of heterogeneity ($I^2 = 0\%$) in the main meta-analysis, we could not carry out a subgroup analysis. Given that there were fewer than 10 included studies in the main meta-analysis on breathlessness using adjusted end-point values, we did not use funnel plots or carry out tests for funnel plot asymmetry.

Quality of the evidence

In the GRADE approach, we downgraded the quality of evidence for breathlessness to very low because of a high risk of bias across studies (−2 levels as a result of very serious study limitations: high risk of bias for selection, performance, detection, attrition and reporting), imprecision (−1 level because of wide 95% CI around the effect estimates that included both benefit and harm) and inconsistency (−1 level as a result of differences between the main meta-analysis and sensitivity analyses).

Study or subgroup	HSPC Mean	HSPC SD	HSPC Total	Control Mean	Control SD	Control Total	Weight (%)	SMD IV, random, 95% CI
Farquhar 2014[75]	3.43	2.95	28	4.42	3.01	26	8.7	−0.33 (−0.87 to 0.21)
Farquhar 2016[76]	4.02	2.49	41	4.05	2.57	38	12.8	−0.01 (−0.45 to 0.43)
Groenvold 2017[148]	36.5	32.5	130	38.7	31	137	43.4	−0.07 (−0.31 to 0.17)
O'Riordan 2019[161]	1.9	2.64	16	2.4	2.58	14	4.8	−0.19 (−0.91 to 0.53)
Vanbutsele 2018[168]	30.86	32.88	92	27.24	34.66	94	30.2	0.11 (−0.18 to 0.39)
Total number of participants (95% CI)			307			309	100.0%	−0.04 (−0.19 to 0.12)

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.33$, df = 4 ($p = 0.68$); $I^2 = 0\%$

Test for overall effect: $z = 0.45$ ($p = 0.65$)

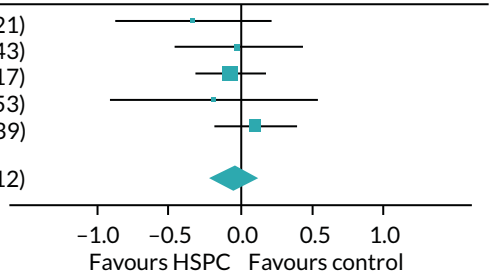

FIGURE 44 Effect of HSPC on patient breathlessness: adjusted end-point values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

Study or subgroup	HSPC Mean	HSPC SD	HSPC Total	Control Mean	Control SD	Control Total	Weight (%)	SMD IV, random, 95% CI
Bajwah 2015[72]	21.6	10.1	22	25	10.7	24	36.0	−0.32 (−0.90 to 0.26)
Higginson 2014[78]	−4.15	1.7	42	−3.57	1.4	40	64.0	−0.37 (−0.80 to 0.07)
Total number of participants (95% CI)			64			64	100.0%	−0.35 (−0.70 to −0.00)

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.02$, df = 1 ($p = 0.90$); $I^2 = 0\%$

Test for overall effect: $z = 1.97$ ($p = 0.05$)

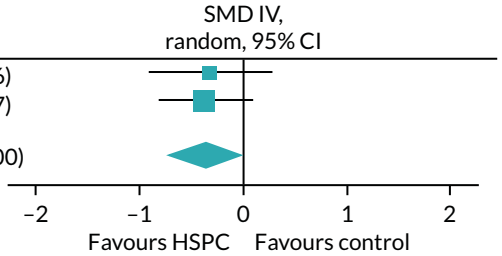

FIGURE 45 Effect of HSPC on patient breathlessness: unadjusted end-point values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

Study or subgroup	HSPC Mean	HSPC SD	HSPC Total	Control Mean	Control SD	Control Total	Weight (%)	SMD IV, random, 95% CI
Bekelman 2018[139]	−0.4	2.44	124	−0.5	2.44	124	53.7	0.04 (−0.21 to 0.29)
Ozcelik 2014[95]	−1.5	1.5	22	−0.2	0.8	22	46.3	−1.06 (−1.70 to −0.43)
Total number of participants (95% CI)			146			146	100.0%	−0.47 (−1.55 to 0.61)

Heterogeneity: $\tau^2 = 0.55$; $\chi^2 = 10.04$, df = 1 ($p = 0.002$); $I^2 = 90\%$

Test for overall effect: $z = 0.86$ ($p = 0.39$)

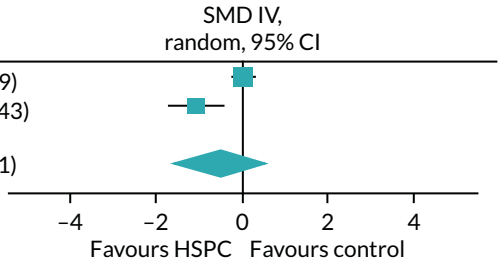

FIGURE 46 Effect of HSPC on patient breathlessness: unadjusted change values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

Adverse events in patients and caregivers

Eight studies, with 1252 participants, reported on adverse events[72,78,97,106,126,139,148,163] (see *Appendix 10*).

Two of these studies involved caregivers.[72,78] Six studies (976 participants) reported no harmful effect.[72,78,97,139,148,163] One study[106] (120 participants) found that more participants in the HSPC group had poorer appetite ($p = 0.04$) than in the control group. Solari *et al.*[126] (156 participants) reported 15 serious adverse events in 13 patients in the HSPC group, and seven adverse events in seven participants in the control group ($p = 0.78$). Serious adverse events reported included aspiration pneumonia, generalised anxiety, breathing difficulty, urine retention/infection, anarthria, contact dermatitis, dysphagia, vomiting, bladder catheter malfunctioning, fever, arrhythmia, necrotising fasciitis, traumatic wound, macrohaematuria, constipation, abdominalgia and bronchitis. Three participants in the HSPC group died, but this was considered to be unrelated to the intervention.

Quality of the evidence

In the GRADE approach, we downgraded the quality of the evidence for adverse events to very low because of a high risk of bias across studies (–2 levels as a result of very serious study limitations: high risk of bias for performance, detection, attrition and reporting) and inconsistency (–1 level because of variability in the results).

Caregiver burden

Two studies with 170 participants presented adjusted end-point values: Dionne-Odom *et al.*[136] (linked to Bakitas *et al.*[73]) and Bekelman *et al.*[139] However, we could not pool them together in a meta-analysis because of how they presented their data. Dionne-Odom *et al.*[136] assessed caregiver burden using the Montgomery–Borgatta Caregiver Burden (MBCB) scale and presented results for three different subscales of the MBCB scale, namely the objective burden scale (range 6–30; 30 indicates worst level of interference with the caregiver's private, social and recreational time and normal daily routine), stress burden scale (range 4–20; 20 indicates worst level of strained emotional demands related to caregiving) and the demand scale (range 4–20; > 15 indicates worst level of caregiver strain by his or her caregiving demands). Bekelman *et al.*[139] assessed caregiver burden using the Zarit Burden Interview (ZBI) (range 0–88; 88 indicates greatest burden).

On the objective burden scale of the MBCB scale, the mean caregiver burden score for the HSPC group was 0.3 points higher (range 6–30; 30 indicates worst) than that of the control group, with adjustment for patient death ($p = 0.64$). On the stress burden scale of the MBCB scale, the mean caregiver burden score for the HSPC group was 0.5 points lower (range 4–20; 20 indicates worst) than that for the control group, with adjustment for patient death ($p = 0.29$). There was no difference between the groups in the mean caregiver burden score, with adjustment for patient death, on the demand scale of the MBCB scale ($p = 0.97$). Bekelman *et al.*[139] reported a mean caregiver burden of 12.9 [standard error (SE) 1.3] in the HSPC group and 14.8 (SE 1.4) in control group at 12 months ($p = 0.30$).

Two studies (108 participants) reported unadjusted end-point data, but we could not pool them in a meta-analysis [Bajwah *et al.*[72] and Dionne-Odom *et al.*[136] (linked Bakitas *et al.*[73])]. Dionne-Odom *et al.*[136] reported the following results: on the objective burden scale of the MBCB scale, the mean caregiver burden score for the HSPC group was 0.3 points higher (range 6–30; 30 indicates worst) than that of the control group ($p = 0.62$). On the stress burden scale of the MBCB scale, the mean caregiver burden score for the HSPC group was 0.6 points lower (range 4–20; 20 indicates worst) than that of the control group. There was no difference between the HSPC and control groups in the mean caregiver burden score on the demand scale of the MBCB scale ($p = 0.99$). Bajwah *et al.*[72] assessed caregiver burden using the ZBI (range 0–88; 88 indicates highest burden), and reported a mean caregiver burden of 22.3 (SD 15.3) in the fast-track group and of 31.7 (SD 17.3) in the control

group at 4 weeks. After the control group was offered HSPC between 4 and 8 weeks, the mean caregiver burden reduced to 25.4 (SD 13.4).

Three studies[72,77,126] reported adjusted change values and found evidence in favour of HSPC (128 participants, MD −3.88, 95% CI −5.95 to −1.80; $I^2 = 0\%$) (*Figure 47*). All three studies assessed caregiver burden using the ZBI.

Bajwah *et al.*[72] (39 participants) was the only study that presented unadjusted change values. It found a 0.1 mean increase in caregiver burden score from baseline to 4 weeks for 16 intervention caregivers, whereas, for 23 caregivers in the control group, caregiver burden decreased by 0.1 points. The effect size at 4 weeks was −0.6 (95% CI −1.2 to 0.1).

Bakitas *et al.*[129] reported on caregiver burden, but did not present usable data for the meta-analysis. The remaining 36 studies did not report on caregiver burden. We did not carry out any further analysis on caregiver burden because of limited number of studies.

Quality of the evidence

In the GRADE approach, we downgraded the quality of the evidence for caregiver burden to very low because of a high risk of bias across studies (−2 levels as a result of very serious study limitations: high risk of bias for performance and reporting) and imprecision (−1 level because of the small number of participants).

Caregiver grief

Only Dionne-Odom *et al.*[137] (linked to Bakitas *et al.*[73]), with 44 participants, provided usable data for caregiver grief. Dionne-Odom *et al.*[137] assessed caregiver grief using the Prigerson Inventory of Complicated Grief-Short Form (PG-13) and reported a mean caregiver grief score in the HSPC group that was 2.2 points lower (range 11–55; 55 indicates highest grief) than that of the control group ($p = 0.21$). There was no evidence of a difference on adjusting for religious preference ($p = 0.40$), baseline depression levels ($p = 0.51$) or patient hospice use ($p = 0.51$).

Quality of the evidence

The quality of the evidence on caregiver grief was downgraded to low because of a high risk of bias (−1 level as a result of serious study limitations: high risk of performance bias) and imprecision (−1 level because of the small number of participants).

Caregiver quality of life

Only Dionne-Odom *et al.*[136] (linked to Bakitas *et al.*[73]) reported adjusted end-point data on caregiver quality of life, and there was no evidence of benefit of HSPC over usual care. Dionne-Odom *et al.*[136] assessed caregiver quality of life using the Caregiver Quality of Life Index (CQOL) (range 0–140; 140 indicates worse quality of life), and found a mean CQOL score in the HSPC group that was 2 points better than that of the control group at 3 months with adjustment for patient death ($p = 0.39$). In decedents' caregivers, a terminal decline analysis indicated a MD of −4.9 points between the HSPC and control groups ($p = 0.07$).

We carried out a sensitivity analysis with unadjusted end-point values. A sensitivity analysis in the two studies (105 participants) that reported unadjusted end-point values showed a pooled effect in favour of HSPC (MD 6.11, 95% CI 0.42 to 11.81; $I^2 = 0\%$) (*Figure 48*). Positive MD indicates better caregiver quality of life and negative MD reflects worse caregiver quality of life. The two studies assessed caregiver quality of life using the CQOL (range 0–140; 140 indicates worse quality of life).

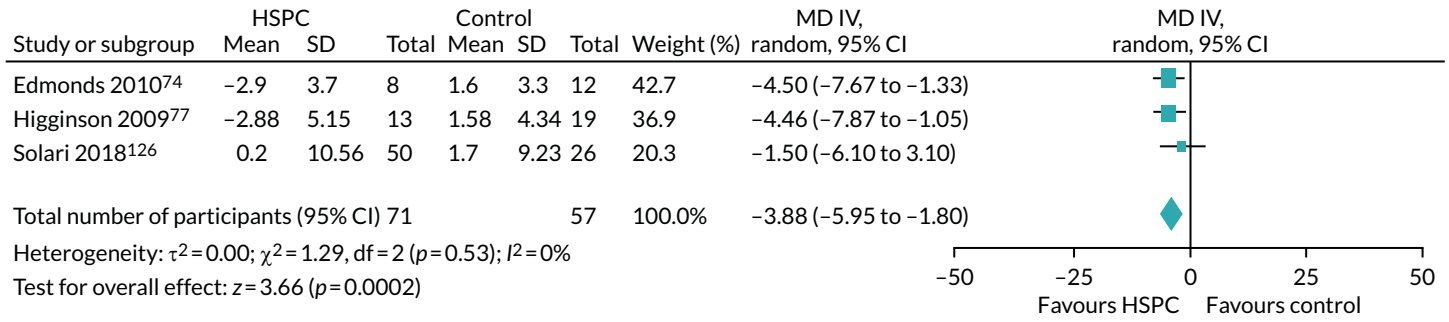

FIGURE 47 Effect of HSPC on caregiver burden: adjusted change values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

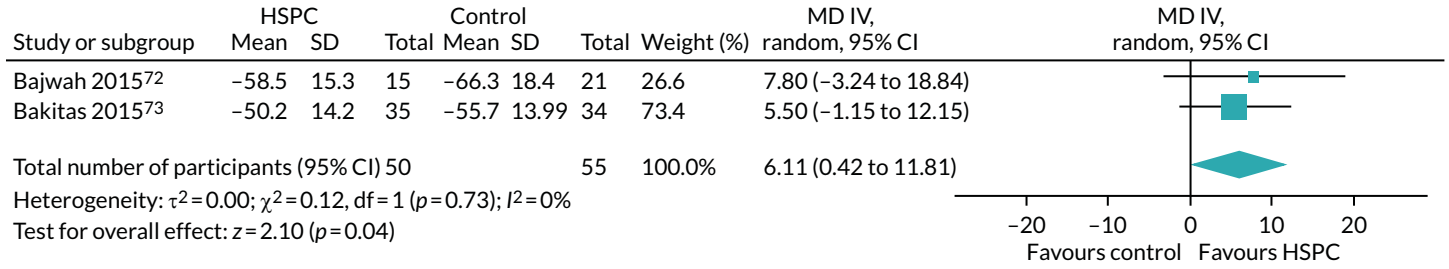

FIGURE 48 Effect of HSPC on caregiver quality of life: unadjusted end-point values. df, degrees of freedom; IV, inverse variance; random, random-effects model.

In addition, Bajwah *et al.*[72] also presented unadjusted change values and assessed caregiver quality of life using the CQOL. Bajwah *et al.*[72] found a 2.5-point mean improvement (range 0–140; 140 indicates worse quality of life) in caregiver quality of life from baseline at 4 weeks for the HSPC group, while, for controls, caregiver quality of life improved by 0.7 points. The effect size at 4 weeks was –0.4 (95% CI –1.1 to 0.2). At 8 weeks, the mean score was 58.3 points (SD 15.6 points) for the HSPC group and 60.2 points (SD 23.9 points) for the control group. The remaining 39 studies did not report on caregiver quality of life.

We could not perform any further analysis because of the limited number of studies.

Quality of the evidence

In the GRADE approach, we downgraded the quality of the evidence for caregiver quality of life to low because of a high risk of bias (–1 level as a result of serious study limitations: high risk of bias for performance reporting) and imprecision (–1 level because of the small number of participants).

Impact of hospital-based specialist palliative care on resource use

We could not carry out a meta-analysis on resource use and costs as a result of the differences in the measurement and reporting, such as type of analysis, tools used, assessment time points or time horizon and statistics reported. Consequently, we provided a narrative synthesis on the economic studies.

Thirty-one studies compared resource use and/or costs between the intervention and control groups. Three studies[81,129,156] collected information on resource use and/or costs through chart review. The Client Service Receipt Inventory (CSRI), or a modified form of it, was used in four studies[75–78] to collect resource use data. Medical/health records were used by eight studies,[35,70,89,96,106,161,165,168] and four studies[73,123,139,163] used a combination of methods. Bekelman *et al.*[139] collected data from medical records and supplemented these with patient or family self-report. Bakitas *et al.*[73] used patient self-report for hospital and ICU days and ED visits, whereas decedents' data for the period between the last patient-reported assessment and death, and chemotherapy use in previous 14 days, were obtained from medical records. Janssens *et al.*[123] collected data from medical records, as well as from contact with patients and their GPs. Rodin *et al.*[163] collected data from patients and their medical charts. Ozcelik *et al.*[95] used a patient expenditure record form to capture resources and their costs, whereas Brumley *et al.*[142] obtained resource use for each patient retrospectively from the non-profit health maintenance organisation's mainframe database. Gade *et al.*[88] used standard data extract protocols to extract information from the managed care organization's database. The methods used in collecting resource use information were unclear in nine RCTs.[82,84,85,101,116,118,148,160,167]

We considered resource use in the following areas: institutional care services use, outpatient clinic services use, community care services use, unpaid caregiver's care, and medications and other resources.

Institutional care services use

Thirty studies compared the effect of HSPC with that of usual care on the use of institutional care. Eight studies[35,70,73,101,123,129,142,165] assessed ED visits and their results were inconsistent (see *Report Supplementary Material 1*, table 2). Two of the studies reported fewer ED visits in favour of the HSPC group.[70,142] Brumley *et al.*[142] found that 20% of intervention group participants had ED visits, compared with 33% of control group participants ($p = 0.01$). Linear regression adjusting for survival, age and severity of illness showed that the intervention reduced ED visits by 0.35 visits ($p = 0.02$). Ma *et al.*[70] reported fewer post-discharge ED visits in the HSPC group than in the control group (1.3% vs. 12.5%; $p = 0.0067$).

Four of the remaining six studies described little or no difference between the HSPC and control groups.[73,101,123,129] Janssens *et al.*[123] initially reported that participants in the HSPC group were twice as likely to be admitted to the emergency ward for respiratory failure than participants in the control

group (incidence rate ratio 2.05, 95% CI 1.11 to 3.94; $p = 0.014$). However, after correction for multiple testing, there was no longer any difference. Rogers *et al.*[165] and Temel *et al.*[35] reported fewer ED visits in the HSPC group than in the control group, but did not present their *p*-values.

Nine studies assessed ICU use (see *Report Supplementary Material 1*, table 3). Six of these studies assessed ICU days,[70,73,82,84129,156] and three assessed number of ICU admissions.[88,89,123] Five of the six studies that assessed ICU days found no difference between the HSPC and control groups.[70,73,82,84,129] Kane *et al.*[156] reported slightly fewer mean number of ICU days per patient in the HSPC group than in the control group (0.2 vs, 0.3), but *p*-values were not stated. Three studies reported contrasting results regarding ICU admission.[88,89,123] Janssens *et al.*[123] compared number of ICU admissions for respiratory failure between the HSPC and control groups in the year before study inclusion (7 vs. 7 incidence rate ratio 0.88, 95% CI 0.26 to 2.96; $p = 0.82$) and also during the study (5 vs. 1, for the HSPC and control groups, respectively; incidence rate ratio 4.42, 95% CI 0.49 to 20.92; $p = 0.16$), but did not find any difference. On the other hand, Gade *et al.*[88] found evidence in favour of HSPC in terms of a reduction in ICU admissions. The median number of ICU admissions in the HSPC group was 12, whereas, in the control group, it was 21 ($p = 0.04$). Grudzen *et al.*[89] reported no difference between the treatment arms in the number of ICU admissions during the index admission ($p > 0.99$), and also at 180 days ($p > 0.99$).

Two studies[70,82] provided details on resource use in the ICU; their findings were varied (see *Report Supplementary Material 1*, table 4). Carson *et al.*[82] found no difference in use of the following resources in the ICU between the HSPC and control groups: dialysis [13 (10%) vs. 15 (12%) participants using the resource; $p = 0.64$], mechanical ventilation [median 40 (31%) vs. 33 (26%); $p = 0.41$], nutrition [median 18 (14%) vs. 21 (17%); $p = 0.60$] and vasopressors [median 18 (14%) vs. 19 (15%); $p = 0.86$]. Ma *et al.*[70] reported less use of tracheostomy (1% vs. 7.8%; $p = 0.035$) and fewer median number of days on mechanical ventilation [4 (IQR 3–7) vs. 6 (IQR 3–13); $p = 0.042$] in the ICU in the HSPC group than in the control group.

Kane *et al.*[156] further reported reduced mean number of nursing home days per patient in favour of the HSPC group (HSPC group, 1 day; control group, 11.4 days; $p < 0.05$).

Twelve studies provided mixed results on hospital admissions[35,70,75,76,81,96,101,118,123,139,142,165] (see *Report Supplementary Material 1*, table 5).

Four studies found no difference in the number of hospital admissions between the HSPC and control groups.[70,81,96,139] Ma *et al.*[70] initially described fewer hospital re-admissions in the intervention group than in the control group (17.3% vs. 33.3%, respectively; $p = 0.024$). Hospital admissions for respiratory failure during the study occurred almost twice as often in the HSPC group than in the control group (incidence rate ratio 1.87, 95% CI 1.04 to 3.48; $p = 0.026$). However, after the Benjamini–Hochberg correction for multiple testing, there was no longer any difference in the number of hospital admissions during the study period. Sidebottom *et al.*[96] reported no association between study group assignment and 30-day inpatient re-admission (adjusting for age, sex and marital status) ($p = 0.50$). Janssens *et al.*[123] described more hospital admissions for respiratory failure in the HSPC group than in the control group in the year before the study (24 vs. 18, respectively; $p = 0.60$), and also during the study period (38 vs. 18, respectively; $p = 0.026$). Two studies found fewer hospital admissions in favour of the HSPC group.[118,142] Brännström *et al.*[118] found fewer mean number of hospitalisations in the HSPC group than in the control group [0.42 (SD 0.60) vs. 1.47 (SD 1.81), respectively; $p = 0.009$]. Brumley *et al.*[142] found fewer hospital admissions in the intervention group than in the control group (36% vs. 59%, respectively; $p < 0.001$). Three studies further reported fewer hospital admissions in the HSPC group, but they did not present their *p*-values.[35,75,101] Farquhar *et al.*[75] reported 7% inpatient admissions in the HSPC group, compared with 12% in the control group, and Mendoza-Galindo *et al.*[101] found that 48% of participants in HSPC group had hospital admissions, compared with 51% in the control group. Temel *et al.*[35] described fewer hospital admissions in the HSPC group than in the control group from enrolment to death (73.5% vs. 76.8%, respectively) and also within 30 days of death (36.7% vs. 53.6%, respectively).

By contrast, Farquhar *et al.*[76] reported more inpatient admissions in the HSPC group than in the control group (15% vs. 11%, respectively), but the *p*-value was not stated. In Rogers *et al.*,[165] during the study, there were more hospitalisations for heart failure (30.7% vs. 29.3% respectively; *p*-value not stated), more hospitalisations for non-heart failure cardiovascular conditions (16% vs. 13%; *p*-value not stated) and fewer hospitalisations for non-cardiovascular conditions (10.7% vs. 24%; *p*-value not stated) in the HSPC group than in the control group.

Length of hospital admission ('length of hospital admissions' was used to compare the length of stay in addition to the frequency of hospital admission) was assessed in 17 studies[35,70,73,77,78,81,82,84,85,88,89,95,101,118,129,142,156] (see *Report Supplementary Material 1*, table 6). Nine studies found no difference in the length of admission between the HSPC and control groups.[70,81,82,84,88,89,95,101,129] Bakitas *et al.*[73] described fewer hospitalisation days in the HSPC group than in the control group [0.69 (95% CI 0.4 to 1.18) vs. 1.39 (95% CI 0.97 to 1.97), respectively; $p = 0.03$], as well as among decedents in the HSPC group [0.95 (95% CI 0.61 to 1.46) vs. 1.3 (95% CI 0.91 to 1.86) in the HSPC and control groups, respectively; $p = 0.26$]. Brännström *et al.*[118] reported that the mean number of days spent in hospital was lower in the HSPC group than in the control group [2.9 (SD 8.3) vs. 8.5 (SD 12.4), respectively; $p = 0.011$]. The numbers of days spent in the Department of Medicine-Geriatrics [100 (range 1–45) vs. 242 (range 2–46)] and surgery (0 vs. 56) were also significantly lower in the HSPC group than in the control group; the authors reported no significant difference between HSPC and usual care in the days spent in other departments [3 (range 1–2) vs. 7 (range 1–6) days for the HSPC and control groups, respectively]. Brumley *et al.*[142] reported fewer hospital days in the HSPC group. Linear regression adjusted for survival, age and severity of illness showed that the intervention reduced the number of hospital days by 4.36 ($p < 0.001$). Kane *et al.*[156] reported total inpatient days, as well as general medicine, hospice, ICU and intermediate care inpatient days. The mean number of total inpatient days per patient did not differ between the HSPC and control groups (51 vs. 47.5, respectively). However, Kane *et al.*[156] found fewer mean general medical inpatient care days (HSPC, 13.2 and control, 20.7; $p < 0.05$) and intermediate inpatient care days per patient (HSPC, 8.3 and control, 26.5; $p < 0.05$) for the HSPC group than for the control group. Four studies described fewer hospital days in the HSPC group than in the control group, but did not report their *p*-values.[35,77,78,85] El-Jawahri *et al.*[85] reported the median duration of hospitalisation in the HSPC group to be 20 days (range 12–102 days), and that in the control group to be 21 days (range 13–40 days). Higginson *et al.*[77] reported that the number of institutional days (hospital admission) increased in the control group. Higginson *et al.*[78] reported the mean number of hospital days to be 4.5 (SD 6.8) in the HSPC group and 4.6 (SD 7.6) in the control group, and Temel *et al.*[35] reported the number of inpatient days from enrolment to death to be 5 (range 0–50) in the HSPC group and 7 (range 0–45) in the control group.

Palliative care visits during hospitalisation were further compared between HSPC and usual care in two studies[85,106] (see *Report Supplementary Material 1*, table 7). El-Jawahri *et al.*[85] reported that HSPC patients had at least two palliative care visits during the first 2 weeks of their hospitalisation (median 4, range 2–7, visits), whereas two control patients received a palliative care consultation (*p*-values were not stated). Tattersall *et al.*[106] highlighted that 86% of patients in the HSPC group had palliative care contact during hospitalisation, compared with 78% of control group patients ($p = 0.37$).

With the exception of days spent in nursing homes reported in one study to be in favour of HSPC, the overall evidence on institutional care use was inconsistent.

Outpatient clinic services use

Seven studies provided inconsistent evidence on the effect of HSPC, compared with usual care, on outpatient clinic visits[35,77,118,148,165,167,168] (see *Report Supplementary Material 1*, table 8). Brännström *et al.*[118] reported fewer outpatient clinic visits in favour of HSPC. Brännström *et al.*[118] found fewer physician visits, nurse visits, telephone calls and prescriptions in the HSPC group than in the control group. Vanbutsele *et al.*[168] reported a difference in favour of the control group for number of consultations with a psychologist at 18 weeks ($p = 0.02$), but not at 24 weeks. Three studies described more contacts with palliative care

teams in the HSPC group than in the control group, but did not present *p*-values.[35,148,167] Temel *et al.*[167] highlighted more palliative care visits in the HSPC group than in the control group [mean 6.54 (range 0–14) vs. 0.89 (range 0–7), respectively]. Temel *et al.*[35] reported that all the patients assigned to HSPC, except for one patient who died shortly after enrolment, had at least one visit with the palliative care service by the 12th week. The average number of visits in the palliative care group was 4 (range 0–8). Ten patients who received usual care (14%) had a palliative care consultation in the first 12 weeks of the study, with seven patients having one visit, and three patients having two visits. In Groenvold *et al.*,[148] 138 patients had at least one face-to-face contact with the HSPC team, compared with 13 patients in the control group. Groenvold *et al.*[148] further reported no difference in the mean number of specialist visits between the HSPC and control groups [4.9 (SD 8.1) vs. 7.0 (SD 9.1), respectively; $p = 0.25$].

Higginson *et al.*[77] described fewer hospital specialist visits in the HSPC group [8 patients (35%)] than in the control group [16 patients (76%)], but *p*-values were not stated. Rogers *et al.*[165] reported a higher mean total number of clinic encounters in the HSPC group than in the control group [21.9 (SD 1.99) vs. 20.8 (SD 1.92), respectively], but did not present *p*-values. There were more visits to the rehabilitation clinic in the HSPC group than in the control group [mean 1.4 (SD 0.68) vs. 0.9 (SD 0.48)] and fewer cardiology visits in the HSPC group than in the control group [mean 2.3 (SD 0.55) vs. 3.2 (SD 1.0)]. Woo *et al.*[116] reported that similar proportions of patients in the HSPC and control groups consulted with a psychiatrist (12% vs. 12%), but did not present *p*-values. Tattersall *et al.*[106] reported more contacts with palliative care physicians in the HSPC group than in the control group by the end of the study [51 patients (85%) vs. 8 patients (13.3%)], and also in the last month of life [16 patients (26.7%) vs. 6 patients (10%)]. However, the *p*-values were not stated.

Community care services use

Fourteen studies compared community care services use between the HSPC group and control group;[35,73,75–77,88,89,96,118,129,142,156,160,165] their findings were inconsistent (see *Report Supplementary Material 1*, table 9). The studies reported on a range of community services. Two UK studies by the same author found different results for the mean number of GP contacts for cancer[75] and non-cancer[76] populations. Farquhar *et al.*[75] reported the mean number of GP contacts to be slightly higher in the control group [1.3 (SD 0.5)] than in the HSPC group [1.2 (SD 0.6)] in cancer populations, whereas Farquhar *et al.*[76] found the mean number of GP contacts to be slightly higher in the HSPC group [1.8 (SD 1.2)] than in the control group [1.6 (SD 0.7)] in non-cancer populations. However, these studies did not provide their *p*-values. Higginson *et al.*[77] described differences in contact with GPs, district/practice nurses, multiple sclerosis nurses and social services, but the *p*-values of the results were not stated.

A US study by Gade *et al.*[88] found longer median length of stay in hospice for the HSPC group (24 days) than for the control group (12 days) ($p = 0.04$), whereas two other US studies[35,142] found no between-group differences. Grudzen *et al.*[89] and Bakitas *et al.*[73] reported no between-group differences in hospice use at 180 days. Sidebottom *et al.*[96] found no evidence of an association between group assignment and hospice use within 6 months, adjusting for age, sex and marital status in the USA. Ma *et al.*[70] highlighted more transfers to hospice care in the HSPC group than in the usual-care group (18.6% vs. 4.9%, respectively; $p = 0.0026$). Brännström *et al.*[118] reported more nurse visits in the HSPC group than in the control group (1075 vs. 230, respectively; $p = 0.000$) in Sweden. By contrast, this study[118] found that telephone calls and prescriptions by doctors were more common in the control group (108 vs. 231 for the control and HSPC groups, respectively), and that physician visits were similar between groups (194 vs. 201 for the HSPC and control groups, respectively). Kane *et al.*[156] and McCaffrey *et al.*[160] both reported more days spent at home in the HSPC group than in the control group, but did not present *p*-values. Kane *et al.*[156] reported a mean of 44.8 days at home per patient for the HSPC group, and a mean of 37.9 days at home per patient for the control group. In McCaffrey *et al.*,[160] the HSPC group spent a mean of 13.1 days (95% CI 8.5 to 17.7 days) at home, compared with 12.1 days (95% CI 5.9 to 18.4 days) for the control group. Rogers *et al.*[165] reported on the frequency of interaction between patients and primary care providers and found fewer interactions in the HSPC group [mean 4.4 (SD 0.93)] than in the control group [mean 5.2 (SD 0.82)]. The authors did not present the *p*-values.

Unpaid caregiver's care

Two studies[75,77] reported on the effect of HSPC and usual care on the support provided by informal caregivers (see *Report Supplementary Material 1*, table 10). Increased care by informal caregivers was reported by Higginson *et al.*,[77] with more hours of informal care provided in the control group. The *p*-value was not stated. Farquhar *et al.*[75] reported more use of informal care in the control group than in the HSPC group. However, the *p*-value was not stated.

Medication and other resources

Seventeen studies reported on the use of medications or other resources, or both: Ahronheim *et al.*,[81] Bakitas *et al.*,[73,129] Brumley *et al.*,[142] Carson *et al.*,[82] Farquhar *et al.*,[75,76] Groenvold *et al.*,[148] Higginson *et al.*,[77] Janssens *et al.*,[123] Kane *et al.*,[156] Ma *et al.*,[70] Markgren *et al.*[120] (linked to Brännström *et al.*[118]), O'Riordan *et al.*,[161] Rodin *et al.*,[163] Rogers *et al.*[165] and Temel *et al.*[35] (see *Report Supplementary Material 1*, table 11). Markgren *et al.*[120] (linked to Brännström *et al.*[118]) assessed the number of patients receiving the target doses of medications based on current guidelines for heart failure among HSPC and control group patients. This study found that the number of patients treated with mineralocorticoid receptor antagonists differed between groups: it increased from 10 out of 36 patients (28%) to 15 out of 31 patients (48%) in the HSPC group, compared with 13 out of 36 patients (35%) to 13 of 33 patients (39%) in the control group. The change in the number of patients receiving full target doses of the angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers and mineralocorticoid receptor antagonists was greater in the HSPC group than in the control group ($p = 0.009$). Conversely, O'Riordan *et al.*[161] found no evidence of a difference in use of guideline-driven heart failure treatments such as beta-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. Similarly, Janssens *et al.*[123] did not find any difference between HSPC and control groups in the use of antibiotics ($p = 0.819$). Temel *et al.*[35] reported a difference in aggressive end-of-life care among decedents, with 33% (16/49) of those in the HSPC group and 54% (30/56) in the control group receiving aggressive end-of-life care ($p = 0.05$). Aggressive end-of-life care was defined as chemotherapy within the 14 days before death, no hospice care or admission to hospice ≤ 3 days before death. Kane *et al.*[156] further reported more use of chemotherapy in the HSPC group, with a mean of 1.3 patients receiving chemotherapy in the HSPC group, compared with 0.49 in the control group ($p = 0.03$). More patients in the HSPC group (mean 0.09) than in the control group (mean 0.01) also received major surgical procedures ($p < 0.05$). Bakitas *et al.*[73] reported no between-group difference in chemotherapy use in the last 2 weeks of life.

Ahronheim *et al.*[81] reported lower use of intravenous therapy for the entire admission for the HSPC group than for the control group, among patients with advanced dementia: 61 (66%) of 92 admissions in the HSPC group received it, compared with 79 (81%) of 98 admissions in control group. On the other hand, the study[81] reported no evidence of a difference in use of other resources, such as feeding tubes, mechanical ventilation, tracheostomy, systemic antibiotics, days with restraints, mechanical restraints and cardiopulmonary resuscitation. In Ma *et al.*,[70] the HSPC group had fewer ventilator days (median 4 vs. 6; $p = 0.042$) and fewer tracheostomies performed (1% vs. 7.8%; $p = 0.035$) than the control group; there was no between-group difference in mechanical ventilation, use of vasopressors, haemodialysis or cardiopulmonary resuscitation. Carson *et al.*[82] found no between-group difference in ventilator days between the HSPC and control groups.

Higginson *et al.*[77] reported differences in resource use such as primary/secondary care, use of specialist wards, occupation therapist/physiotherapist, palliative care nurse, dietitian, chiropodist, day centre and respite care. However, the *p*-values of the differences were not stated. Rogers *et al.*[165] reported more hospital encounters with the HSPC team [mean 2.5 (SD 0.45) vs. 2.4 (SD 0.35)] and more telephone contacts [mean 12.6 (SD 1.2) vs. 10.6 (SD 0.88)] in the HSPC group than in the control group, but did not present *p*-values. Groenvold *et al.*[148] also highlighted that 116 patients in the HSPC group had at least one telephone contact with the HSPC team, compared with nine patients in the control group. However, they did not report their *p*-value.

Two studies[129,142] reported no evidence of a difference in referral to palliative care/hospice care. Bakitas *et al.*[129] reported that 34 (23%) of 145 patients were referred to palliative care in the HSPC group, compared with 39 (29%) out of 134 patients in control group ($p = 0.34$), and that 6 (3.7%) out of 161 patients in the HSPC group and 4 (2.5%) out of 161 patients in control group were referred to hospice care ($p = 0.75$). Brumley *et al.*[142] presented results on hospice referral for only one of the sites in their study and reported that 25% of patients in the HSPC group were referred to hospice care, compared with 36% of patients in the control group ($p = 0.15$). Rodin *et al.*[163] described more referrals to palliative care [22 patients (100%) vs. 1 patient (5%) in the HSPC and control groups, respectively], but not psychiatry [1 patient (4.5%) vs. 1 patient (5%) in the HSPC and control groups, respectively], in the HSPC group than in the control group. The *p*-values for the differences were not stated. There was no difference in referral to social work services between HSPC and control groups [22 patients (100%) vs. 20 patients (100%), respectively].

Other resource use with no between-group difference include hospital discharge disposition.[82] Both Farquhar *et al.*[75,76] studies reported differences between HSPC and control groups in the use of services provided by nurses, social care, other health professionals and other hospital services, but the *p*-values for these differences were not stated.

Quality of the evidence

In the GRADE approach, we downgraded the certainty of evidence for resource use to very low because of a high risk of bias across studies (−2 levels as a result of very serious study limitations: high risk of bias for performance, detection, attrition, reporting, size of study and other bias) and inconsistency (−1 level as a result of variability in results).

Costs and cost-effectiveness of hospital-based specialist palliative care

Thirteen economic studies (2103 participants) reported on cost. Resources included were ED or A&E visits, inpatient and outpatient hospital care, home and community care, care in nursing homes (or skilled nursing homes), inpatient stay and day care in hospice, hospice care at home, informal care, drugs and equipment. Four studies[75–77,160] reported the results of cost-effectiveness analyses using outcome measures that were relevant to their research questions (palliative outcome, carer's burden, QALYs) and hospital costs or total costs. Results of cost-effectiveness analyses were reported by ICERs and/or costs per QALY (point estimates or cost-effectiveness planes).

Two studies found evidence of reduced cost with HSPC.[88,142] When compared with usual care, Mendoza-Galindo *et al.*[101] reported a reduction in the cost of hospitalisation days in the HSPC group. However, no difference was found between groups in the cost of emergency room visits. In Brännström *et al.*,[118] this was unclear, as no *p*-value was presented for the difference in cost between HSPC and usual care. We identified four full economic studies.[75–77,160] The evidence on the cost-effectiveness of the HSPC, compared with usual care, was equivocal.

The first relevant study that we identified was carried out by Kane *et al.*[156] Kane *et al.*[156] was a US study that provided services across multiple settings. It compared the cost of hospice care provided across multiple settings with that of conventional care among cancer patients. Participants in the hospice care group had lower total costs when compared with those receiving conventional care. However, this was not statistically significant. The estimated mean expenditure per patient was US$15,263 (£29,058 at 2018 conversion rates) in the HSPC group and US$15,493 (£29,496 at 2018 conversion rates). Resource use was measured in hospice stays, hospital stays, surgical procedures, chemotherapy and radiotherapy, and costs were calculated using different assumptions. However, difference in survival (days since enrolment in the study), as well as other factors (e.g. age, severity of diseases) that might be associated with costs, was not adjusted for.

Brumley *et al.*[142] compared resource use and costs between the HSPC and usual-care group and the usual-care only group among terminally ill patients with cancer and terminally ill patients with non-cancer diagnoses (i.e. mixed diagnoses) in the USA. A wider range of resource use was included from the health insurance database: hospital days, number of ED visits, physician office visits, skilled nursing facility days, home health and palliative visits, palliative physician home visits and days in hospice care. Service use was significantly lower in the intervention group than in the usual-care group, even after adjusting for age, survival and severity of illness, measured using the Palliative Performance Scale. Hospital stay decreased by 4.36 days and the number of ED visits decreased by 0.35. Owing to the difference in the survival (days on service), mean costs per patient were adjusted using regression analysis, controlling for survival, age, severity of illness and primary disease. The mean cost per patient was lower in the intervention group [AU$12,670 (SD AU$12,523), which converts to £8383 (SD £8285) at 2018 rates] than in the usual-care group [AU$20,222 (SD AU$30,026), which converts to £13,379 (SD £19,866) at 2018 rates]. The average daily cost per patient was also significantly lower in intervention group (AU$95.30, which converts to £63.05 at 2018 rates) than in the usual-care group (AU$212.80, which converts to £140.76 at 2018 rates) ($p = 0.02$).

Gade *et al.*[88] used the health insurance database to extract resource use and unit cost of services of hospitalised patients with life-limiting illnesses (mixed cancer and non-cancer diagnoses), who were randomly assigned to a HSPC intervention or usual care. Resources included were ED visits, clinic and hospital outpatient visits, home health visits, hospital admission, skilled nursing facility admissions and prescriptions filled. The cost of the palliative care team was calculated as the intervention cost. Patients in the HSPC group stayed longer in hospice after the index hospitalisation (24 days) than usual-care patients (12 days) ($p = 0.08$), had significantly shorter ICU stays on re-admission (12 times vs. 21 times, $p = 0.04$) and had significantly lower total health-care costs [US$14,486 (£15,013 at 2018 rates) vs. US$21,252 (£22,025 at 2018 rates); $p = 0.001$]. Gade *et al.*[88] was a US study that involved an inpatient consult model of HSPC.

Temel *et al.*[35] compared the effectiveness of the early palliative care integrated with standard oncologic care (HSPC) with that of standard oncologic care only among patients with newly diagnosed metastatic non-small cell lung cancer. It was a US study that involved an outpatient model of HSPC. Data on health resource use and end-of-life care were collected from patients' medical records: anticancer therapy, medication prescriptions, referral to hospice, hospital admissions and ED visits. Patients in the standard-care group received more aggressive end-of-life care [54% (30/56) vs. 33% (16/49); $p = 0.05$], and had longer stays in hospice care (median 11 days vs. 4 days; $p = 0.09$) than those in the intervention group. Patients in the HSPC group had less aggressive care, and quality of life and survival improved more in this group than in the control group. However, this was not conclusive as the sample size of the study did not allow the statistical power to test the differences in service use. Detailed analyses of costs and cost-effectiveness were conducted and reported later, although lacking in statistical power to detect the difference in Greer *et al.*[108] Comparisons of costs per day alive and costs for the previous 30 days were made between the HSPC and usual-care groups and the cost-effectiveness per life-year saved was calculated. The total costs per day were, on average, lower in the HSPC group than in the control group [MD US$117 (SE US$74), which is £103 (SE £65) at 2018 rates; $p = 0.13$], and total costs for the last 30 days were also reduced [MD US$2527 (SE US$3311), which is £2230 (SE £2922) at 2018 rates; $p = 0.44$]. The cost-effectiveness ratio was US$41,938 per life-year saved. More use of hospice care [MD –US$1053 (SE US$538), which is –£929 (SE £475) at 2018 rates; $p = 0.07$] and less use of chemotherapy [MD US$757 (SE US$365), which is £668 (SE £322) at 2018 conversion rates; $p = 0.03$] for the last 30 days implied that the cost savings might come from shifting care from inpatient to outpatient settings.

Higginson *et al.*[78] assessed the effectiveness of early introduction of palliative care among patients with chronic breathlessness in the UK. The intervention (HSPC) was provided across multiple settings and included patients with mixed cancer and non-cancer diagnoses. Patients were randomly allocated to the HSPC group or to the usual-care group. Resource use data, such as health, voluntary and social

care received, were collected using the CSRI over the previous 3 months at baseline and since the last interview at 6 weeks' follow-up. Limited results on resource use and costs were reported: hospital inpatient stays [mean 4.5 (SD 6.8) in the HSPC group and 4.6 (SD 7.6) in the control group] and costs of formal care use [mean £1422 (95% CI £897 to £2101), which is £1611 (95% CI £1016 to £2380) in 2018 prices, in the HSPC group, and mean £1408 (95% CI £899 to £2023), which is £1595 (95% CI £1018 to £2292) in 2018 prices, in the control group]. There was no difference between the two groups.

Brännström *et al.*[118] compared service use between patients randomised to the Palliative advanced home caRE and heart FailurE caRe (PREFER) intervention and patients randomised to usual care among patients with severe chronic heart failure. The advanced home care unit was based in a county hospital. The PREFER intervention was an outreach model of HSPC. Use of the following resources was assessed: inpatient days, hospital admissions, physician and nurse visits, telephone calls and drug prescriptions. The intervention group had significantly fewer hospitalisations than the control group (0.42 ± 0.60 vs. 1.47 ± 1.81, respectively; $p = 0.009$) and the length of stay in hospital was also significantly lower among patients in the intervention group than in the control group [mean 2.9 (SD 8.3) vs. mean 8.5 (SD 12.4), respectively; $p = 0.011$]. The number of total days or total contacts per trial group were compared between the intervention and control groups, and an additional cost analysis was reported in Sahlen *et al.*[121] QALY gain was 0.25 years between baseline and end of the intervention across the palliative advance home care group and usual-care group ($p = 0.025$). Over 6 months, the total cost was Swedish krona (SEK) 1.4M (€140,000, converts to £126,132 in 2018 prices) in the HSPC group and SEK2.0M (€205,000, converts to £180,188 in 2018 prices) in the control group, and the difference, SEK600,000 (€61,000), was the savings achieved by providing the palliative advance home care in addition to the usual heart failure care.

Ozcelik *et al.*[95] compared duration of hospitalisation and direct cost between the HSPC and usual-care groups. It was an inpatient consult model of HSPC. A patient cost record form was used to document cost and it consisted of all expenses incurred while in hospital. Direct expenses assessed were consultations, professional care, medicines used from the start of a patient's stay in hospital, medical equipment, laboratory and diagnosis tests, and hospital stay expenses (including those of companions). After discharge from hospital, costs were recorded on the form by obtaining the expenses list from the clinic secretary. In the HSPC group, the mean direct cost was US$68.869 (SD US$48.522) [converts to £60.154 (SD £42.382) in 2018 prices]; in the control group, it was US$81.076 (SD US$72.70) [converts to £70.816 (£63.500) in 2018 prices] ($p = 0.76$). There was no difference in duration of hospitalisation ($p = 0.07$), with a mean length of stay in hospital of 9.4 days (SD 6.27 days) in the intervention group and 13.9 days (SD 11.5 days) in the control group.

Among included studies, Higginson *et al.*[77] was the first study to use a robust cost-effectiveness analysis method. The cost-effectiveness analysis was carried out alongside a feasibility trial of a new palliative care service among patients with multiple sclerosis, randomised to either fast-track of the new palliative care intervention or usual care. Costs of health, social and voluntary services were measured; informal care provided by family or friends was also included in the analysis from a broad perspective. As the usual unit costs were applied for the formal services, 'shadow price' was used for informal care. The cost-effectiveness analysis used the differences in costs and outcomes (POS-8 and ZBI) between baseline and follow-up at 12 weeks. The total costs for 12 weeks, measured at follow-up, were lower in the fast-track intervention group than in the usual-care group by £1789 (95% CI −£5224 to £1902), which converts to £2424 (95% CI −£7077 to £2577) in 2018 prices. After excluding inpatient care and informal care, mean service costs for 12 weeks were £1195 lower for the intervention group (95% CI −£2916 to £178), which converts to £1619 (95% CI −£3950 to £241) in 2018 prices. Cost-effectiveness planes showed that 33.8% of the replications for POS-8 indicated that patients in the intervention group had lower costs and better outcomes than patients in the control group, and 54.9% had lower costs but worse outcomes. For ZBI, 47.3% of the replications showed lower costs and better outcomes, whereas 48% indicated higher costs and better outcomes.

The McCaffrey *et al.*[160] study was an Australian study that estimated incremental net monetary benefit (INMB) and cost-effectiveness acceptability curves for 1 extra day at home among patients with mixed cancer and non-cancer diagnoses with complex or unstable symptom management and a high level of care needs. McCaffrey *et al.*[160] provided services across multiple settings. The data on resource use that were collected included days at home, specialist palliative care service, acute hospital and palliative care unit inpatient days, and outpatient visits. Intervention costs were calculated based on staff administration, travel and direct patient contact time, overheads, and consumables. Analysis was conducted from a health-care provider perspective and bootstrapping was used to calculate the CIs around the INMB and cost-effectiveness acceptability curves. Total costs were AU$6452 (95% CI AU$4469 to AU$8586) [converts to £5750 (95% CI £3983 to £7652) at 2018 rates] in the HSPC group and AU$5425 (95% CI AU$2404 to AU$8531) [converts to £4835 (95% CI £2142 to £7602) at 2018 rates] in the control group. The incremental cost between the two groups was AU$1027 (95% CI –AU$2612 to AU$4738) [converts to £915.22 (95% CI –£2327.71 to £4222.32]. When the INMB of 1 more day at home was compared with varying threshold values, the intervention was preferred to usual care at > AU$1068. Sensitivity analyses with different inclusion ranges of costs (using hospital inpatient costs only and excluding high cost outliers) indicated that home-based palliative care was preferred at > AU$2547 (converts to £2270 at 2018 rates) and AU$846 (converts to £754 at 2018 rates). It was concluded that the intervention had a potential to be cost-effective, especially in trials with longer follow-up. The meaning of the threshold value for 1 extra day at home remains for future research.

Both Farquhar *et al.*[75,76] studies reported the cost-effectiveness of the Breathlessness Intervention Service (BIS), a multidisciplinary complex intervention underpinned by a palliative care approach for patients with advanced cancer and advanced non-malignant disease separately. The BIS was a model of HSPC in which service provision traversed multiple settings in the UK.

In Farquhar *et al.*,[75] data from patients with advanced cancer were analysed from a societal perspective by including costs of informal care. Total health/social costs, including informal care for 8 weeks prior to the baseline assessment, were £6137 (SD £6099) [or £6952 (SD £6909) in 2018 prices] in the HSPC group and £5461 (SD £6099) [or £6186 (SD £6909) in 2018 prices] in the usual-care group. Costs between baseline and follow-up at 2 weeks were £794 (SD £866) [or £899 (SD £981) in 2018 prices] for HSPC and £1121 (SD £1635) [or £1270 (SD £1852) in 2018 prices] for usual care.

The intervention cost for HSPC was £119 (SD £62), or £135 (SD £70) in 2018 prices. Total costs were £354 lower for HSPC (95% CI –£1020 to £246) [or £401 (95% CI –£1155 to £279) in 2018 prices] and incremental QALY gain was 0.0002 years (95% CI –0.001 to 0.002), after controlling for baseline. The chance of HSPC having lower total costs and providing better outcomes in terms of reduced distress due to breathlessness was 80.9% according to cost-effectiveness planes, and the chance of HSPC having higher costs and better outcomes was 16.4%. The chance of HSPC having lower total costs and greater QALY gains was 50.9%, and the chance of HSPC having higher costs and greater QALY gains was 11%.

An NHS perspective was taken in the analysis of data from patients with advanced non-malignant disease. In Farquhar *et al.*,[76] total health/social costs for 8 weeks prior to the baseline assessment were £1952 (SD £3290) [or £2211 (SD £3727) in 2018 prices] for the HSPC group and £3630 (SD £5588) [or £4112 (SD £6330) in 2018 prices] for the usual-care group. Costs between baseline and follow-up at 4 weeks were £1371 (SD £2948) [or converts to £1553 (SD £3339) in 2018 prices] for HSPC and £659 (SD £1253) [or £746 (SD £1419) in 2018 prices] for usual care.

The intervention cost for HSPC was £156 (SD £80), or £177 (SD £91) in 2018 prices. On adjusting for baseline, the total cost was £799 higher for HSPC (95% CI –£237 to £1904) [or £905 (95% CI –£268 to £2157) in 2018 prices] than for usual care, and the HSPC group gained 0.003 extra QALYs (95% CI –0.001 to 0.007). The cost per QALY for HSPC was £266,333 (£301,692 in 2018 prices). The chance

of the BIS having lower total costs and greater QALYs was 7% according to cost-effectiveness planes. There was an 86.5% likelihood of HSPC having higher total costs and greater QALY gains. The HSPC intervention appeared to be more cost-effective among patients with cancer, but not among patients with non-malignant disease.

Mendoza-Galindo *et al.*[101] compared resource use and costs between the early palliative care group and usual-care group in patients with a cancer diagnosis in Mexico. The study involved an outpatient model of HSPC and assessed number/days of hospitalisation and emergency room, visits as well as their costs. The number of emergency room visits in the early palliative care group was 39, whereas, in the control group, it was 50 ($p = 0.074$). There was also no difference in the number of hospitalisations (48% vs. 51%) or in days of hospitalisation (78 vs. 90 days; $p = 0.808$) between the groups. The median cost associated with emergency room visits was lower in the early palliative care group (US$21.99, which converts to £16.97 at 2018 rates) than in the usual-care group (US$46.35, which converts to £35.76 at 2018 rates) ($p = 0.081$). The authors further reported a lower median cost of hospitalisation days for the early palliative care group (US$167.57, which converts to £129.30 at 2018 rates) than for the usual-care group (US$295.05, which converts to £227.66 at 2018 rates) ($p = 0.015$).

Ma *et al.*[70] assessed resource use and operating costs between an early palliative care intervention and usual care for patients in the ICU setting. It was an inpatient consult model of HSPC. Resources used were extracted from patients' electronic medical records, and included mechanical ventilation, vasopressors, haemodialysis, tracheostomy, cardiopulmonary resuscitation, ED visit, hospital re-admission, duration of hospital stay and ICU duration. Early palliative care patients had fewer ventilator days (median 4 vs. 6; $p = 0.042$), fewer tracheostomies performed (1% vs. 7.8%; $p = 0.035$), fewer post-discharge ED visits (1.3% vs. 12.5%; $p = 0.007$), fewer days on mechanical ventilation [median 4 (IQR 3–7) vs. 6 (IQR 3–13); $p = 0.042$] and fewer hospital re-admissions (17.3% vs. 33.3%; $p = 0.0024$) than usual care patients. There was no difference between the intervention and control groups in ICU length of stay (median 5 days vs. 5.5 days, respectively), numbers on mechanical ventilation (53.6% vs. 56.9%, respectively; $p = 0.64$), numbers on vasopressors (48.5% vs. 50%, respectively; $p = 0.83$), days on vasopressors (median 3 vs. 3, respectively; $p = 0.91$), numbers on haemodialysis (15.5% vs. 23.5%, respectively; $p = 0.15$), numbers receiving cardiopulmonary resuscitation (5.2% vs. 6.9%, respectively; $p = 0.61$) or hospital length of stay (median 10 days vs. 11 days, respectively). An analysis of operating costs was conducted, although it lacked statistical power to detect the difference. Intervention patients had lower medical ICU costs [US$9860 (converts to £7608.08 at 2018 rates) vs. US$15,660 (converts to £12083.42 at 2018 rates); $p = 0.004$] and lower pharmacy costs [US$3430 (converts to £2646.62 at 2018 rates) vs. US$5850 (converts to £4513.92 at 2018 rates); $p = 0.016$] per patient than the control group. However, the total operating cost per patient was not different between the intervention and control groups [US$37,310 (converts to £28,788.78 at 2018 rates) vs. US$45,790 (converts to £35,332.04 at 2018 rates), respectively; $p = 0.14$]. An estimated US$880 (£679.02 in 2018 prices) of the intervention group's per-patient total operating cost was due to the added cost of the palliative care consultation.

Quality of the evidence

In the GRADE approach, we downgraded the quality of evidence for cost and cost-effectiveness to very low because of a high risk of bias across studies (–2 levels as a result of very serious study limitations: high risk of bias for performance, detection, attrition, reporting, size of study and other bias) and inconsistency in the direction of the results (–1 level as a result of variability in results) (see *Table 2*).

Synthesis of nested or embedded qualitative studies that explored stakeholders' views and experiences of hospital-based specialist palliative care

Ten studies, with a total of 322 participants [245 patients, 20 carers, 9 HSPC team members, 29 physicians (including oncologists), 14 oncology nurse practitioners, 1 consultant in interstitial lung disease, 1 clinical nurse specialist in interstitial lung disease, 1 community matron, 1 community palliative care nurse and 1 GP]

also had qualitative components that were used to explore stakeholders' views and experiences of HSPC [Bajwah *et al.*,[72] Farquhar *et al.*,[75,76] Hopp *et al.*,[93] Veron *et al.*[187] (linked to Janssens *et al.*[123]), Lowther *et al.*[100] (linked to Lowther *et al.*[97]), Maloney *et al.*[132] (linked to Bakitas *et al.*[129]), Giovannetti *et al.*[127] (linked to Solari *et al.*[126]), Talabani *et al.*[122] (linked to Brännström *et al.*[118]) and Wallen *et al.*[170]] (see *Report Supplementary Material 1*, table 12). The number of patients interviewed by Wallen *et al.*[170] was unclear. However, a study[171] reporting the same data by the authors stated that 34 patients were involved in the qualitative analysis.

Four studies had HSPC models that involved service provision across multiple settings [Farquhar *et al.*,[75,76] Maloney *et al.*[132] (linked to Bakitas *et al.*[129]) and Wallen *et al.*[170]], and another four used hospital outreach services [Bajwah *et al.*,[72] Talabani *et al.*[122] (linked to Brännström *et al.*[118]), Veron *et al.*[187] (linked to Janssens *et al.*[123]) and Giovannetti *et al.*[127] (linked to Solari *et al.*[126])]. Only Lowther *et al.*[100] (linked to Lowther *et al.*[97]) used an outpatient HSPC model, whereas Hopp *et al.*[93] used an inpatient consult model.

Four studies used framework analysis[72,75,76,127] and three studies used thematic analyses[130,132,171] as their analyses methods. Three studies described the use of content analysis/thematic content analysis;[100,122,187] this was unclear in Hopp *et al.*[93] Semistructured interviews were carried out in all the studies except Slota *et al.*[171] and Hopp *et al.*[93] The method of data collection in Slota *et al.*[171] was open-ended, qualitative questions on a questionnaire, whereas Hopp *et al.*[93] involved qualitatively reviewing clinical records.

Data from the studies were synthesised into two themes: valued components and challenges to HSPC provision.

Valued components

Participants valued the patient- and family-centredness of the HSPC intervention, as it helped to address the varied needs of patients and their caregivers/families. Benefits described included better symptom control, psychosocial support and coping, empowerment, reduced isolation, and improved use of devices. The psychosocial support provided as part of HSPC ensured that patients and their caregivers/families were able to ask questions, they were listened to and they received much needed emotional and practical support. Patients particularly valued services that they received in the secure environment of their homes and the support provided to their families. HSPC further facilitated care-planning and the discussion of advanced care plans. Although HSPC was viewed favourably by participants in these studies, there was also evidence that some participants questioned its usefulness. For instance, in Veron *et al.*[187] (linked to Janssens *et al.*[123]), there were mixed reactions among advanced COPD patients about the value of the HSPC intervention. Authors described poor recollection of the HSPC consultation by patients and patients tended not to consider themselves to be sick, while ascribing their functional limitations to health problems other than COPD. Patients in this study avoided talking about the future and end-of-life issues and wanted to focus on the present.

Patients and their caregivers/families found the information provided during the HSPC intervention to be useful, as it ensured a better understanding of illness and treatment options. Patients and their caregivers/families valued the multidisciplinary nature of the HSPC team and their specialist expertise. Health-care professionals such as oncologists tended to describe better patient care resulting from integration of palliative care with oncology at the time of diagnosis of advanced cancer.

Challenges to hospital-based specialist palliative care provision

Challenges to HSPC provision in these studies were identified, including lack of referral to HSPC by other health professionals, perception of palliative care as being synonymous with imminent death, lack of willingness to engage with palliative care, organisational barriers (e.g. insufficient services) and issues with the experimental study design (e.g. inadequate duration of the HSPC intervention).

Chapter 4 Discussion

Low- to very low-quality evidence was found for the primary and secondary outcomes.

Patient health-related quality of life

The results of the 10 studies[35,48,73,85,106,129,161,163,167,168] that reported adjusted end-point values, including a total of 1344 participants, showed that HSPC may improve patient HRQoL, on average, by 0.26 SMD over usual care (95% CI 0.15 to 0.37; $I^2 = 3\%$; low-quality evidence). Positive SMDs indicate better patient HRQoL, whereas negative SMDs indicate lower patient HRQoL. Owing to the low quality of the evidence, we are uncertain about the effect of HSPC on patient HRQoL; the true effect may be substantially different. The result obtained from the adjusted end-point values was supported from sensitivity analyses using unadjusted end-point values (SMD 0.41; nine studies with 1201 participants) and unadjusted change values (SMD 0.67; nine studies with 1278 participants). Sensitivity analyses evaluating the use of an estimate of 0.02 in adjusting for clustering in the cluster RCT (McCorkle *et al.*[48]) with adjusted end-point data (SMD 0.29; nine studies with 1280 participants) and unadjusted end-point data (SMD 0.46; eight studies with 1137 participants) were also in favour of HSPC.

Patient symptom burden

Data from the six studies,[35,73,85,106,129,163] including a total of 761 participants, in the main analysis suggested that HSPC may reduce patient symptom burden, on average, by −0.26 SMD over usual care (95% CI −0.41 to −0.12; $I^2 = 0\%$; very low-quality evidence). Negative SMDs indicate benefit (lower level of symptom burden) and positive SMDs reflect a higher level of symptom burden. Again, we are uncertain about the effect of HSPC on symptom burden, and the true effect may be substantially different. Sensitivity analyses using unadjusted end-point values, adjusted change values and unadjusted change values, as well as sensitivity analyses evaluating the use of an estimate of 0.02 in adjusting for clustering in the cluster RCT by McCorkle *et al.*,[48] showed little to no difference between HSPC and usual care.

Patient satisfaction with care

Data from two studies,[88,163] including a total of 337 participants, in the main analysis suggest that HSPC may improve patient satisfaction with care, on average, by 0.36 SMD over usual care (95% CI 0.14 to 0.57; $I^2 = 0\%$; low-quality evidence). Positive SMDs indicate a higher level of patient satisfaction whereas negative SMDs indicate a lower level of patient satisfaction. We are uncertain about the effect of HSPC on patient satisfaction with care; the true effect is likely to be substantially different.

Caregiver satisfaction with care

Carson *et al.*[82] was the only study that presented adjusted end-point values. Family satisfaction with care was assessed using the FS-ICU survey (range 0–100, 100 = best unpaid caregiver satisfaction). It found no between-group difference between the HSPC and usual-care groups. The mean satisfaction in the HSPC group was 81.1 (95% CI 78.3 to 83.9), whereas that in the usual-care group was 84.3 (95% CI 81.3 to 87.3), with a difference of −3.1 (95% CI −7.3 to 1.0) between groups ($p = 0.13$). Due to the very low quality of the evidence, we are uncertain about the effect of HSPC on family satisfaction with care; the true effect is likely to be substantially different.

Achieving patient preferred place of death (measured by number of patients with home death)

The number of home deaths was used as a proxy measure for achieving preferred place of death. Results from the seven studies,[35,72,73,106,129,142,160] including a total of 861 participants, showed that HSPC may enable people to die in their preferred place, which is reflected in 1.63-times higher odds of home death (OR 1.63, 95% CI 1.23 to 2.16; $I^2 = 0\%$; low-quality evidence). The OR of 1.63 translates to a risk ratio of 1.22 (95% CI 1.08 to 1.39). This means that those who had HSPC had a 22% increase in the relative risk of home deaths. Given the low quality of the evidence, the effects of HSPC on achieving preferred place of death are uncertain, and the true effect may be substantially different.

Achieving patient preferred place of care

One study, by Bajwah *et al.*,[72] with 47 participants reported on this outcome. Results at the end of the study showed that, in the intervention group that received HSPC immediately after randomisation, all eight patients (100%) who died achieved their preferred place of care, compared with 11 patients (84%) in the control group, who received HSPC after 4 weeks. Owing to the very low quality of the evidence, we are uncertain about the effects of HSPC on this outcome; the true effect is likely to be substantially different.

Mortality/survival

Results from the 36 studies[35,48,70,72–79,81,82,84,85,88,89,93,96,97,106,116,118,123,126,129,139,142,147,148,156,160,161,165,167,168] (7103 participants) that reported on this outcome were of very low quality, and suggested that the effect of HSPC on mortality is inconsistent. Consequently, we are uncertain about the result.

Pain (patients)

Data from four studies[148,161,163,168] (525 participants) suggest that there is little to no effect of HSPC on pain (SMD −0.16, 95% CI −0.33 to 0.01; $I^2 = 0\%$; very low-quality evidence). Results from the sensitivity analysis using unadjusted change values also showed no difference (two studies with 291 participants). However, a sensitivity analysis using adjusted change values was in favour of HSPC (SMD −0.47; two studies with 218 participants). Given the very low quality of the evidence, we are uncertain about the effect of HSPC on pain; the true effect may be substantially different.

Patient anxiety

The main analysis on patient anxiety suggests that the effect of HSPC on patient anxiety is inconsistent (MD −0.63, 95% CI −2.22 to 0.96; $I^2 = 76\%$; five studies[48,75,76,85,161] with 384 participants; very low-quality evidence). A negative MD indicates benefit (lower level of anxiety) and a positive MD reflects harm (higher level of anxiety). Owing to the very low quality of the evidence, we are uncertain about the effect of HSPC on patient anxiety, and the true effect is likely to be substantially different. A sensitivity analysis using unadjusted end-point values, and also using an estimate of 0.02 in adjusting for clustering in McCorkle *et al.*[48] with unadjusted end-point data, showed no difference between HSPC and usual care. Sensitivity analyses with unadjusted change values, and also using an estimate of 0.02 in adjusting for clustering in McCorkle *et al.*[48] with adjusted end-point data, showed evidence in favour of HSPC. Given the high level of heterogeneity observed ($I^2 = 76\%$) in the main analysis, we carried out subgroup analyses. In the studies presenting adjusted end-point data, subgroup analysis by different patient populations did not fully explain heterogeneity, and there was no subgroup effect. Subgrouping by early versus late palliative care and also by countries also did not fully explain heterogeneity and there were

no subgroup effects. The validity of the subgroup analysis is uncertain because of the small number of studies and heterogeneity.

Caregiver anxiety

Only one study, by Carson *et al.*[82] (312 participants), presented adjusted end-point data. Carson *et al.*[82] reported a higher level of mean caregiver anxiety in the HSPC group (HADS: seven items; 0–21 scale, 21 = maximum distress) than in the control group at 3 months on adjusting for baseline and multiple respondents [mean 7.2 (95% CI 6.6 to 7.9) vs. 6.4 (95% CI 5.7 to 7.1), respectively; MD 0.8 (95% CI −0.1 to 1.8); $p = 0.09$]. Adjustments for three variables (baseline, multiple respondents and study sites) and six variables (baseline, multiple respondents, study sites, race, sex and primary/additional surrogate) also produced similar results, with *p*-values of 0.11 and 0.12, respectively. Owing to the very low quality of the evidence, we are uncertain about the effect of HSPC on caregiver anxiety, and the true effect is likely to be substantially different. A sensitivity analysis with unadjusted end-point data also showed no difference between the HSPC and usual-care groups.

Patient depression

The results of eight studies[73,75,76,85,129,161,163,167] that reported adjusted end-point data, including a total of 1096 participants, indicate that HSPC may improve patient depression, on average, by −0.22 SMD over usual care (95% CI −0.34 to −0.10; $I^2 = 0\%$; very low-quality evidence). Negative SMDs indicate benefit (lower level of depression) and positive SMDs indicate harm (higher level of depression). As a result of the very low quality of the evidence, we are uncertain about the effect of HSPC on patient depression; the true effect may be substantially different. Sensitivity analyses using unadjusted end-point values and adjusted change values found no difference between HSPC and usual care. By contrast, a sensitivity analysis using unadjusted change data (SMD −0.38, 95% CI −0.58 to −0.18; $I^2 = 12\%$; four studies with 488 participants), and a sensitivity analysis testing an estimate of 0.02 in adjusting for clustering in McCorkle *et al.*[48] with unadjusted end-point data (SMD −0.34, 95% CI −0.65 to −0.03; $I^2 = 42\%$; four studies with 286 participants) were in favour of HSPC.

Caregiver depression

The results of the studies that presented adjusted end-point data suggest that HSPC has little to no effect on caregiver depression (SMD −0.02, 95% CI −0.21 to 0.18; $I^2 = 0\%$; two studies[82,139] with 413 participants; very low-quality evidence). Negative SMDs indicate benefit (lower level of depression) and positive SMDs indicate harm (higher level of depression). Owing to the very low quality of the evidence, we are uncertain about the effect of HSPC on caregiver depression; the true effect is likely to be substantially different. A sensitivity analysis using unadjusted end-point values showed similar results.

Patient breathlessness

The data that we pooled from studies that reported adjusted end-point values indicate that HSPC may make little to no difference to breathlessness, when compared with usual care (SMD −0.04, 95% CI −0.19 to 0.12; $I^2 = 0\%$, five studies[75,76,148,161,168] with 616 participants; very low-quality evidence). Negative SMDs indicate benefit (reduced breathlessness) and positive SMDs reflect harm (worsened breathlessness). As a result of the very low quality of the evidence, we are uncertain about the effect of HSPC on breathlessness; the true effect is likely to be substantially different. A sensitivity analysis with unadjusted change values also showed that an increase or decrease in breathlessness is possible with HSPC. On the other hand, a sensitivity analysis with unadjusted end-point values was in favour of HSPC.

Adverse events in patients and caregivers

Of the eight studies[72,78,97,106,126,139,148,163] (1252 participants) that reported on adverse events, there was no evidence of serious harm. Only one study reported a non-significant increase in adverse events in the HSPC group: 15 serious adverse events in 13 patients in the HSPC group (seven in seven patients in the control group), whereas another study found that the mild adverse event of poorer appetite was higher in the HSPC group.

Caregiver burden

We could not pool data from the two studies (170 participants) that reported adjusted end-point data [Bekelman *et al.*[139] and Dionne-Odom *et al.*[136] (linked to Bakitas *et al.*[73])]. Both studies suggest that HSPC may make little to no difference to caregiver burden (very low-quality evidence). As a result of the very low quality of the evidence, we are uncertain about the effect of HSPC on caregiver burden; the true effect is likely to be substantially different. Dionne-Odom *et al.*[136] assessed caregiver burden using the MBCB scale, comprising objective burden (range 6–30; 30 indicates highest burden), demand burden (range 4–20; 20 indicates highest burden) and stress burden (range 4–20; 20 indicates highest burden) scales. On the objective burden scale of the MBCB scale, the mean caregiver burden score for the HSPC group was 0.3 points higher than that of the control group, with adjustment for patient death ($p = 0.64$). On the stress burden scale of the MBCB scale, the mean caregiver burden score for the HSPC group was 0.5 points lower than that of the control group, with adjustment for patient death ($p = 0.29$). There was no difference in the mean caregiver burden score, with adjustment for patient death, on the demand scale of the MBCB scale ($p = 0.97$). Bekelman *et al.*[139] assessed caregiver burden using the ZBI (range 0–88; 88 indicates highest burden) and reported a mean caregiver burden of 12.9 (SE 1.3) in the HSPC group and 14.8 (SE 1.4) in the control group at 12 months ($p = 0.30$). Only the sensitivity analysis with adjusted change values could be pooled in a meta-analysis, and the result was in favour of HSPC (MD −3.88, 95% CI −5.95 to −1.80; $I^2 = 0\%$; three studies with 128 participants). Two studies reported unadjusted end-point data, but we also could not pool them in a meta-analysis [Bajwah *et al.*[72] and Dionne-Odom *et al.*[136] (linked to Bakitas *et al.*[73])]. They both found no between-group differences between the HSPC and usual-care groups.

Caregiver grief

Only Dionne-Odom *et al.*[137] (linked to Bakitas *et al.*[73]) provided usable data on caregiver grief, with no evidence of a difference between the HSPC and usual-care groups (low-quality evidence). Owing to the low quality of the evidence, we are uncertain about the effect of HSPC on caregiver grief; the true effect may be substantially different. Dionne-Odom *et al.*[137] assessed caregiver grief using the PG-13 (range 11–55; 55 indicates highest level of grief), and reported a mean caregiver grief score in the HSPC group that was 2.2 points lower than that of the control group ($p = 0.21$). On adjusting for religious preference ($p = 0.40$), baseline depression levels ($p = 0.51$) and patient hospice use ($p = 0.51$), there was still no between-group difference.

Caregiver quality of life

Only Dionne-Odom *et al.*[136] (linked to Bakitas *et al.*[73]) reported adjusted end-point data on caregiver quality of life, with no evidence of benefit of HSPC over usual care (low-quality evidence). Owing to the low quality of the evidence, we are uncertain about the effect of HSPC on caregiver quality of life; the true effect may be substantially different. Dionne-Odom *et al.*[136] assessed caregiver quality of life using the CQOL (range 0–140; 140 indicates worse quality of life), and found a mean caregiver quality-of-life score in the HSPC group that was 2 points higher than that of the control group at 3 months,

with adjustment for patient death ($p = 0.39$). A sensitivity analysis with unadjusted end-point data suggests that HSPC may improve caregiver quality of life (MD 6.11, 95% CI 0.42 to 11.81; $I^2 = 0\%$; two studies with 105 participants).

Evidence from the qualitative studies that explored stakeholders' views and experiences of HSPC suggested that HSPC was beneficial as it ensured personalised and holistic care for patients and their families, while also fostering open communication and improved understanding of illness. Patients found the specialist expertise and multidisciplinary nature of the HSPC teams to be helpful, and there was oncologist support for early palliative care for patients with newly diagnosed advanced-stage cancer.

Resource use and costs

Very low-quality evidence suggests that the effect of HSPC, compared with that of usual care, on resource use, cost and cost-effectiveness is inconclusive. The evidence on resource use was varied across the different areas assessed. Two studies[88,142] found reduced cost with HSPC, when compared with usual care, whereas one study[101] found a reduction in the cost of hospitalisation days, but no difference in the cost of emergency room visits. The difference in cost was unclear in one study,[118] and the remaining nine studies[35,70,75–78,95,156,160] indicated no difference between HSPC and usual care. It was hard to tell if the costs were shifted to other settings (e.g. from acute sector to community) when data on resource use were limited to hospital. Regarding cost-effectiveness, the evidence from the full economic studies was also inconsistent. One study[77] reported cost-effectiveness planes of the POS-8 and unpaid caregiver burden (ZBI) against total costs, and found that 34% and 47% of bootstrapped differences in costs and outcomes indicated lower costs and better outcomes for the intervention. Another study[75] also presented cost-effectiveness planes with bootstrapping, whereby 66% of replicated combinations of costs and outcomes of distress due to breathlessness (NRS) against total cost indicated lower costs and better outcomes. However, another study[76] found that the intervention was not cost-effective: the ICER was £266,333 per QALY, and there was only about a 7% likelihood of lower cost and more QALYs. The last cost-effectiveness study[160] calculated the INMB of HSPC and found that the intervention was cost-effective when the willingness-to-pay threshold was > AU$1027 (£915 in 2018 prices) for 1 extra day at home.

Overall completeness and applicability of evidence

The electronic search strategy was highly sensitive to ensure that we captured the breadth of evidence on the topic. We also contacted 15 experts for grey literature and unpublished studies. Consequently, we had a large number of references to screen, and included 42 relevant RCTs, including one study published in Chinese. Importantly, the number of studies reporting on different outcomes varied, especially as we decided to report adjusted end-point values as the main meta-analysis. We presented adjusted values as the main meta-analysis because they control for differences, and also provide the most precise and least biased estimates of treatment effects. Although we had indicated that we would be carrying out subgroup analyses by disease type, HSPC team composition (e.g. physician-led vs. nurse-led vs. MDT-led services and 24 hours' access vs. temporarily restricted access), models of HSPC and country of origin, in order to explain heterogeneity, we could carry out subgroup analyses on patient anxiety only because of the lack of heterogeneity or limited heterogeneity in other studies. Owing to the small number of studies available for the subgroup analyses we carried out, their findings are uncertain. In the published protocol, we initially had stated that we would be carrying out a subgroup analysis using frailty associated with advanced age. However, no study reported on frailty. In addition, there is a need for better reporting of the findings of studies. Some studies could not be included in the meta-analysis because they did not present analysable data.

The main domains of care addressed in the studies that included either certified experts in palliative care or those described as palliative care clinicians were symptom control, coping and support, and decision-making. Many of the studies also addressed care co-ordination and future-planning. With the exception of future-planning, studies that were unclear about palliative care training of those delivering the HSPC intervention had less focus on these domains.

Most studies were carried out in hospitals with specialised palliative care teams and were largely based in the USA and UK. Palliative care, health policy and resources in these developed countries differ from those of low- and middle-income countries where resources are limited. Recent evidence suggests that, when compared with other countries, European countries and the USA tend to have the highest level of palliative care development.[172] The results obtained from these developed health-care systems cannot be extrapolated to settings with few resources. Furthermore, regulatory environment can have a significant impact on the provision and impact of HSPC on hospitals, patients and unpaid caregivers. For example, in the USA, non-hospital palliative care is provided through a large number of varied private for-profit and non-profit entities, whose effectiveness and success may vary significantly. This aspect of the service also makes the hospital to home-based care transition difficult and lacking in continuity of care. This review has shown that HSPC is expanding to other patient populations besides those with cancer.

Quality of the evidence

With the exception of Ahronheim *et al.*[81] and a foreign-language study by Jingfen *et al.*,[80] all the other studies had a high risk of bias in at least one domain. Nine studies had a high risk of bias in four or more domains.[72,74,84,118,123,161,163,165,167]

The quality of the evidence ranged from very low to low using the GRADE approach. Generally, we downgraded the evidence mainly because of serious/very serious study limitations (high risk of bias), inconsistency resulting from unexplained heterogeneity and imprecision due to a small number of participants. There were differences across studies in the models of HSPC and usual care, patient population, outcome measures and time point of primary analysis. The evidence on mortality/survival was also quite varied. These could have resulted because of the diverse patient populations in the studies, as well as the heterogeneous models of the intervention. Although the included studies assessed a wide range of outcomes, there is still a need for more evidence on the effect of HSPC on outcomes such as achieving patient preferred place of care, patient satisfaction with care, caregiver satisfaction with care, caregiver grief, caregiver quality of life, caregiver burden, caregiver depression and caregiver anxiety.

This review provided evidence of low and very low quality concerning the effectiveness on HSPC on the primary outcomes of patient HRQoL and patient symptom burden, respectively. Given the quality of the evidence, the findings should be interpreted circumspectly. Findings from ongoing studies (see *Appendix 2*) and other future studies may assist in further strengthening the certainty of the effect estimates on the effectiveness of HSPC.

Potential biases in the review process

Given that the decisions taken during the process of conducting a systematic review and meta-analysis may be affected by subjective decisions,[188] it is important to consider potential biases that may have occurred. Generally, the methods of a meta-analysis provide for transparency and standardisation, thereby enhancing reproducibility of the process. The aim was to bring together the evidence on effectiveness and cost-effectiveness of a complex intervention. For continuous outcomes such as patient HRQoL and patient symptom burden, we combined studies that presented adjusted end-point values as our main meta-analyses. We pooled heterogeneous outcome measures using SMDs.

Restricting the main meta-analyses to studies reporting adjusted end-point values reduced the number of studies we could pool together.

We could not include some studies in the meta-analyses because they did not present analysable data. Outcomes that were not reported in a usable format may be systematically different from those that were included in the meta-analyses, thereby introducing selective outcome reporting bias.[58] We followed the GRADE approach in assessing the quality of the evidence for different outcomes. Although the GRADE approach may not always ensure consistency of conclusions, we believe that it offers the advantage of a systematic and transparent process of judging the quality of the evidence.[189]

An important step in preventing bias in systematic reviews is to address publication bias. Publication bias has implications for the validity and generalisability of the findings of a meta-analysis.[190] To reduce the possibility of publication bias, we searched different sources, such as electronic databases, carried out citation-tracking, hand-searched relevant studies and reviews, and contacted experts for grey literature and unpublished studies. We drew on a comprehensive search strategy, with input from the information specialist from the Cochrane Pain, Palliative and Supportive Care group, to minimise the chances of missing relevant studies. We believe that this synthesis includes an unbiased sample that covers the populations targeted by this review. Nonetheless, we cannot rule out time-lag bias, which occurs when the results of negative trials take longer to publish than those of positive trials.[191]

To be included in this review, the intervention had to be delivered by a MDT. We defined a MDT quite broadly, encompassing studies in which different professionals delivered the intervention, and those in which one single professional led the service and included other professionals as needed. Studies such as Maltoni *et al.*[192] and Schenker *et al.*[193] were excluded because they did not meet our definition of a MDT. Furthermore, studies such as Brims *et al.*[194] and Wong *et al.*[195] were also excluded because palliative care was an integral part of routine usual care. Our decision to include studies in which the training of the palliative care team was unclear might have implications for the effect estimates that we found, with the possibility of smaller effect sizes in the review. Moreover, in almost half of the studies ($n = 20$), there was palliative care involvement in the control group. This could have resulted in a smaller effect of the intervention in these studies. Owing to differences in the reporting of the cost-effectiveness results, and also the lack of cost-effectiveness studies in this review, we could not carry out a subgroup analysis to explore differences in cost-effectiveness across countries.

We included studies in which the authors stated that the intervention that they provided was early palliative care or if this was their intention. Given that the definition of early palliative care is still an area of ongoing debate,[18] there is a need for consensus on its definition. Early palliative care being the intention of the study authors in this review will assist in having a common definition in future studies, and future reviews could pool these studies to assess its effect.

Agreements and disagreements with other studies or reviews

Four relevant systematic reviews have been published prior to this review.[9,17,18,196] Three included HSPC, whereas Haun *et al.*[18] assessed the effectiveness of early palliative care for cancer patients only. None of these previous reviews included all the RCTs in this review. This review is the first, to our knowledge, to assess the effectiveness and cost-effectiveness of HSPC on different outcomes in people with cancer, people who do not have cancer and people who have mixed diagnoses.

Dalgaard *et al.*[196] assessed the best methods for early identification of palliative trajectories in patients with cancer, patients with chronic heart failure and patients with COPD, while also identifying preconditions for early integration of general palliative care in hospitals, and outcomes for patients and relatives. This review included only one of the seminal papers on early palliative care by Temel *et al.*,[35] which found that early

integration of palliative care with standard oncology care for patients with non-small cell lung cancer led to significantly better quality of life and mood, as well as longer survival. This review concluded that evidence about outcomes was sparse and mostly relates to cancer patients receiving specialised palliative care.

Gaertner *et al.*[17] assessed the effect of specialist palliative care on quality of life and other outcomes in adults with advanced illness in hospital, hospice or community settings. This review included eight RCTs that we also identified in our review and concluded that specialist palliative care had a small beneficial effect on quality of life. The benefits were better among those who received palliative care early for cancer.[17] The review found that the results for pain and other secondary outcomes [fatigue, nausea, dyspnoea, psychosocial variables (distress, depression, anxiety, spiritual well-being, social well-being and satisfaction), survival time, place of death, cost of care and attrition (or completion rate)] were inconclusive.

Haun *et al.*[18] assessed the effectiveness of early palliative care on different outcomes such as HRQoL, depression, symptom intensity and survival among patients with advanced cancer. This review included six RCTs that were also part of our review and concluded that 'early palliative care interventions may have more beneficial effects on quality of life and symptom intensity among patients with advanced cancer than among those given usual/standard cancer care alone'.[18] The authors found only small effect sizes. The effects on mortality and depression were uncertain. The authors further stated that results should be interpreted with caution because of the very low to low certainty of the evidence and between study differences regarding participant populations, interventions and methods.

Higginson *et al.*[9] is the oldest review that was relevant. Its objective was to assess whether or not hospital-based palliative care teams improved the process or outcomes of care for patients and families at the end of life, through a qualitative meta-synthesis and quantitative meta-analysis. It did not include any of the studies in our review, and there was only one RCT. The authors found a small positive effect for hospital-based palliative care teams. Higginson *et al.*[9] further highlighted the need for better-designed studies comparing different models of HSPC, as well as the use of standardised outcome measures for assessing symptoms.

Our review agrees with these past reviews in some respects, especially with regards to HRQoL. We found evidence that HSPC may be effective in improving patient HRQoL and patient symptom burden at a small effect size. We also found that HSPC may lead to benefits on some of our secondary outcomes, such as patient satisfaction with care, achieving patient preferred place of death (measured by number of home deaths) and patient depression. The quality of the evidence ranged from very low to low. The findings of the review by Gaertner *et al.*[17] on HRQoL were comparable to our results on patient HRQoL. Gaertner *et al.*[17] found a small effect of specialist palliative care on HRQoL (seven studies, 1218 participants, SMD 0.16, 95% CI 0.01 to 0.31, moderate-quality evidence). The Cochrane review by Haun *et al.*[18] also showed a small effect of early palliative care on HRQoL (seven studies, 1028 participants, SMD 0.27, 95% CI 0.15 to 0.38, low-quality evidence).

Authors' conclusions

Implications for practice

We pooled the evidence on the effectiveness and cost-effectiveness of HSPC. Given the quality of the evidence, we suggest that these findings should be interpreted with caution until more studies are available.

For patients and carers

Patients with advanced illness may benefit from HSPC with respect to improvements in patient HRQoL and symptom burden. HSPC may improve patient satisfaction and patient depression, and may increase the chances of patients dying in their preferred place. Interviews exploring views and experiences of HSPC suggest that HSPC is beneficial as it ensures personalised and holistic care for patients and their

families, while also fostering open communication and shared decision-making, with respectful and compassionate care. HSPC does not appear to cause any serious harm. Patients could approach their clinicians and request referral to HSPC.

For clinicians

We found evidence that HSPC may improve patient HRQoL, symptom burden, patient depression and patient satisfaction with care, and may improve the chances that patients achieve their preferred place of death without causing serious harm. Although these are only small effect sizes, they may be clinically relevant at an advanced stage of disease with limited prognosis, and are person-centred outcomes important to many patients and families. It is not possible to draw firm conclusions from the limited and inconsistent evidence on survival, or on the most effective models of care.

For policy-makers

Given that population-based projections have indicated that palliative care needs will increase in the future,[197] one area that this evidence suggests policy-makers could prioritise is the further commissioning of HSPC. Importantly, this review showed that those receiving HSPC may have 1.63-times higher odds of dying in their preferred place (measured by number of patients with home deaths), in addition to benefits to patient HRQoL and patient symptom burden at no greater cost. The 1.63-times higher odds translates to an increase in the relative risk of dying in a patient's preferred place of 22% (8% to 39%). There is an urgent need for well-powered high-quality RCTs on the effect of HSPC in populations with non-cancer and mixed diagnoses, ward-based care, 24 hours' access (out-of-hours care), achieving patient preferred place of care, patient satisfaction with care, unpaid caregiver outcomes (satisfaction with care, burden, depression, anxiety, grief, quality of life) and cost-effectiveness.

For funders of the intervention

When compared with usual care, HSPC may improve patient HRQoL, symptom burden, patient satisfaction and patient depression, while also helping patients die in their preferred place (measured by number of home deaths). It appears that HSPC carried no greater cost than usual care and did not cause any serious harm.

Implications for research

General

This review has shown that there is a need for larger, well-conducted RCTs assessing different models of HSPC in non-cancer and mixed diagnoses populations. Compared with cancer studies, studies involving non-cancer and mixed diagnoses are fewer. This review found only a limited number of RCTs assessing ward-based HSPC models and 24 hours' access (out-of-hours care), and no study assessing relatively new constructs such as frailty or a focus on multimorbidity. These are areas that need to be explored in future RCTs that are sufficiently powered to detect differences between the intervention and control groups. There is also an urgent need for studies to consider the varied regulatory environment and conduct more systems-wide research looking at HSPC spanning more than one setting and how integrated HSPC across hospital and community changes outcomes and costs. To expand the existing evidence base, it is paramount that more RCTs are carried out in low- and middle-income countries with a good description of the intervention and usual care. More RCTs on the effectiveness of HSPC on other outcomes besides patient HRQoL and patient symptom burden are also needed. For instance, patient satisfaction with care, achieving patient preferred place of care, caregiver outcomes (e.g. satisfaction with care, burden, depression, anxiety, grief, quality of life) and cost-effectiveness should be further explored. There is an urgent need for more cost-effectiveness studies on HSPC, as we only identified four such studies in this review. A clearer definition of early palliative care by the palliative care community would assist future RCTs evaluating it to be more focused.

Design

Future RCTs need to be larger, well designed and well conducted, with high-quality reporting of their methods. Interventions should be described clearly under the different models we have proposed for HSPC. To strengthen the internal validity of effect estimates, future studies need to be rigorous in both design and delivery, and should be based on sufficient power. To ensure fidelity of delivery of the intervention, detailed descriptions of the components of the intervention should be provided in the methods, including training of staff involved in the provision of HSPC. In addition, the delivery of HSPC (including frequency and duration of treatment), receipt of HSPC and enactment of HSPC should be clearly described. When possible, usual-care groups should not include access to HSPC and, if this does happen, there should be clear documentation.

When possible, investigators should aim to control for selection bias (i.e. to ensure adequate allocation concealment), performance bias (i.e. to blind study participants) and detection bias (i.e. to blind outcome assessors). However, this will continue to be a challenge in this area. With respect to settings, interventions that span acute and community settings are needed. Concerning heterogeneity of samples, there is a need to investigate disease-homogeneous samples to better account for disease-specific trajectories and multimorbidity.

In addition, future studies should also consider effectiveness–implementation hybrid designs, combining elements of clinical effectiveness and implementation research to enhance public health impact. In particular, strategies to encourage implementation of evaluation findings should be incorporated and be based on a scientific understanding of the behaviours that need to change, the relevant decision-making processes, and the barriers to and facilitators of change. This will speed the translation of research findings into routine practice.

Measurement

Use of sensitive outcome measures that have been validated in palliative populations would enable changes in outcomes such as patient HRQoL to be more readily detected. Most of the available quality-of-life measures do not include domains that have been found to be important in palliative populations such as existential or spiritual domains;[198,199] this could potentially underestimate the effect of palliative care interventions, including HSPC. Furthermore, many of the HRQoL measures have been validated on the assumption that scores deteriorate towards death, and so exhibit floor effects in palliative care. In addition, they are not individualised. Pain, although an appropriate primary outcome in studies of participants with malignancies, does not appear to be an appropriate outcome for studies of participants with non-malignant diagnoses. Better outcome measures are needed, which are person-centred and can be used across studies. It is also important that RCTs report adequately on outcomes they stated in their protocol to avoid selective outcome reporting bias. There is a need for more studies reporting adjusted end-point values. It appears that consensus is needed by palliative care researchers on whether end-point scores or change scores are the most informative for this population. The ongoing focus on improvement of outcomes may be leading to discounting of the effectiveness of HSPC in slowing deterioration, compared with usual care. Concerning economic measurements, data sources such as health insurance databases and hospital medical records are more reliable and accurate, but the information on services in community and/or at home (including delivery of care by unpaid caregivers) requires different approaches. For example, hospital records (e.g. Hospital Episode Statistics) linked with community service data (e.g. Clinical Practice Research Datalink) would help in understanding the change of resource use and its implication on costs/cost-effectiveness. Moreover, future studies need to collect primary data from patients or family members, using tools such as the CSRI, which will provide information on delivery of care by unpaid caregivers, as well as collecting primary data on health and social care use.

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Adejoke O Oluyase (https://orcid.org/0000-0002-1506-7262) (Postdoctoral Research Associate) was involved in the design, data collection, data analysis and interpretation, drafting the review and critical revision of the review.

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Sabrina Bajwah (https://orcid.org/0000-0001-5338-8107) (Clinical Senior Lecturer and Honorary Consultant in Palliative Care) won funding for the project, and led both the review and the project team. She was involved in the design, data collection, data analysis and interpretation, drafting the review and critical revision of the review.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

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Appendix 1 Search strategies

MEDLINE

Date range searched: 1947 to 27 August 2019.

Search strategy

1. exp Palliative Care/
2. exp Terminal Care/
3. exp Terminally Ill/
4. palliat*.mp.
5. (terminal* adj5 (care or caring)).mp.
6. ((advanced or terminal) adj5 (ill* or disease*)).mp.
7. (end stage or end of life or last year of life or LYOL or life's end).mp.
8. or/1-7
9. (home adj5 (hospital or palliat*)).mp.
10. ((outreach or hospital at home or outpatient or out-patient or ambulatory or posthospital or post-hospital or consult*) adj2 (care or center* or centre* or interven* or management or model* or nurs* or program* or service* or team* or therap* or treat*)).mp.
11. exp Outpatients/
12. exp Hospitals/
13. exp Inpatients/
14. ((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.
15. hospice*.mp.
16. or/9-15
17. 8 and 16
18. (child* or adolescent* or infant* or baby or babies or neonat* or juvenil* or pediatric* or paediatric* or young person* or young people or youth* or young adult*).ti.
19. 17 not 18
20. randomized controlled trial.pt.
21. controlled clinical trial.pt.
22. randomized.ab.
23. placebo.ab.
24. randomly.ab.
25. trial.ab.
26. groups.ab.
27. (random* or control* or intervention* or evaluat*).tw.
28. ("before and after" or case control* or cohort study or quasi experiment* or time series).tw.
29. or/20-28
30. 19 and 29
31. 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/
32. (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.
33. 31 or 32
34. 19 and 33
35. 30 or 34

36. (animals not (humans and animals)).sh.
37. 35 not 36.

EMBASE

Date range searched: 1974 to 27 August 2019.

Search strategy

1. exp palliative therapy/
2. exp terminal care/
3. exp terminally ill patient/
4. palliat*.tw.
5. (terminal* adj5 (care or caring)).tw.
6. ((advanced or terminal) adj5 (ill* or disease*)).tw.
7. (end stage or end of life or last year of life or LYOL or life's end).tw.
8. or/1-7
9. (home adj5 (hospital or palliat*)).tw.
10. ((outreach or hospital at home or outpatient or out-patient or ambulatory or posthospital or post-hospital or consult*) 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*)).tw.
11. exp outpatients/
12. or/9-11
13. hospice*.tw.
14. 12 or 13
15. exp hospital/
16. exp hospital patient/
17. ((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*)).tw.
18. or/15-17
19. 14 or 18
20. (child* or adolescent* or infant* or baby or babies or neonat* or juvenil* or pediatric* or paediatric* or young person* or young people or youth* or young adult*).tw.
21. 19 not 20
22. random$.tw.
23. factorial$.tw.
24. crossover$.tw.
25. cross over$.tw.
26. cross-over$.tw.
27. placebo$.tw.
28. (doubl$ adj blind$).tw.
29. (singl$ adj blind$).tw.
30. assign$.tw.
31. allocat$.tw.
32. volunteer$.tw.
33. crossover procedure/
34. double-blind procedure.tw.
35. randomized controlled trial/
36. single blind procedure/
37. ("before and after" or case control* or cohort study or quasi experiment* or time series).tw.
38. or/22-37
39. 8 and 21 and 38

40. 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/
41. (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.
42. 40 or 41
43. 8 and 21 and 42
44. 39 or 43
45. (animal/or nonhuman/) not human/
46. 44 not 45.

PsycINFO

Date range searched: 1806 to 28 August 2019.

Number	Search strategy
1	exp Palliative Care/
2	exp Terminally Ill Patients/
3	palliat*.tw.
4	(terminal* adj5 (care or caring)).tw.
5	((advanced or terminal) adj5 (ill* or disease*)).tw.
6	(end stage or end of life or last year of life or LYOL or life's end).tw.
7	or/1-6
8	(home adj5 (hospital or palliat*)).tw.
9	((outreach or hospital at home or outpatient or out-patient or ambulatory or posthospital or post-hospital or consult*) 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*)).tw.
10	exp OUTPATIENTS/
11	or/8-10
12	exp HOSPICE/
13	11 or 12
14	exp HOSPITALS/
15	exp Hospitalized Patients/
16	((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*)).tw.
17	or/14-16
18	13 or 17
19	(child* or adolescent* or infant* or baby or babies or neonat* or juvenil* or pediatric* or paediatric* or young person* or young people or youth* or young adult* or matern*).tw.
20	18 not 19
21	exp Clinical Trials/
22	(randomis* or randomiz*).tw.
23	(random$ adj3 (allocat$ or assign$)).tw.
24	((clinic$ or control$) adj trial$).tw.

Number	Search strategy
25	((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
26	(crossover$ or "cross over$").tw.
27	exp Random Sampling/
28	exp Experiment Controls/
29	exp PLACEBO/
30	placebo$.tw.
31	exp Program Evaluation/
32	exp Treatment Effectiveness Evaluation/
33	((effectiveness or evaluat$) adj3 (stud$ or research$)).tw.
34	or/21-33
35	("before and after" or case control* or cohort study or quasi experiment* or time series).tw.
36	34 or 35
37	7 and 20 and 36
38	(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.
39	exp BUDGETS/
40	exp health care costs/or exp "costs and cost analysis"/
41	exp Resource Allocation/
42	exp Health Care Economics/
43	or/38-42
44	7 and 20 and 43
45	37 or 44
46	limit 45 to human

Cumulative Index to Nursing and Allied Health Literature search strategy

Date range searched: 1982 to 28 August 2019.

Number	Search strategy
S45	S43 not S44
S44	TI (animals not (humans and animals))
S43	S33 or S42
S42	S8 and S21 and S41
S41	S34 or S35 or S36 or S37 or S38 or S39 or S40
S40	MH economic value of life
S39	MH resource allocation
S38	MH fees and charges
S37	MH economics
S36	MH costs and cost analysis
S35	MH budgets

Number	Search strategy
S34	TX ((cost* or economic*)) OR AB ((cost* N2 (effective* or utilit* or benefit* or minimi*)) OR ((economic model* or (budget* or fee* or financ* or price* or pricing or resourc* allocat* or (value N2 (monetary or money))
S33	S8 and S21 and S32
S32	S30 or S31
S31	TX ("before and after" or case control* or cohort study or quasi experiment* or time series)
S30	S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29
S29	TX (allocat* random*)
S28	MH quantitative studies
S27	MH placebos
S26	TX placebo*
S25	TX (random* allocat*)
S24	MH random assignment
S23	TX (Randomi?ed control* trial*)
S22	TX (singl* blind*) or (doubl* blind*) or (tripl* blind*) or (trebl* blind*) or (trebl* mask*) or (tripl* mask*) or (doubl* mask*) or (singl* mask*)
S21	S19 not S20
S20	TI (child* or adolescent* or infant* or baby or babies or neonat* or juvenil* or pediatric* or paediatric* or young person* or young people or youth* or young adult*)
S19	S14 or S18
S18	S15 or S16 or S17
S17	TX ((hospital* or inpatient*) N2 (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*))
S16	MH inpatients
S15	MH hospitals
S14	S12 or S13
S13	TX hospice*
S12	S9 or S10 or S11
S11	MH outpatients
S10	TX (outreach or hospital at home or outpatient or out-patient or ambulatory or posthospital or post-hospital or consult*) and (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*))
S9	TX home and (hospital or palliat*)
S8	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7
S7	TX (end stage or end of life or last year of life or LYOL or life's end)
S6	TX ((advanced or terminal) N5 (ill* or disease*))
S5	TX (terminal* N5 (care or caring))
S4	TX palliat*
S3	MH terminally ill patients
S2	MH terminal care
S1	MH palliative care

The Cochrane Library

- CENTRAL: issue 8 of 12, 2019.
- Cochrane Database of Systematic Reviews: issue 8 of 12, 2019.
- DARE: issue 2 of 4, 2015.
- HTA Database: issue 4 of 4, 2016.
- NHS EED: issue 2 of 4, 2015.

Search strategy

1. MeSH descriptor: [Palliative Care] explode all trees
2. MeSH descriptor: [Terminal Care] explode all trees
3. MeSH descriptor: [Terminally Ill] explode all trees
4. palliat*:ti,ab,kw
5. (terminal* near/5 (care or caring)):ti,ab,kw
6. ((advanced or terminal) near/5 (ill* or disease*)):ti,ab,kw
7. (end stage or end of life or last year of life or LYOL or life's end):ti,ab,kw
8. #1 or #2 or #3 or #4 or #5 or #6 or #7
9. (home near/5 (hospital or palliat*)):ti,ab,kw
10. ((outreach or hospital at home or outpatient or out-patient or ambulatory or posthospital or post-hospital or consult*) near/2 (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*)):ti,ab,kw
11. MeSH descriptor: [Outpatients] explode all trees
12. #9 or #10 or #11
13. hospice*:ti,ab,kw
14. #12 or #13
15. MeSH descriptor: [Hospitals] explode all trees
16. MeSH descriptor: [Inpatients] explode all trees
17. ((hospital* or inpatient*) near/2 (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*)):ti,ab,kw
18. #15 or #16 or #17
19. #14 or #18
20. #8 and #19
21. (child* or adolescent* or infant* or baby or babies or neonat* or juvenil* or pediatric* or paediatric* or young person* or young people or youth* or young adult*):ti
22. (#20 and not #21).

CareSearch

Date range searched: inception to 12 September 2019.

Search strategy

1. Inpatient
2. Hospital
3. #1 OR #2
4. (((Palliative) OR Terminal) OR End stage) OR End of life
5. #3 AND #4
6. Outpatient
7. Outreach
8. Hospital at home
9. Ambulatory

10. Post-hospital
11. Consult
12. #6 OR #7 OR #8 OR #9 OR #10 OR #11
13. Hospice
14. 12 or 13
15. (((Palliative) OR Terminal) OR End stage) OR End of life
16. #14 AND #15
17. #5 OR #.

Appendix 2 List of excluded studies

Ongoing studies

ACTRN12618001045202: Poon P. Collaborative supportive care for life-limiting chronic conditions: a prospective randomised controlled study comparing supportive care with standard care. Ongoing study, July 2018.

CHICTR1800014482: Zhang L. Palliative care in end-stage heart failure and application of deep learning. Ongoing study, January 2016.

Courtright KR, Madden V, Gabler NB, Cooney E, Small DS, Troxel A, *et al.* Rationale and design of the Randomized Evaluation of Default Access to Palliative Services (REDAPS) trial. *Ann Am Thorac Soc* 2016;**13**:1629–39.

DRKS00013922: Becher MU. Early palliative care for patients with symptomatic heart failure. Ongoing study, May 2019.

Graney BA, Au DH, Barón AE, Cheng A, Combs SA, Glorioso TJ, *et al.* Advancing Symptom Alleviation with Palliative Treatment (ADAPT) trial to improve quality of life: a study protocol for a randomized clinical trial. *Trials* 2019;**20**:355.

Hutt E, Da Silva A, Bogart E, Le Lay-Diomande S, Pannier D, Delaine-Clisant S, *et al.* Impact of early palliative care on overall survival of patients with metastatic upper gastrointestinal cancers treated with first-line chemotherapy: a randomised phase III trial. *BMJ Open* 2018;**8**:e015904.

IRCT20160521027993N1: Lemeski AT. The effect of palliative care education on self efficacy of elderly with chronic heart failure. Ongoing study, June 2018.

IRCT20160914029817N6: Nouhi E. Effect of non-drug palliative care on quality of life in patients with chronic obstructive pulmonary disease. Ongoing study, June 2018.

IRCT20180531039925N1: Vashani HB. The effect of palliative care program on the quality of life of children with leukemia. Ongoing study, June 2018.

Kluger BM, Katz M, Galifianakis N, Pantilat SZ, Kutner JS, Sillau S, *et al.* Does outpatient palliative care improve patient-centered outcomes in Parkinson's disease: rationale, design, and implementation of a pragmatic comparative effectiveness trial. *Contemp Clin Trials* 2019;**79**:28–36.

Matsumoto Y. Early specialized palliative care in Japan: a feasibility study. *Ann Oncol* 2016;**27**(Suppl. 7):mdw466.

NCT01828775. Responsible party: City of Hope Medical Centre. Integration of palliative care for cancer patients on phase I trials. Ongoing study, September 2014.

NCT01846520. Responsible party: City of Hope Medical Centre. A randomized trial of a family caregiver palliative care intervention. Ongoing study, October 2013.

NCT01983956. Responsible party: University Hospital Inselspital. A structured early palliative care intervention for patients with advanced cancer – a randomized controlled trial with a nested qualitative study (SENS Trial) (SENS). Ongoing study, December 2013.

NCT02139917. Responsible party: Tam BML. Effects of a transitional palliative care model on patients with end-stage renal failure (ESRF). Ongoing study, August 2014.

NCT02308865. Responsible party: University Hospital, Lille. Impact of early palliative care on quality of life and survival of patients with non-small-cell metastatic lung cancer in Northern France. Ongoing study, October 2014.

NCT02375997. Responsible party: Shen Lin. Early palliative care with standard oncology care versus standard oncology care alone in Metastatic Esophageal Squamous Carcinoma (ESCC) and gastric cancer. Ongoing study, October 2014.

NCT02533921. Responsible party: University of Colorado, Denver. Does outpatient palliative care improve patient-centered outcomes in Parkinson's Disease? Ongoing study, October 2015.

NCT02543541. Responsible party: Case Comprehensive Cancer Centre. A pilot study of structured palliative care for patients enrolled on phase I clinical trials. Ongoing study, October 2015.

NCT02631811. Responsible party: Hospices Civils de Lyon. Impact on quality of life of an early management supportive care of patients with acute leukemia in first relapse. Ongoing study, November 2015.

NCT02712229. Responsible party: Schenker Y. A cluster randomized trial of a primary palliative care intervention (CONNECT) for patients with advanced cancer. Ongoing study, July 2016.

NCT02719938. Responsible party: University of North Carolina, Chapel Hill. Triggered palliative care for advanced dementia. Ongoing study, March 2016.

NCT02786524. Responsible party: Harris Katherine. A randomized study to evaluate the effect of outpatient symptom management on symptom burden in advanced stage or recurrent gynecologic oncology patients receiving chemotherapy. Ongoing study, February 2016.

NCT02868112. Responsible party: Nipp R. Pilot study of a transdisciplinary intervention integrating geriatric and palliative care with oncology care for older adults with cancer. Ongoing study, October 2016.

NCT02929966. Responsible party: Nava S. Effect of palliative care in patients with end stage pulmonary fibrosis: a randomized control study. Ongoing study, July 2016.

NCT02975869. Responsible party: El-Jawahri A. Randomized trial of a collaborative palliative and oncology care model for patients with acute myeloid leukemia. Ongoing study, November 2016.

NCT03022630. Responsible party: Bernard G. The Creation of Models for Palliative Assessments to Support Severe Illness (COMPASS) investigation: testing early and ongoing implementation of palliative care for incurable non-malignant diseases. Ongoing study, February 2017.

NCT03088202. Loge JH. PALLiON – PALLiative Care In ONcology – a cluster-randomized trial to improve the care for cancer patients with a short life expectancy. Ongoing study, March 2017.

NCT03170466. Responsible party: Kavalieratos D. Primary palliative care in heart failure: a pilot trial. Ongoing study, October 2017.

NCT03181854. Responsible party: Yun YH. Randomized controlled trial of integrated early palliative care for advanced cancer patients. Ongoing study, September 2017.

NCT03229343. Responsible party: Assistance Publique – Hôpitaux de Paris. Impact of a systematic palliative care on quality of life, in advanced idiopathic pulmonary fibrosis (IPF). A randomized multi-center trial. Ongoing study, December 2017.

NCT03310918. Responsible party: El-Jawahri A. Randomized trial of a collaborative palliative and leukemia care model for patients with acute myeloid leukemia receiving non-intensive therapy. Ongoing study, October 2017.

NCT03456323. Responsible party: Baldwin M. Post-ICU palliative care consultation intervention pilot trial in older survivors of acute respiratory failure. Ongoing study, March 2018.

Weber C, Stirnemann J, Herrmann FR, Pautex S, Janssens JP. Can early introduction of specialized palliative care limit intensive care, emergency and hospital admissions in patients with severe and very severe COPD? A randomized study. *BMC Palliat Care* 2014;**13**:47.

Study awaiting classification

Aljohani A. *Early Interdisciplinary Palliative Care for Patients with Non-small-cell Lung Cancer*. 20th Congress of the Asian Pacific Society of Respirology, 3–6 December 2016, Kuala Lumpur, Malaysia, abstract no. 75.[69]

Commentary/discussion only

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Community

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Appendix 3 Description of intervention and control conditions

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed
Ahronheim *et al.*[81]	Inpatient consulting model: the intervention consisted of palliative care consultation by the team nurse and physician, who visited the patient and discussed management with available members of the primary health-care team in the hospital, excluding weekends. The palliative care team also held meetings with family caregivers or other surrogates when possible. If face-to-face meetings were not possible, discussions were held over the telephone. During encounters with health professionals or family caregivers, the palliative care team discussed various care options. The goal of the intervention was to enhance patient comfort. Recommendations regarding palliative care interventions were made to the inpatient team at the hospital but contact between or after hospitalisations were generally with the family, because there was considerable variation among patients as to the nature, location or existence of a consistent physician. On re-admission, the patient was identified through a computerised system, usually < 24, and no more than 48, hours after admission. Consent to continue in the study was obtained from the surrogate by telephone, and the inpatient providers were contacted	Initial randomisation until final discharge or in-hospital death	The control group was treated by the primary care team without the input of the palliative care team	• Outcomes: ○ Mortality ○ Site of discharge ○ Length of stay ○ Number of re-admissions ○ Use of non-palliative procedures ○ DNR orders and CPR ○ Systemic antibiotics ○ Whether or not a decision was made to forgo life-sustaining treatments ○ Antibiotics ○ Intravenous fluids ○ Blood-drawing ○ Whether or not a decision was made to adopt an overall palliative care plan • Resource use: ○ Number of hospital admissions ○ Number of rehospitalisations ○ Mean length of stay post randomisation

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed

Bajwah *et al.*[72]
 	
• Associated report: Bajwah *et al.*[117]
	Hospital at home or hospital outreach model: the intervention was offered alongside standard care. The fast-track group received the intervention after 1 week, whereas the control group was offered it after 4 weeks. The intervention involved a palliative care assessment and care co-ordination between specialist and community settings. A palliative care specialist nurse who had received training delivered the intervention. Supervision was provided to support the nurse. Before the case conference, the nurse contacted the patient and carer to identify their current palliative care concerns and their expectations from the case conference. During the case conference, current and anticipated palliative care concerns and end-of-life issues were discussed. An action plan was agreed on for each concern and an individualised care plan developed. The care plan was shared with the patient and carer, the ILD specialist team, the GP, all attendees at the case conference, and any other health professional identified by the patient as involved in their care. The nurse carried out telephone follow-up to check if the areas highlighted in the care plan had been addressed	8 weeks	All patients had best standard care during the study: patients had ILD specialist care throughout. This included services provided by ILD physicians, ILD clinical nurse specialist, occupational therapist, physiotherapist and oxygen assessment and treatment services. All patients were able to access inpatient ILD treatment as needed. Patients were referred to community health professionals when needed	• Primary outcome:
				  ○ POS assessed by the patient
				
				• Secondary outcomes:
				  ○ POS assessed by carer
				  ○ Breathlessness assessed using the Dyspnoea-12 questionnaire and MRC breathlessness scale
				  ○ Symptom control
				  ○ Patient QoL assessed using the KBILD questionnaire and the SGRQ
				  ○ Carer's QoL assessed using the CQOL
				  ○ Patient anxiety and depression assessed using the HADS
				  ○ Carer anxiety and depression assessed using the HADS
				  ○ Carer burden assessed using the ZBI
				  ○ Preferred place of care and death
				  ○ Patient use of other services
				  ○ Consent and recruitment rates
				  ○ Percentage of patients in fast-track group receiving case conferences within 14 days

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed
Bakitas *et al.*[129] • Associated reports: Bakitas *et al.*[130,131] Maloney *et al.*[132] and O'Hara *et al.*[133]	Multiple models: the intervention, based on the chronic care model, used a case management, educational approach to encourage patient activation, self-management, and empowerment. The strategies used in the author's prior studies were refined and converted to a manualised, telephone-based format to improve access to palliative care in a rural population. A nurse with specialist training in palliative care carried out four initial structured educational and problem-solving sessions and at least monthly telephone follow-up sessions until the participant died or the study ended. A bereavement follow-up call was made to the caregiver	Enrolment until death or study completion	Usual care involved access to oncology and supportive services. Patients and family members were often followed through death and bereavement	• Primary outcomes: o Patient-reported QoL measured by the FACIT-Pal o Symptom intensity measured by a modified ESAS o Resource use • Secondary outcomes: o Mood measured by the CES-D o Caregiver burden measured by the MBCB scale o Perceptions of end-of-life care measured by a revised version of the After-Death Bereaved Family Member Interview o Survival • Resource use: o Number of hospital days o Number of ICU days o Number of ED visits

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed
Bakitas *et al.*[73] • Associated reports: Dionne-Odom *et al.*[134–138]	Multiple models: the ENABLE study comprised an initial in-person, standardised outpatient palliative care consultation by a board-certified palliative care clinician and six structured weekly telephone coaching sessions by an advanced practice nurse using a manualised curriculum. Sessions covered problem-solving, symptom management, self-care, identification and co-ordination of local resources, communication, decision-making and advance care planning as well as a life-review approach that supported participants to redefine advanced illness. After the sessions, the nurse followed up patients via the telephone to provide further support. Nurse coach training included self-study, review of treatment manuals and scripts, and role-playing with feedback. The study principal investigator met with the nurse coaches weekly to review and provide feedback on difficult cases	Enrolment until death or study completion	Usual oncology care was directed by a medical oncologist and consisted of anticancer and symptom control treatments and consultation with oncology and supportive care specialists, including a clinical palliative care team. Palliative care was provided when requested	• Outcomes: ○ Patient-reported QoL measured by the FACIT-Pal and Treatment Outcome Index ○ Caregiver QoL measured by the CQOL-Cancer ○ Symptom impact measured by the Quality of Life at End of Life Symptom Impact subscale ○ Patient and caregiver mood, measured by the CES-D ○ One-year and overall survival ○ Location of death ○ Caregiver grief measured by the PG-13 ○ Caregiver burden measured by the MBCB scale • Resource use: ○ Patient-reported hospital and ICU days and ED visits ○ Chemotherapy use in previous 14 days

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed

Bekelman *et al.*[139]
 	
• Associated reports: Bekelman *et al.*[140] and Flint *et al.*[141]
	Multiple models: the CASA intervention had three components. A social worker, registered nurse and a team (including the nurse and social worker, a primary care clinician, palliative care physician and cardiologist) reviewed the care provided to the patient and, when needed, ordered tests and medications. The patient and the nurses decided on the symptoms that needed to be addressed, with the nurse using a structured guideline for this. Training in communication, motivational interviewing and the symptom guidelines was received by the nurse. Six follow-up assessments were carried out via telephone (1 or 2 per month). The social worker provided telephone-based psychosocial care to patients, while also supporting patients' informal caregivers as needed. The social worker was trained in psychosocial interventions and also received follow-up supervision. The nurse and the social worker had weekly meetings during which they discussed patients with the wider team	6 months	Usual-care group patients received care at the discretion of their clinicians. A sheet containing information on self-care for HF was given to patients. Patients with significant depressive symptoms were informed about this and their clinicians were also contacted. Clinicians may choose to treat depression at their discretion	• Primary outcome:
				  ○ Patient-reported HF-specific health status assessed using the KCCQ
				
				• Secondary outcomes:
				  ○ Depression measured by the PHQ-9
				  ○ Anxiety measured by the Generalised Anxiety Disorder-7 questionnaire
				  ○ Overall symptom distress measured by the General Symptom Distress Scale
				  ○ Pain measured by the PEG (three items derived from the BPI)
				  ○ Fatigue measured by the Patient-Reported Outcomes Measurement Information System – Short Form
				  ○ Shortness of breath measured by the Memorial Symptom Assessment Scale
				  ○ Number of hospitalisations
				  ○ Mortality
				
				• Resource use:
				  ○ Number of hospitalisations
				  ○ Use of other services

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed
Brännström *et al.*[118] • Associated reports: Brännström *et al.*,[119] Markgren *et al.*,[120] Sahlen *et al.*,[121] Talabani *et al.*[122]	Hospital outreach model: patients in the intervention group were offered a multidisciplinary approach involving collaboration between specialists in palliative and HF care. The intervention (structured, person-centred care, PCC) was delivered at home. PCC involves joint working between patients/carers and professional caregivers, including documenting the partnership. The nurses used a model of PCC that incorporated the six Ss, namely self-image, self-determination, social relationships, symptom control, synthesis and surrender. The clinical team was responsible for managing co-morbidities. Symptom assessment, QoL, and risks of decubitus, falling, and malnutrition were done using validated questionnaires	6 months	Usual care was provided mainly by GPs or doctors and/or the nurse-led HF clinic at the Medicine-Geriatrics department	• Outcomes: ○ Symptom burden assessed using the ESAS ○ HRQoL assessed using the EQ-5D ○ QoL assessed using the KCCQ ○ Functional classes ○ Mortality ○ Cost-effectiveness • Resource use: ○ Number of hospitalisations; number of days spent in hospital; number of physician and nurse visits, telephone calls and/or drug prescriptions at the outpatient clinics of the hospitals and at the primary health-care centres

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed

Brumley *et al.*[142]
 	
• Associated report: Enguidanos *et al.*[143]
	Multiple models: the IHPC programme is an interdisciplinary home-based service aimed at managing symptoms and enhancing patient's QoL. It was modelled after hospice programmes. However, it differed from hospice in the following ways: (1) physicians were not required to give a 6-month prognosis, (2) patients did not have to withdraw from curative care and (3) patients' care was co-ordinated by a palliative care physician. In addition to receiving home visits from the palliative care physician, the IHPC programme allowed patients to maintain their primary care provider
	
	The IHPC programme used an interdisciplinary team approach, with the core care team consisting of the patient and family plus a physician, nurse and social worker with expertise in symptom management and biopsychosocial intervention. The core team co-ordinated and managed care across all settings. Other team members, including spiritual counsellor or chaplain, bereavement co-ordinator, home health aide, pharmacist, dietitian, volunteer, physical therapist, occupational therapist and speech therapist, joined the core care team when needed. The team convened to develop a care plan jointly with the patient and the family. In addition, patients and families were trained in the use of medications, self-management skills and crisis intervention in the home to reduce ED visits and acute care admissions
		Participants enrolled in the IHPC arm received palliative care until death or transfer to a hospice programme	Usual care consisted of standard care to meet the needs of the patients and followed Medicare guidelines for home health-care criteria. These services included various numbers and levels of home health services, acute care services, primary care services, and hospice care. Patients were treated for conditions and symptoms when they presented them to attending physicians. In addition, they received ongoing home care when they met the Medicare-certified criteria for an acute condition	• Outcomes:
				  ○ Patient satisfaction with care assessed using the Reid–Gundlach Satisfaction with Services instrument
				  ○ Site of death
				  ○ Service use
				  ○ Cost of care
				  ○ Survival
				
				• Resource use:
				  ○ ED visits, hospitalisation, enrolment and days in hospice

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed

Carson *et al.*[82]
 	
• Associated report: Nelson *et al.*[83]
	Inpatient consulting model: a validated brochure describing chronic critical illness was provided to the family surrogate decision-makers. Research co-ordinators then arranged meetings with the support and information team. The first meeting took place after 7 days of mechanical ventilation. A second meeting took place afterwards. At the request of the family, ICU physician or support and information team clinicians, further meetings could be held. The support and information team clinicians met with the ICU physicians to review the patient before meeting with the patient. The support and information team clinicians received training on the protocol. In the intervention group, ICU clinicians were blinded to the templates for the structured meeting	The first meeting took place after 7 days of mechanical ventilation. The second meeting was carried out after further treatment was provided for a period approximating the mean duration of mechanical ventilation after tracheostomy for patients who achieved ventilator liberation	The ICU clinicians managed all family meetings according to standard practice without involving palliative care specialists. Family surrogate decision-makers in the control group received the same brochure as the intervention group. Clinicians could consult palliative care clinicians if needed	• Primary outcome:
				  ○ Anxiety and depression of surrogate
				• Secondary outcomes:
				  ○ PTSD of the surrogate
				  ○ Discussion of patient preferences
				  ○ Hospital length of stay for patients
				  ○ 90-day survival of patients
				• Resource use:
				  ○ Hospital length of stay
				  ○ Number of ICU days
				  ○ Ventilator days

Cheung *et al.*[84]	Inpatient consulting model: the intervention was a consultation and subsequent management by a palliative care team. The first consultation occurred within 24 hours of randomisation. The intervention was provided in addition to usual ICU care, commensurate with the patient's medical condition. No further information was provided	Enrolment to after the patient had died or been discharged from the ICU	The control group received usual ICU care, but no palliative care consultation	• Primary outcomes:
				  ○ ICU and hospital length of stay
				  ○ Satisfaction with quality of care of families, intensivists and bedside nursing staff
				• Secondary outcomes:
				  ○ ICU and hospital mortality
				  ○ Number of medical teams caring or consulting for the patient
				  ○ Individual domain scores of the satisfaction questionnaire
				• Resource use:
				  ○ ICU and hospital length of stay

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed
Edmonds *et al.*[74] • Associated report: Higginson *et al.*[144]	Multiple models: following the initial assessment of patient symptoms and psychosocial and advanced care planning needs, as well as carer needs, an action plan was developed and shared with the primary health-care team and other involved professionals as appropriate. Follow-up telephone calls or visits were arranged depending on clinical need. The clinical team had weekly meetings during which the palliative care consultant made recommendations about patient management. Based on the information collected during patient assessments and response to measures in the action plan, the consultant assessed if patients had ongoing specialist palliative care needs. Those who did were referred on to existing specialist community palliative care teams. Patients also received standard care	12 weeks	Among the services available to control patients were nurses (including nurses specialising in MS), physiotherapy, neurology and rehabilitation services. In addition, district nurses, social services and GPs provided support in the community. Inpatient care was available as needed. Other specialist services included continence advice, psychiatry and/or psychology. Charities such as the MS Society also provided support	• Outcomes: o Patient symptoms and concerns assessed using the POS and MS-POS o QoL assessed using the physical and psychological subscales of the Multiple Sclerosis Impact Scale o Caregiver burden assessed using the 12-item ZBI o Caregiver mastery assessed using the modified Lawton positivity questionnaire

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed
El-Jawahri *et al.*[85] • Associated reports: El-Jawahri *et al.*[86] and VanDusen *et al.*[87]	Inpatient consulting model: intervention patients met with the inpatient palliative care physician or advanced practice nurse within 3 days of randomisation. At least twice per week, the palliative care clinician followed up patients during hospitalisation to address symptom management. Additional visits could be carried out as needed. There was no outpatient palliative care follow-up after discharge. After each visit, the palliative care clinicians communicated their recommendations to the transplant team and documented their recommendations in the medical record	Period of hospitalisation	Control patients received standard transplant care, with the supportive care measures instituted by the transplant team. Patients, caregivers and transplant clinicians were permitted to request consultation with palliative care clinicians	• Primary outcome: ○ QoL assessed using the Functional Assessment of Cancer Therapy – Bone Marrow Transplant • Secondary outcomes: ○ Mood (depression and anxiety) was assessed using the HADS. Depression was also assessed using the PHQ-9 ○ Fatigue was assessed using the FACT fatigue subscale ○ Symptom burden was assessed using the revised ESAS ○ PTSD was assessed with the PTSD Checklist – Civilian Version ○ Distress was assessed using the National Comprehensive Cancer Network Distress Thermometer Checklist ○ Incidence of acute and chronic graft vs. host disease ○ Non-relapse mortality ○ Overall survival ○ Caregiver QoL assessed using the CareGiver Oncology Quality of Life questionnaire ○ Caregiver's mood (depression and anxiety) assessed with the HADS and PHQ-9 • Resource use: ○ Number of palliative care visits

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed
Farquhar *et al.*[75] • Associated reports: Farquhar *et al.*[145] and Javadzadeh *et al.*[146]	Multiple models: the BIS was a multidisciplinary complex intervention combining non-pharmacological and pharmacological interventions to support breathless patients with advanced disease, theoretically underpinned by a palliative care approach. Consultations took place in a patient's home. First-stage interventions were mainly non-pharmacological, whereas second-stage interventions were mainly pharmacological	2 weeks	Standard care was defined as specialist outpatient appointments in secondary care, which may include specialist nurse input and primary care services	• Primary outcome: o Patient distress due to breathlessness measured using a NRS • Secondary outcomes: o Disease-specific HRQoL assessed using the CRQ o Patient anxiety and depression using the HADS o Carer distress due to patient breathlessness measured using a NRS o Carer anxiety and depression using the HADS o Service use assessed using the CSRI o Patients' and carers' expectations and experiences of the BIS explored using qualitative topic-guided interviews o For health economic analyses: EQ-5D and measure of service use assessed using the CSRI • Resource use: o Measure of service use assessed using the CSRI o Informal care (unpaid hours per week from family/friends performing specific tasks) was valued at average UK wages (£11.21 per hour). Costs of BIS visits were estimated at £91 (based on specialist nurse contacts, which averaged the rehabilitation specialists' wages) and telephone contacts at one-quarter of this

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed
Farquhar *et al.*[76] • Associated reports: Farquhar *et al.*[145]	Multiple models: the BIS was a multidisciplinary complex intervention combining non-pharmacological and pharmacological interventions to support breathless patients with advanced disease, theoretically underpinned by a palliative care approach. Consultations took place in a patient's own home. First-stage of intervention was non-pharmacological (selection and application as clinically indicated), whereas the second stage of the intervention depended on the result of the first-stage interventions and included pharmacological interventions	4 weeks	Standard care was defined as specialist outpatient appointments in secondary care (e.g. oncology), which may include specialist nurse input and primary care services	• Primary outcome: o Patient distress due to breathlessness measured using a NRS • Secondary outcomes: o Patient QoL measured by the CRQ o Patient anxiety and depression measured by the HADS o Carer-reported outcome measures included a NRS for carer distress due to patient breathlessness o Carer anxiety and depression measured by the HADS o Patient use of other services assessed using the CSRI o Patients' and carers' expectations and experiences of the BIS were explored using qualitative topic-guided interviews o For health economic analyses: EQ-5D and the CSRI • Resource use: o Measure of service use assessed using the CSRI o The cost of the intervention was calculated at £91 per contact, based on specialist nursing input costs, with telephone contacts costed at 25% of this

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed

Franciosi *et al.*[147]	Multiple models: patients had a meeting with the palliative care team within 2 weeks of enrolment, and at least every 2–3 weeks thereafter for 24 weeks. Additional visits with the palliative care team were available based on request from the patient, oncologist or palliative care provider. General guidelines for the palliative care visits were adapted from the protocol of the Temel 2010[35] study. Care provided was documented in a patient's medical record by the palliative care team. Physical and psychosocial symptoms were assessed using validated instruments, and services were provided based on patients' needs	Enrolment to 6 months	Patients assigned to standard care received anticancer and symptom control treatments provided by oncologists and nurses without formal palliative care training. Palliative care referral was available, if requested. Those who were referred to the palliative care team did not cross over to the intervention group or follow the specified palliative care protocol	• Primary outcomes:
				  ○ QoL at 12 weeks assessed using Functional Assessment of Cancer Therapy-General Measure
				• Secondary outcomes:
				  ○ Survival
				  ○ Use of end-of-life care defined as the percentage of deceased patients who used the following in the 30 days preceding death – chemotherapy use, hospital admission and emergency room visit

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed

Gade *et al.*[88]	Inpatient consulting model: all teams provided care in accordance with key palliative care components, which were adapted from Weismann 1997.[200] The teams carried out individualised care and assessed patients' needs for symptom management, psychosocial and spiritual support, end-of-life planning, and posthospital care. Before each consultation, the team met to discuss the patient's medical record and baseline questionnaires. The team also met with the patient and their family to address diagnosis, symptoms, prognosis, goals of care, psychosocial and spiritual concerns, and advance directives. After the meeting with the patient/family, the team developed a palliative care plan and also arranged follow-up with the patient. The team was available Monday–Friday, with a palliative care physician on call after hours. The teams worked with the discharge planners in preparing for the patient's discharge. The palliative care discharge plan was shared with the primary care physicians. Cases were reviewed across the three sites and protocol adherence promoted via biweekly telephone conferences	Period of hospitalisation	San Francisco and Portland hospitals were part of a MCO's delivery system. Denver's community hospital had a contract with the MCO. All hospitals had MCO hospitalist physicians. At two sites, hospitalists served as the attending physicians. Portland's hospital used a combination of MCO hospitalists and primary care internists. The majority of Portland patients (72%) were followed by hospitalists. All hospitals had social workers and chaplains on staff who provided direct patient services to usual care patients	• Primary outcomes:
				  ○ Symptom control assessed using the Physical Area scale of the MCOHPQ
				  ○ Levels of emotional and spiritual support assessed using the MCOHPQ Emotional/Relationship Area and Spiritual Area scales
				  ○ Patient satisfaction assessed using the MCOHPQ Place of Care Environment scale and the Doctors, Nurses/ Other Care Providers Communication scale
				  ○ Total health services costs at 6 months post index hospitalisation
				• Secondary measures:
				  ○ Survival
				  ○ Number of advance directives at discharge
				  ○ Hospice utilisation within the 6 months post index hospitalisation
				• Resource use:
				  ○ Health-care costs
				  ○ Intensive care admissions
				  ○ Hospice utilisation

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed

Groenvold *et al.*[148]
 	
• Associated reports: Johnsen *et al.*[149,150]
	Multiple models: intervention group patients met with the specialist palliative care team. Patient's needs determined how often they met with the specialist palliative care team. The processes and activities carried out were those routinely used by the team. There was no assessment of intervention fidelity	8 weeks	There was very limited description of standard care. Standard care potentially included palliative care provided by the departments of oncology, GPs or home care services	• Primary outcome:
				  ○ Change in the patient's primary need (the most severe of the seven EORTC QLQ-C30 scales)
				
				• Secondary outcomes:
				  ○ Change in the seven EORTC QLQ-C30 scales
				  ○ Survival
				
				• Resource use:
				  ○ Contact with specialist palliative care team
				  ○ Assessment of health-care service use stated in protocol

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed

Grudzen *et al.*[89]
 	
• Associated reports: Grudzen *et al.*,[90] Kandarian *et al.*[91] and Kistler *et al.*[92]
	Inpatient consulting models: for participants in the intervention arm, the palliative care team was consulted within a few hours. Intervention participants received a comprehensive palliative care consultation by the inpatient team on the same or following day. At Mount Sinai Hospital, inpatient comprehensive palliative care consultation comprised symptom assessment and treatment, goals of care and advance care plans, and transition planning. The team made recommendations for symptom management using NCCN guidelines. They shared these recommendations with consulting physicians verbally, either in person or by telephone, and electronically through standardised palliative care team medical chart notes. The team worked with the patients' social workers and families to facilitate transition management consistent with goals of care. After discharge, patients were referred to outpatient palliative care if needed	Enrolment to discharge from hospital	Participants assigned to the usual-care group completed the same baseline interviews and follow-up as intervention participants. If requested by the admitting team or oncologist, usual care participants received a palliative care consultation	• Primary outcomes:
				  ○ QoL at 12 weeks assessed using the Functional Assessment of Cancer Therapy – General Measure
				• Secondary outcomes:
				  ○ Survival at 1 year
				  ○ Depression at 12 weeks assessed using the PHQ-9
				  ○ Health-care utilisation at 180 days (hospital days, hospice use and ICU admission)
				• Resource use:
				  ○ Hospital days
				  ○ Hospice use
				  ○ ICU admission

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed
Higginson *et al.*[77] • Associated reports: Higginson *et al.*[144,151–153]	Multiple models: patients in the intervention group received the new palliative care service immediately (fast track). Patients were visited in their own homes or sometimes outpatient clinics, nursing homes, or hospital. The palliative care team undertook assessments; suggested ways to improve physical, emotional, social and other problems; provided specialist welfare benefits advice and bereavement support; and liaised with and acted as a catalyst for local services, both primary and specialist teams. After initial assessment, treatment was recommended. Patients had one to three contacts (visits and/or telephone calls) from the palliative care team, although a small number (around 12%) were referred for longer-term 'community' palliative care	3 months	Patients in the control group received usual care for 12 weeks, after which they were offered the palliative care service. For patients randomised to the control group, community and hospital services (including neurologists, MS nurses, rehabilitation, neurological and social services) were offered as usual	• Outcomes: o Cost o POS score o POS-pain score o Caregiver burden • Resource use: o Health, social and voluntary services [district/practice nurse, MS nurse, palliative care nurse, other nurse, general practice, specialist (home), specialist (hospital), specialist (ward), specialist (other), occupational therapist/physiotherapist, dietitian/chiropodist/dentist, speech therapist, social services, informal caregiver, day centre, inpatient care, respite care]

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed

Higginson *et al.*[78]
 	
• Associated reports: Bausewein *et al.*[154] and Dzingina *et al.*[155]
	Multiple models: the breathlessness support service is an additional service to usual UK NHS care. It is a multiprofessional integrated service that combines respiratory, physiotherapy, occupational therapy, and palliative care assessment and management. It brought together assessment and treatment of physical, emotional, psychological and spiritual concerns, through one point of access. The service included an outpatient clinic appointment with respiratory medicine and palliative care clinicians to assess treatment and concerns. The patient (may also include family) received a breathlessness pack and a crisis plan was developed. This was followed by a home assessment 2–3 weeks after by a physiotherapist and/or occupational therapist. Four weeks after the outpatient appointment, there was a final clinic appointment with a palliative care specialist to agree further actions and a discharge plan	6 weeks	Patients randomly assigned to the control group continued with optimum management as provided by their usual services in accordance with relevant UK guidance to ensure best practice. After the 6-week (primary end point) research interview, these patients were offered the breathlessness support service	• Primary outcome:
				  ○ Breathlessness mastery at 6 weeks determined according to one domain of the QoL measure, the CRQ
				
				• Secondary outcomes:
				  ○ Severity of breathlessness on average, at worst, at rest and on exertion in the previous 24 hours
				  ○ Activity (assessed by London Chest Activity of Daily Living questionnaire)
				  ○ Other domains of the CRQ (breathlessness, fatigue and emotional function)
				  ○ QoL
				  ○ Palliative needs
				  ○ Depression and anxiety
				  ○ Spirometry
				  ○ Patient survival
				
				• Resource use:
				  ○ Hospital inpatient days in previous 3 months

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed
Hopp *et al.*[93]	Inpatient consulting model: the PCC team included a physician and advanced nurse practitioner. Other professionals (chaplains and social workers) participated as requested. Clinical interviews assessed for uncontrolled distressing symptoms, goals of care, advance care planning, code status, and desired post-treatment residential setting. All PCC patients had at least one palliative care consultation, with the opportunity for additional meetings as desired	3–6 months after randomisation	Not described	• Primary outcome: o The primary outcome assessed after 3–6 months was a dichotomous (election vs. non-election) measure of comfort-oriented care, which included – outpatient hospice – inpatient hospice – a DNR order during the index or a subsequent hospitalisation, or – a DNR order at home or at a nursing home, as assessed by means of telephone interviews and medical records • Secondary outcomes were not stated
Janssens *et al.*[123] • Associated reports: Veron *et al.*[187] and Weber *et al.*[125]	Hospital outreach model: patients assigned to the early palliative care group met the community ambulatory palliative care team after inclusion, and monthly for 12 months. Nurses performed home visits during which they assessed symptoms using the ESAS [if intensity of pain, dyspnoea, mood, anxiety and appetite were > 4/10 and the patient agreed, a consultation with a palliative care physician (or other specialist) was suggested], nutrition (Mini Nutritional Assessment Scale), understanding of illness and coping, anticipation and decision-making, support of relatives, social–spiritual needs, co-ordination between different health providers and alternative approaches such as relaxation, reflexology and massages. Patients were discussed with a specialist in palliative care, whom the patient could consult if needed. The intervention group also received standard care during the study	12 months	Patients in the control group had no contact with the palliative care team. For all patients under long-term oxygen therapy and/or home non-invasive ventilation, specialised nurses provided regular home visits to provide respiratory support. Health-care workers following those in the control group were not informed of the content of the 'palliative care' intervention. The palliative care team was different from the standard care team	• Primary outcomes: o Admissions to emergency wards o Hospitalisations o Admissions to ICUs • Secondary outcomes: o Symptoms assessed using the ESAS o HRQoL assessed using the SF-36 o Mood disturbances assessed using the HADS o ACP o Survival o Appreciation of intervention

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed
Jingfen *et al.*[80]	Ward-based model: intervention included three stages – (1) (hospitalisation 1–3 days) promote health knowledge, (2) (hospitalisation 4–6 days) establish healthy beliefs and (3) (hospitalisation 7 days to discharge) form behaviour. All patients in the study group were given a 3-month nursing intervention	Unclear	Control patients received routine nursing intervention	• Outcomes: ○ Cancer-related fatigue assessed using the Piper Fatigue Scale ○ QoL assessed using the Chinese version of the EORTC QLQ-C30 ○ Nursing satisfaction assessed using hospital self-made survey questionnaire
Kane *et al.*[156] • Associated reports: Kane *et al.*[157,158] and Wales *et al.*[159]	Multiple models: hospice patients were referred to the hospice programme, which conducted its own assessment and developed a treatment plan	Enrolment to death	Control patients continued under their current care	• Outcomes: ○ Pain was measured using the McGill Pain Scale ○ The symptom scale was adapted from the California Pain Assessment Profile. ○ Depression was measured using the CES-D ○ Anxiety was measured using a section of the General Well-Being Measure used in the RAND Health Insurance Study[201] ○ Satisfaction with care – interpersonal care measured using the interpersonal care scale adapted from the Ware scale, question on the degree of satisfaction with involvement in care adapted from the National Cancer Institute's Hospice Study and physical environment satisfaction scale adapted from McCaffree and Harkins[185]

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed

				• Resource use:
				  ○ Total inpatient days – general medical, hospice, ICU and intermediate care
				  ○ Nursing home days
				  ○ Number of days at home
				  ○ Radiation treatments
				  ○ Chemotherapy treatments
				  ○ Use of surgical procedures – major and minor surgical procedures
				  ○ Use of diagnostic procedures

Lowther *et al.*[97]
 	
• Associated reports: Lowther *et al.*[98–100]
	Outpatient model: nurses used a standardised multidimensional assessment and care-planning instrument for all patients allocated to the intervention group to provide holistic patient-centred care. The instrument was developed from existing assessment schedules from palliative care services across the region and systematically addressed physical, psychological, social, and spiritual well-being and patients' understanding of their illness and adherence to ART. The instrument also included space to plan and review care against prioritised needs. The intervention nurses had a weekly clinical support session with their clinical palliative care mentor to review complex cases. Patients in the intervention group met the trained nurse immediately after allocation, then at 2 weeks, 4 weeks, and for three subsequent monthly appointments, with a total of six appointments over 4 months	5 months	Patients allocated to the control group received usual care from the HIV clinic, consisting of monthly clinical assessments once ART was established, with investigations and treatment for any relevant symptoms or problems. Nurses with no exposure to palliative care provided this service, because no palliative care was available beyond the hospice. Patients in the control group received usual monthly appointments (i.e. five appointments during the study)	• Primary outcome:
				  ○ Pain
				
				• Secondary outcomes:
				  ○ Psychological morbidity
				  ○ Palliative care-related problems and concerns
				  ○ Adherence to ART
				  ○ QoL

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed

Ma *et al.*[70]
 	
• Associated report: Burnham *et al.*[94]
	Inpatient consult model: intervention group patients received a palliative care consultation within 48 hours of medical ICU admission. This consultation was provided by an interprofessional palliative care team and included chart review of a patient's hospitalisation, meeting with the patient and available health-care proxies, identification of physical and psychosocial needs of the patient and family, discussion with the primary team, and communication within the team to address patient goals, values and treatment decisions. A board-certified palliative care physician or nurse practitioner performed the initial evaluation, and a care plan for each consultation was discussed by the palliative care team, with additional team members when needed. The palliative care team followed up the patient until discharge from the hospital	Hospitalisation to discharge	The control arm received standard care. Palliative care could be consulted when needed by the medical ICU clinicians	• Primary outcome:
				  ○ Proportion of patients who transitioned to DNR/DNI preference before hospital discharge
				
				• Secondary outcomes:
				  ○ Medical ICU length of stay
				  ○ Hospital length of stay
				  ○ Discharge to hospice
				  ○ Duration of mechanical ventilation
				  ○ Duration of vasopressors
				  ○ Tracheostomy
				  ○ CPR
				  ○ Mortality
				  ○ Post-discharge ED visits
				  ○ Hospital re-admissions

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed

McCaffrey *et al.*[160]	Multiple models: PEACH was an individualised care package for community and inpatients. Services were rapidly mobilised, and allied health was co-ordinated with nursing services provided for up to 5 days, compared with usual care	28 days	Usual care included conventional discharge planning with existing community services, including specialist palliative care, access to an after-hours number, and equipment from loan pools	• Primary outcome:
				  ○ Number of days out of institutional care (determined from medical records of admissions to hospital and patient/ caregiver report of date of admission to residential care)
				• Secondary outcomes:
				  ○ Place of death
				  ○ Days at home
				• Resource use:
				  ○ Number of days at home
				  ○ PEACH intervention costs (staff administration, travel and direct patient contact time, overheads and consumables)
				  ○ Cost of specialist palliative care service use
				  ○ Cost of acute hospital and palliative care unit inpatient lengths of stay and outpatient visits

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed

McCorkle *et al.*[48]	Multiple models: the 10-week standardised intervention comprised symptom control, assessing patients' status, conducting complex care procedures, educating patients and family caregivers and responding to their needs, discussion of the patient's illness, care co-ordination, improving QoL, and working with other professionals. The study APN trained lung and gynaecological clinic staff before recruitment started, and they each team-worked as a palliative care unit to deliver the intervention. Clinic APNs first contacted patients within 24 hours, and then weekly clinic visits and five telephone calls were carried out	10 weeks	The enhanced usual-care group received routine oncological care, but did not get the intervention. Both groups received a copy of the Symptom Management Toolkit, and a resource manual outlining the symptoms and problems associated with cancer treatment	• Primary outcome:
				  ○ Symptom distress
				  ○ Health distress
				  ○ Depression
				  ○ Functional status
				  ○ Self-reported health
				• Secondary outcomes:
				  ○ QoL
				  ○ Anxiety
				  ○ Uncertainty
				  ○ Self-efficacy

McWhinney *et al.*[79]	Hospital outreach model: the team was a consulting and support service for family physicians and home care nurses. Within 72 hours of referral by a family doctor or nurse, one of the team nurses carried out home assessment. The assessment was discussed with the team doctor, and also shared with the family doctor, visiting nurse and home care case manager. If needed, a consultation with the team doctor could be requested. All new and active cases were discussed at the weekly team meeting. A nurse from the team, with physician back-up, was available 24 hours per day. Patients were given a number to call if needed	Not stated	Control patients 'waiting list' group waited 4 weeks for assessment by the team. Emergency consultation by the team physician was made available for patients in the waiting list group if requested by the family physician	• Primary outcomes:
				  ○ Pain assessed using the McGill Pain Questionnaire
				  ○ Nausea assessed using the Melzack Nausea Questionnaire
				• Secondary outcomes:
				  ○ Patient's QoL assessed using the Functional Living Index – Cancer
				  ○ Caregiver's health assessed using the CES-D

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed
Mendoza-Galindo *et al.*[101] • Associated report: Ramirez-Morales *et al.*[102]	Outpatient model: intervention was provided by a palliative team, which included psychological, nutritional and symptom support	Not clear	Standard care was given by the attending physician	• Outcomes: o Number of emergency room consultations o Number of hospitalisations o Hospitalisation duration • Resource use: o Cost of emergency room consultations o Cost of hospitalisation days
Nottelmann *et al.*[103] • Associated reports: Nottelmann *et al.*[104,105]	Hospital outpatient model: the intervention consisted of a 'basic offer' and tailored elements. The basic offer was two mandatory consultations and the option of contacting a palliative rehabilitation team directly during the 12-week participation period, if needed. Furthermore, patients and family caregivers could be offered participation in a 12-week patient/caregiver school, combined with individually tailored physical exercise in groups, individual consultations with members of the palliative rehabilitation team, or both. At the end of the first consultation, the patient and family caregivers were given the team's contact information. All specialist palliative care team members except the chaplain offered individual consultations to patients and family caregivers in the palliative rehabilitation clinic or over the telephone. The specialist palliative care team had weekly multidisciplinary conferences during which they discussed patients	12 weeks	The control group receives standard care at the Department of Oncology. All patients had access to paramedical services as well as anticancer care. These services were not available to caregivers	• Primary outcomes: o Symptom/problem prioritised on an adapted form of the EORTC QLQ-C30 by patients • Secondary outcomes: o QoL assessed using the EORTC QLQ-C30 o Survival o Health service use including number and duration of hospital admissions and treatments, and visits to outpatient clinics, emergency rooms and GPs

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed
O'Riordan *et al.*[161] • Associated report: O'Riordan *et al.*[162]	Multiple model: patients randomised to the SMS-HF group received a 6-month palliative care intervention provided by the interdisciplinary SMS-HF inpatient palliative care team consisting of a nurse practitioner, physician, social worker and chaplain. The SMS-HF team provided direct care to the patient, including prescribing medications for symptoms, discussing advance care planning and completing appropriate documentation, and providing psychosocial and spiritual support and services. The patients first contact the SMS-HF team occurring during hospitalisation. The intervention consisted of seven components. They received a 1-week, in-person follow-up assessment, and five monthly consultations, of which at least two were in person, with the remainder conducted via telephone and including all members of the SMS-HF team. Additional contacts with the SMS-HF team were scheduled as needed. Patients in the SMS-HF group who were re-admitted to the same hospital were followed by the inpatient palliative care team. Standard electronic health record templates were used to document in-person and telephone care and recommendations were communicated to the cardiology team. Standardised, evidence-based protocols for symptom management were developed and used	6 months	The patients randomised to usual care received guideline-driven HF treatment. Authors assessed all symptoms and QoL at enrolment, and symptoms, QoL, satisfaction, advance care planning documentation and resource use at follow-up 3 and 6 months later	• Outcomes: ○ QoL assessed using the Minnesota Living with Heart Failure Questionnaire and the FACIT–Pal ○ Pain assessed using the BPI ○ Anxiety and depression assessed using the HADS ○ Symptoms assessed using the ESAS ○ Fatigue assessed using the Brief Fatigue Inventory ○ Dyspnoea assessed using the BORG Scale ○ Patient satisfaction assessed using an unvalidated scale • Resource use: ○ Number of re-admissions to hospital ○ Number of hospital visits

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed

Ozcelik *et al.*[95]	Inpatient consulting model: a multidisciplinary team delivered palliative care, using the case management model. The intervention addressed symptoms, psychosocial stress, social and family needs, as well as training needs. Patients could see the team again for uncontrolled symptoms	The period of hospitalisation: day of admission to hospital until the day of discharge	Usual-care patients received routine oncological care. Following oncological review and tests, treatment plans were developed and given to the ward nurses to be implemented. An educational book was also given to the usual-care group	• Outcomes:
				  ○ Level of symptoms assessed using the ESAS
				  ○ QoL assessed using the EORTC QLQ-C30 – Turkish version
				  ○ Patient and family satisfaction assessed using forms created by researchers
				  ○ Costs
				• Resource use:
				  ○ Length of stay in hospital
				  ○ Direct costs

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed

Rodin *et al.*[163]
 	
• Associated report: Rodin *et al.*[164]
	Multiple model: EASE integrated a novel psychotherapeutic intervention (EASE-psy) with screening of physical symptoms and triggered referral for early palliative care (EASE-phys) to address traumatic stress and physical symptoms. EASE-psy included 8–12 psychotherapeutic sessions over 8 weeks by a trained mental health clinician. It was based on principles of supportive psychotherapy and trauma-focused CBT applied to patients with life-threatening or advanced disease. EASE-phys consisted of systematic screening of physical symptoms with the ESAS-AL, with triggered referral to early palliative care. The ESAS-AL was administered up to three times weekly during the inpatient stay and weekly after discharge. When there was a score of ≥ 4 (moderate to severe) on any physical symptom, a palliative care referral was triggered and ESAS-AL screening for that participant was taken over by the EASE-phys team until all symptom scores were < 4. A palliative care physician and nurse constituted the core EASE-phys team, with other MDT members involved as necessary. The EASE-phys team used routine symptom control guidelines for symptom management. If symptom scores were ≥ 4, follow-ups from the EASE-phys team occurred three times weekly for inpatients in person and weekly for outpatients, in person or by telephone	12 weeks	Care was provided by a MDT including physicians, nurses and allied health personnel dedicated to the treatment of acute leukaemia. Participants in the control group received no formal trial intervention, but referral to psychosocial or palliative care services was allowed if needed. At the end of the study, the control group was offered EASE	• Primary outcome:
				  ○ Severity of traumatic stress symptoms measured by the 30-item Stanford Acute Stress Reaction Questionnaire
				
				• Secondary outcomes:
				  ○ Physical symptom burden measured by the Memorial Symptom Assessment Scale
				  ○ Pain assessed using the BPI
				  ○ QoL measured using the FACIT-Sp
				  ○ Depression assessed by the Beck Depression Inventory-II
				  ○ Patient satisfaction with care measured using the 16-item Family Satisfaction with Care-Patient Version
				  ○ Attachment security assessed with the Brief Experiences in Close Relationships Scale
				  ○ Emotional support assessed with Clinical Evaluation Questionnaire

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed

Rogers *et al.*[165]
 	
• Associated report: Mentz *et al.*[166]
	Multiple models: the study team assessed and managed the different domains of QoL for patients with advanced HF. A certified palliative care nurse practitioner co-ordinated patient care in collaboration with a hospice and palliative medicine board-certified physician. The intervention was performed in collaboration with each patient's clinical cardiology team and focused on shared goal-setting to combine HF symptom amelioration with palliative care goals. After hospital discharge, the PAL-HF nurse practitioner actively participated in the ongoing management of the patients in the outpatient environment. After the 6-month intervention period was completed, the nurse practitioner continued to contact the patients in the intervention arm every 3 months to provide ongoing support and clinical care	6 months	Patients under usual care were managed by a cardiologist-directed team with HF expertise. Inpatient care focused on symptom relief and use of evidence-based therapies as detailed in current guidelines. Inpatient palliative care consultation was available on request. After discharge, patients received outpatient follow-up with their GPs, as well as with a HF cardiologist or nurse practitioner	• Primary outcomes:
				  ○ QoL assessed by two different questionnaires (KCCQ and FACIT-Pal scale)
				
				• Secondary outcomes:
				  ○ Depression and anxiety assessed using the HADS
				  ○ Spiritual well-being assessed using the FACIT-Sp
				  ○ Hospitalisations
				  ○ Mortality
				
				• Resource use:
				  ○ Number of hospital encounter records
				  ○ Number of clinic encounter records
				  ○ Number of primary care contacts
				  ○ Number of cardiology contacts
				  ○ Number of telephone contacts
				  ○ Number of rehabilitation clinic contacts
				  ○ Number of ED/urgent care contacts
				  ○ Number of hospitalisations

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed

Sidebottom *et al.*[96]	Inpatient consulting model: following randomisation, the intervention group received a palliative care consult from the hospital palliative care team. The intervention was not the same as the standard palliative care process as baseline assessments of depression, QoL and symptoms could be reviewed before patients were seen by the team, as well as changes to payment for the hospital palliative care service. Areas covered by the hospital palliative care team during patient visits included symptom assessment; psychosocial, emotional and spiritual care; care co-ordination; treatment recommendation referrals; and future care-planning assessment and discussions	Period of hospitalisation	This was not described	• Primary outcomes:
				  ○ Symptom burden assessed using the ESAS
				  ○ Depressive symptoms assessed using the PHQ-9
				  ○ QoL assessed using the Minnesota Living with Heart Failure questionnaire
				• Secondary outcomes:
				  ○ ACP
				  ○ Inpatient 30-day re-admission
				  ○ Hospice use
				  ○ Mortality
				• Resource use:
				  ○ 30-day inpatient re-admission
				  ○ Hospice use

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed

Solari *et al.*[126]
 	
• Associated reports: Giovannetti *et al.*[127] and Solari *et al.*[128]
	Hospital outreach model: after a comprehensive assessment of the dyad needs, the palliative care team defined the contents of the intervention, involving the dyad and the patient's physician. The team verified programme implementation and reviewed it as necessary. The team was not on call for dyads. In emergencies, dyads contacted a patient's physician or emergency medical services. All activities were recorded in the patient study record at the patient's home and the information was available to health professionals and caregivers. Three and 6 months after trial initiation, the palliative care team met again to share experiences, refine the protocol and discuss difficult cases	6 months	Usual care comprised health and social services provided by the Italian National Health Service in the study area. Dyads assigned to usual care received the three examiner visits (visits 1–3) and the monthly telephone interviews, but not the palliative care team visits (except visit 0). Dyads that received usual care were offered the palliative care service at the end of the study	• Primary outcome:
				  ○ HRQoL assessed using the SEIQoL-DW
				  ○ Symptom burden assessed using the Palliative care Outcome Scale-Symptoms-MS
				
				• Secondary outcomes:
				  ○ QoL assessed using the EQ-5D-3L
				  ○ Anxiety and depression assessed using the HADS
				  ○ Functional independence assessed using the Functional Independence Measure
				  ○ Carer QoL assessed using the SF-36 and the EQ-5D-3L
				  ○ Carer depression and anxiety assessed using the HADS
				  ○ Carer burden assessed using the ZBI
				  ○ Adverse events

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed

Tattersall *et al.*[106]	Outpatient model: patients assigned to the early palliative care group met with a palliative care nurse consultant member of the HSPC team. She provided support by highlighting available palliative care services to patients and also called them monthly	The intervention continued during the lifespan of the patient	Standard care was provided according to the recommendation of oncologists. Control patients were referred to the palliative care service, if needed, by the oncologist	• Primary outcomes:
				  ○ QoL assessed using the MQOL
				  ○ Symptom severity assessed using the Rotterdam Symptom Checklist
				  ○ Feeling supported assessed using the Supportive Care Needs – Short-Form questionnaire
				• Secondary outcomes:
				  ○ End-of-life experiences
				  ○ Number of lines of chemotherapy
				  ○ Place of death
				• Resource use:
				  ○ Contact with palliative care services – palliative care nurse and physician

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed

Temel *et al.*[35]
 	
• Associated reports: Greer *et al.*,[107,108] Jacobsen *et al.*,[109] Nipp *et al.*,[110,111] Pirl *et al.*,[112] Temel *et al.*[113,114] and Yoong *et al.*[115]
	Outpatient model: patients assigned to early palliative care met with a member of the palliative care team, comprising board-certified palliative care physicians and advanced practice nurses, within 3 weeks of enrolment and at least monthly thereafter in the outpatient setting until death. Additional visits with the palliative care service could be requested by the patient, oncologist or palliative care provider. Guidelines for the palliative care visits were adapted from the National Consensus Project for Quality Palliative Care. Palliative care clinicians documented the care they provided according to these guidelines. All the participants continued to receive routine oncologic care throughout the study period	Those assigned to the intervention group met with a member of the palliative care team within 3 weeks of enrolment and at least monthly thereafter in the outpatient setting until death	Patients in the standard care group did not meet with the palliative care service unless a meeting was requested by the patient, the family or the oncologist. Those who were referred to the service did not cross over to the palliative care group or follow the specified palliative care protocol	• Primary outcome:
				  ○ Change in QoL from baseline to week 12 assessed using the FACT-L scale
				
				• Secondary outcomes:
				  ○ Mood assessed using the HADS and PHQ-9
				  ○ Survival
				  ○ Location of death
				  ○ Cost analysis
				
				• Resource use:
				  ○ Number of palliative care visits
				  ○ Use of health services and end-of-life care including anticancer therapy, medication prescriptions, referral to hospice, hospital admissions, ED visits

Temel *et al.*[167]	Multiple model: intervention group patients had early palliative care delivered by the outpatient palliative care team within 4 weeks of recruitment to the study and not less than once every month until death. The palliative care clinician, patient or oncologist could request additional palliative care visits when needed. The palliative care team used the National Consensus Project for Quality Palliative Care guidelines	The intervention continued at least once per month until the patient's death	Patients who were assigned to usual oncology care were able to meet with a palliative care clinician only on request by the oncologist, patient or family. When these patients received palliative care services, they did not cross study groups or follow the intervention protocol. All patients, regardless of group assignment, continued to receive routine oncology care throughout the study period	• Primary outcome:
				  ○ Change in QoL from baseline to week 12
				
				• Secondary outcomes:
				  ○ Change in QoL from baseline to week 24
				  ○ Depression
				  ○ Differences in end-of-life communication
				
				• Resource use:
				  ○ Number of palliative care visits

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed
Vanbutsele *et al.*[168] • Associated report: Vanbutsele *et al.*[169]	Multiple model: those in the early palliative care group had a consultation with a specialised palliative care nurse within 3 weeks of enrolment. Monthly consultations were organised between patients and the palliative care nurses until the patient died; symptom assessment was done using the ESAS. The early palliative care intervention was informed by Temel *et al.*'s[35] 2010 study	Hospital consultations between patients and palliative care nurses were organised monthly until the patient's death	Usual oncological care involved a MDT including oncologists, other medical specialists, social workers, psychologists, dietitians and specialist nurses. Some patients in the usual-care group had a consultation with the palliative care team, and were not excluded from the study and did not cross over to the intervention group	• Primary outcomes: o QoL assessed using the global health status/QoL scale of the EORTC QLQ C30. QoL was also assessed using the MQOL • Secondary outcomes: o Patient's mood assessed using the HADS and PHQ-9 o Understanding of illness and perception of goals of therapy assessed through forward–backward translation of the questionnaire used by Temel 2010[35] o EORTC QLQ C30 functioning and symptoms scales o MQOL functioning scales o Overall survival • Resource use: o Number of consultations with the palliative care team o Frequency of contact with a psychologist, dietitian, social worker or a specialist nurse

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed

Wallen *et al.*[170]
 	
• Associated report: Slota *et al.*[171]
	Multiple model: the hospital-based pain and palliative care service was a consult team available to patients who were seen in inpatient and outpatient settings. The team had two full-time attending physicians, three nurse practitioners, a nurse thanatologist (member of the team who specialised in the psychosocial and emotional aspects of death and dying) and one physician fellow in hospice and palliative medicine. Each consult included assessment of pain and other symptoms, treatment options, and emotional and spiritual distress. The team aimed to improve QoL by providing comfort care earlier in the disease trajectory	The intervention was provided until 12 months: interviews were conducted pre surgically and at follow-up visits up to 1 year	Standard pain and symptom management provided to the control group were considered to be good clinical practice, which, at times, included individual consultations such as nutrition, social work, spiritual ministry, recreation therapy, occupational therapy, physical therapy, and/or clinical psychiatry. Patients were allowed to cross over to the treatment arm of the study at the clinical discretion of the attending physician	• Primary outcomes:
				  ○ Pain assessed using the Gracely Pain Intensity and Unpleasantness Scales
				  ○ Symptom burden assessed with the Symptom Distress Scale
				
				• Secondary outcomes:
				  ○ Mood assessed with the CES-D
				  ○ Satisfaction with pain and social support assessed using open-ended qualitative questions

Study	Intervention condition	Intervention duration	Control condition	Outcomes assessed

Woo *et al.*[116]	Hospital outpatient model: the early palliative care intervention included the following: (1) nursing assessment of pain and depression, (2) pain control based on NCCN guidelines, (3) depression control by psychoeducation and/or consultation with a psychiatric specialist and (4) patient education. Patients were managed by research nurses trained in symptom assessment and medication adherence; pain and depression education; and in making treatment adjustments according to NCCN guidelines. Patients with CES-D scores of > 25 were referred to psychiatric specialists. The interventions were delivered by telephone or during regularly scheduled outpatient care. Follow-up intervention visits or telephone coaching were scheduled daily until BPI worst pain score was ≤ 3. Telephone calls were triggered when patients reported inadequate symptom improvement, non-adherence to medication, adverse effects or suicidal ideation, or when patients requested to be contacted	12 months	The control group received no formal intervention, but were informed of their depressive and pain symptoms. Their screening results were provided to their physician. Usual oncology care was directed by an attending physician and consisted of anticancer and symptom control treatments and consultation with psychiatric and pain care specialists. Pain care specialists were provided whenever requested, regardless of group assignment	• Primary outcomes:
				  ○ Pain assessed using the BPI
				  ○ Depression assessed using the CES-D
				• Secondary outcomes:
				  ○ QoL assessed using the EORTC QLQ-C30
				  ○ Sleep disturbance assessed using the Insomnia Severity Index
				  ○ Satisfaction with pain control
				  ○ Patient and investigator's global assessment
				  ○ Clinical global impression score assessed using the Clinical Global Impression Improvement scale
				  ○ Survival

ACP, advance care planning; APN, advanced practice nurse; ART, antiretroviral therapy; CASA, Collaborative Care to Alleviate Symptoms and Adjust to Illness; CBT, cognitive–behavioural therapy; CPR, cardiopulmonary resuscitation; DNI, do not intubate; DNR, do not resuscitate; EASE, Emotion And Symptom-focused Engagement; EASE-phys, Emotion And Symptom-focused Engagement – physical; EASE-psy, Emotion And Symptom-focused Engagement – psychotherapeutic; ENABLE, Educate, Nurture, Advise, Before Life Ends; EQ-5D-3L, EuroQol-5 Dimensions, three-level version; ESAS-AL, Edmonton Symptom Assessment System modified for Acute Leukaemia; FACIT-Sp, Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being Scale; HF, heart failure; IHPC, In-home Palliative Care; ILD, interstitial lung disease; KBILD, King's Brief Interstitial Lung Disease; MCO, managed care organization; MQOL, McGill Quality of Life questionnaire; MS, multiple sclerosis; MRC, Medical Research Council; NCCN, National Comprehensive Cancer Network; PAL-HF, Palliative care in Heart Failure; PCC, Palliative Care Consultation; PEACH, Palliative Care Extended Packages at Home; PEG, Pain, Enjoyment of Life and General Activity; PTSD, post-traumatic stress disorder; QoL, quality of life; SF-36, Short Form questionnaire-36 items; SGRQ, St George's Respiratory Questionnaire; SMS-HF, Symptom Management Service for Heart Failure.

Appendix 4 Taxonomy of the components of hospital-based specialist palliative care in studies that included either certified experts in palliative care or those described as palliative care clinicians

Study	Components of HSPC				
	Symptom control (e.g. assess symptoms, prescribing of medications)	Decision-making (e.g. enquire about goals of care)	Future-planning (e.g. advance care planning)	Coping and support (e.g. emotional and practical support)	Care co-ordination (e.g. helping with co-ordinating care)
Bajwah *et al.*[46]	Yes	Yes	Yes	Yes	Yes
Bakitas *et al.*[129]	Yes	Yes	Yes	Yes	Yes
Bakitas *et al.*[73]	Yes	Yes	Yes	Yes	Yes
Bekelman *et al.*[139]	Yes	Yes	No	Yes	Yes
Brännström *et al.*[118]	Yes	Yes	No	Yes	Yes
Brumley *et al.*[142]	Yes	Yes	Yes	Yes	Yes
Carson *et al.*[82]	No	Yes	No	Yes	No
Edmonds *et al.*[74]	Yes	Yes	Yes	Yes	Yes
El-Jawahri *et al.*[85]	Yes	No	No	Yes	No
Farquhar *et al.*[75]	Yes	Yes	Yes	Yes	No
Farquhar *et al.*[76]	Yes	Yes	Yes	Yes	No
Franciosi *et al.*[147]	Yes	Yes	No	Yes	Yes
Gade *et al.*[88]	Yes	Yes	Yes	Yes	No
Higginson *et al.*[77]	Yes	No	Yes	Yes	Yes
Higginson *et al.*[78]	Yes	Yes	Yes	Yes	Yes
Janssens *et al.*[123]	Yes	Yes	Yes	Yes	Yes
Kane *et al.*[156]	Yes	No	Yes	Yes	No
Lowther *et al.*[97]	Yes	Yes	Yes	Yes	No
Ma *et al.*[70]	Yes	Yes	No	Yes	Yes
McCorkle *et al.*[48]	Yes	Yes	No	Yes	Yes
McWhinney *et al.*[79]	Unclear	Unclear	Unclear	Yes	Unclear
Nottelmann *et al.*[104]	Yes	Yes	Yes	Yes	Yes
Rodin *et al.*[163]	Yes	No	No	Yes	No
Rogers *et al.*[165]	Yes	Yes	Yes	Yes	Yes
Sidebottom *et al.*[96]	Yes	Yes	Yes	Yes	Yes
Solari *et al.*[126]	Unclear	Unclear	Unclear	Yes	Unclear
Tattersall *et al.*[106]	Yes	No	No	Yes	No

Study	Components of HSPC				
	Symptom control (e.g. assess symptoms, prescribing of medications)	Decision-making (e.g. enquire about goals of care)	Future-planning (e.g. advance care planning)	Coping and support (e.g. emotional and practical support)	Care co-ordination (e.g. helping with co-ordinating care)
Temel *et al.*[35]	Yes	Yes	No	Yes	Yes
Temel *et al.*[167]	Yes	Yes	No	Yes	Yes
Vanbutsele *et al.*[168]	Yes	Yes	No	Yes	Yes
Wallen *et al.*[170]	Yes	No	No	Yes	No

Appendix 5 Taxonomy of the components of hospital-based specialist palliative care in studies that were unclear about training in palliative care

Study	Components of HSPC				
	Symptom control (e.g. assess symptoms, prescribing of medications)	Decision-making (e.g. enquire about goals of care)	Future-planning (e.g. advance care planning)	Coping and support (e.g. emotional and practical support)	Care co-ordination (e.g. helping with co-ordinating care)
Ahronheim *et al.*[81]	Yes	No	Yes	Yes	No
Cheung *et al.*[84]	Unclear	Unclear	Unclear	Unclear	Unclear
Groenvold *et al.*[148]	Unclear	Unclear	Unclear	Unclear	Unclear
Grudzen *et al.*[89]	Yes	Yes	Yes	Yes	No
Hopp *et al.*[93]	Yes	Yes	Yes	Yes	No
Jingfen *et al.*[80]	Yes	Yes	No	Yes	No
McCaffrey *et al.*[160]	Unclear	Unclear	Unclear	Unclear	Yes
Mendoza-Galindo *et al.*[101]	Yes	No	No	Yes	No
O'Riordan *et al.*[161]	Yes	No	Yes	Yes	No
Ozcelik *et al.*[95]	Yes	No	Yes	Yes	No
Woo *et al.*[116]	Yes	No	No	Yes	No

Appendix 6 Assessment of methodological quality of economic studies

Study design	Brumley *et al.*[142]	Farquhar *et al.*[75]	Farquhar *et al.*[76]	Gade *et al.*[88]	Higginson *et al.*[77]	Higginson *et al.*[78]	Ozcelik *et al.*[95]	Temel *et al.*[35]/ Greer *et al.*[108]	Kane *et al.*[156]	McCaffrey *et al.*[160]	Ma *et al.*[70]	Mendoza-Galindo *et al.*[101]	Brännström *et al.*[118]/ Sahlen *et al.*[121]
1. The research question is stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. The economic importance of the research question is stated	Yes	No	No	Yes	Yes	Yes	No	Yes	Unclear	Yes	Yes	No	Yes
3. The viewpoint(s) of the analysis are clearly stated and justified	Unclear	No	No	Unclear	Yes	Unclear	No	Unclear	No	Yes	No	No	Yes
4. The rationale for choosing the alternative programmes or interventions compared is stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. The alternatives being compared are clearly described	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
6. The form of economic evaluation used is stated	Unclear	Yes	Yes	Unclear	Yes	Yes	No	Unclear	Unclear	Yes	No	No	Yes
7. The choice of form of economic evaluation is justified in relation to the questions addressed	Unclear	No	No	No	Yes	No	No	No	No	Yes	No	No	Yes

Study design	Brumley *et al.*[142]	Farquhar *et al.*[75]	Farquhar *et al.*[76]	Gade *et al.*[88]	Higginson *et al.*[77]	Higginson *et al.*[78]	Ozcelik *et al.*[95]	Temel *et al.*[35]/ Greer *et al.*[108]	Kane *et al.*[156]	McCaffrey *et al.*[160]	Ma *et al.*[70]	Mendoza-Galindo *et al.*[101]	Brännström *et al.*[118]/ Sahlen *et al.*[121]
Data collection													
8. The source(s) of effectiveness estimates used are stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Details of the design and results of effectiveness study are given	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
10. The primary outcome measure(s) for the economic evaluation are clearly stated	Unclear	Yes	Yes	Yes	Yes	Yes	No	Unclear	No	Yes	No	No	Yes
11. Methods to value health states and other benefits are stated	N/A	Yes	Yes	Yes	Yes	Yes	N/A	N/A	Yes	Yes	N/A	N/A	Yes
12. Details of the subjects from whom valuations were obtained are given	N/A	Yes	Yes	N/A	Yes	Yes	N/A	Yes	N/A	N/A	N/A	N/A	Yes
13. Productivity changes (if included) are reported separately	N/A	N/A	N/A	N/A	No	No	N/A	N/A	No	N/A	N/A	N/A	No
14. The relevance of productivity changes to the study question is discussed	No	No	No	No	No	No	No	N/A	No	No	No	No	No
15. Quantities of resources are reported separately from their unit costs	Unclear	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	No
16. Methods for the estimation of quantities and unit costs are described	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes

Study design	Brumley *et al.*[142]	Farquhar *et al.*[75]	Farquhar *et al.*[76]	Gade *et al.*[88]	Higginson *et al.*[77]	Higginson *et al.*[78]	Ozcelik *et al.*[95]	Temel *et al.*[35]/ Greer *et al.*[108]	Kane *et al.*[156]	McCaffrey *et al.*[160]	Ma *et al.*[70]	Mendoza-Galindo *et al.*[101]	Brännström *et al.*[118]/ Sahlen *et al.*[121]
17. Currency and price data are recorded	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
18. Details of currency of price adjustments for inflation or currency conversion are given	No	Yes	Yes	No	No	No	No	No	No	No	No	No	No
19. Details of any model used are given	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
20. The choice of model used and the key parameters on which it is based are justified	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Analysis and interpretation of results													
21. Time horizon of costs and benefits is stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
22. The discount rate(s) is stated	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
23. The choice of rate(s) is justified	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
24. An explanation is given if costs or benefits are not discounted	No	No	No	N/A	N/A	N/A	No	N/A	N/A	Yes	N/A	N/A	N/A
25. Details of statistical tests and CIs are given for stochastic data	Unclear	No	Unclear	Yes	Yes	Yes	No	No	No	Yes	No	No	Yes
26. The approach to sensitivity analysis is given	N/A	Yes	N/A	N/A	N/A	N/A	N/A	No	Yes	Yes	N/A	N/A	Yes
27. The choice of variables for sensitivity analysis is justified	N/A	No	N/A	N/A	N/A	N/A	N/A	N/A	Yes	Yes	N/A	N/A	Yes

Study design	Brumley *et al.*[142]	Farquhar *et al.*[75]	Farquhar *et al.*[76]	Gade *et al.*[88]	Higginson *et al.*[77]	Higginson *et al.*[78]	Ozcelik *et al.*[95]	Temel *et al.*[35]/ Greer *et al.*[108]	Kane *et al.*[156]	McCaffrey *et al.*[160]	Ma *et al.*[70]	Mendoza-Galindo *et al.*[101]	Brännström *et al.*[118]/ Sahlen *et al.*[121]
28. The ranges over which the variables are varied are stated	N/A	No	N/A	N/A	N/A	N/A	N/A	N/A	Yes	Yes	N/A	N/A	Yes
29. Relevant alternatives are compared	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
30. Incremental analysis is reported	Yes	Yes	Yes	No	Yes	No	No	No	Yes	Yes	No	No	Unclear
31. Major outcomes are presented in a disaggregated as well as aggregated form	No	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	No	Unclear
32. The answer to the study question is given	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
33. Conclusions follow from the data reported	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
34. Conclusions are accompanied by the appropriate caveats	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Total number of 'yes' answers	13	20	19	17	21	21	12	12	18	25	12	7	22

N/A, not applicable.

Appendix 7 Assessment of methodological quality of economic studies using the Consensus on Health Economic Criteria list

CHEC list	Brumley *et al.*[142]	Farquhar *et al.*[75]	Farquhar *et al.*[76]	Gade *et al.*[88]	Higginson *et al.*[77]	Higginson *et al.*[78]	Ozcelik *et al.*[95]	Temel *et al.*[35]/ Greer *et al.*[108]	Kane *et al.*[156]	Ma *et al.*[202]	McCaffrey *et al.*[160]	Mendoza-Galindo *et al.*[101]	Brännström *et al.*[118]/ Sahlen *et al.*[121]
1. Is the study population clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Are competing alternatives clearly described?	No	No	No	No	No	Yes	Yes	No	No	No	No	No	No
3. Is a well-defined research question posed in answerable form?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Is the economic study design appropriate to the stated objective?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
5. Is the chosen time horizon appropriate to include relevant costs and consequences?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
6. Is the actual perspective chosen appropriate?	No	No	No	No	Yes	No	No	Yes	No	No	Yes	No	No
7. Are all important and relevant costs for each alternative identified?	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	No
8. Are all costs measured appropriately in physical units?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No
9. Are costs valued appropriately?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No
10. Are all important and relevant outcomes for each alternative identified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Are all outcomes measured appropriately?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

CHEC list	Brumley *et al.*[142]	Farquhar *et al.*[75]	Farquhar *et al.*[76]	Gade *et al.*[88]	Higginson *et al.*[77]	Higginson *et al.*[78]	Ozcelik *et al.*[95]	Temel *et al.*[35]/ Greer *et al.*[108]	Kane *et al.*[156]	Ma *et al.*[202]	McCaffrey *et al.*[160]	Mendoza-Galindo *et al.*[101]	Brännström *et al.*[118]/ Sahlen *et al.*[121]
12. Are outcomes valued appropriately?	No	Yes	Yes	No	No	No	No	Yes	Yes	No	Yes	No	No
13. Is an incremental analysis of costs and outcomes of alternatives performed?	No	Yes	Yes	No	Yes	No	No	No	No	No	Yes	No	No
14. Are all future costs and outcomes discounted appropriately?	No	No	No	No	No	No	No	No	No	No	No	No	No
15. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	No	Yes	Yes	No	Yes	No	No	No	No	No	Yes	No	No
16. Do the conclusions follow from the data reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
17. Does the study discuss the generalisability of the results to other settings and patient/ client groups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
18. Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes
19. Are ethical and distributional issues discussed appropriately?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Total number of 'yes' answers	10	16	16	12	15	13	14	14	14	9	16	7	9

Appendix 8 Health-related quality-of-life scales and dimensions covered

Study, primary end point, disease group	Scales used	Dimensions covered in scales
Bajwah *et al.*[72] • 4 weeks • Advanced fibrotic lung disease	KBILD (used in meta-analysis)	The KBILD is a 15 item questionnaire consisting of three domains (breathlessness and activities, chest symptoms and psychological) – secondary outcome
	SGRQ	SGRQ is a 50-item instrument designed to measure impact on overall health, daily life and perceived well-being in patients with obstructive airways disease. Part 1 has a symptoms component (frequency and severity) with a 1-, 3- or 12-month recall (several scales); part 2 has an activities component, looking at activities that cause or are limited by breathlessness, and an impact component, looking at social functioning, psychological disturbances resulting from airways disease and referring to current state as the recall [dichotomous (true/false)] except last question (4-point Likert scale) – secondary outcome
Bakitas *et al.*[129] • 13 months • Cancer	FACIT-Pal	Measures physical, emotional, social and functional well-being in addition to concerns relevant to persons with life-threatening illness (e.g. feeling peaceful, reconciling with others) – primary outcome
Bakitas *et al.*[73] • 3 months • Cancer	FACIT-Pal (used in meta-analysis)	Measures physical, emotional, social, and functional well-being and additional concern subscales – study did not specify whether primary or secondary outcome
	Treatment Outcome Index	Treatment Outcome Index, composed of FACIT-Pal physical, functional and additional concern subscales
Bekelman *et al.*[139] • 6 months • Heart failure	KCCQ	KCCQ is a valid, reliable measure of heart failure-specific health status that is responsive to change. No further details provided in the study
Brännström *et al.*[118] • 6 months • Heart failure	EQ-5D (used in meta-analysis)	A generic, single index that defines health in the five dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression – did not specify primary or secondary outcomes
	KCCQ	Full data not shown in study
Edmonds *et al.*[74] • 12 weeks • Multiple sclerosis	MSIS	The MSIS is a 29-item measure of disease impact. It has two subscales: physical and psychological
El-Jawahri *et al.*[85] • 2 weeks • Cancer	FACT-BMT	The 47-item FACT-BMT, which includes subscales assessing physical, functional, emotional and social well-being, and bone marrow transplant–specific concerns during the previous week, was used to assess patients' QoL – primary outcome
Franciosi *et al.*[147] • 12 weeks • Cancer	FACT-G	The FACT-G scale is a 27-item internationally validated questionnaire divided into four primary HRQoL domains: physical well-being, social/family well-being, emotional well-being and functional well-being. The total FACT-G score is the sum of the four subscale scores

Study, primary end point, disease group	Scales used	Dimensions covered in scales
Gade *et al.*[88] • At hospital discharge • A mix of diseases comprising cancer and non-cancer	MCOHPQ	• MCOHPQ Physical Area scale, Emotional/Relationship Area and Spiritual Area scales and MCOHPQ-Place of Care Environment scale. Physical Area scale addresses pain, fatigue, sleep changes, nausea, constipation, diarrhoea, dry mouth, change in appetite and shortness of breath. Emotional support items included anxiety, burden to family, support they received, isolation, opportunity to discuss illness and possible death, and treatment wishes/goals. Spiritual support included the importance of participation in spiritual or religious experiences from the Spiritual Area scale, and two items developed by the investigators: ability to find meaning in one's life, and support given by religion or spiritual belief • MCOHPQ-Place of Care Environment scale addressed experiences receiving pain management and symptom relief, psychological and social support, discharge planning and end-of-life planning – primary outcome
Grudzen *et al.*[89] • 12 weeks • Cancer	FACT-G	FACT-G (not specified in study) – primary outcome
Higginson *et al.*[78] • 6 weeks • A mix of diseases comprising cancer and non-cancer	CRQ HRQoL (presented in meta-analysis)	Measures breathlessness mastery, breathlessness, fatigue and emotional function – secondary outcome
	EQ-5D	A generic, single index that defines health in the five dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression
Janssens *et al.*[123] • 12 months • COPD	SF-36	A generalised self-assessment scale assessing different dimensions including vitality, mental health, general health, physical functioning, role physical, role emotional, bodily pain, social functioning and health transition
Jingfen *et al.*[80] • 3 months • Cancer	EORTC QLQ-C30-Chinese version	Not specified as primary or secondary outcome
McCorkle *et al.*[48] • Not stated, but 3 months used in meta-analysis • Cancer	FACT-G (presented in meta-analysis)	No information provided in study on dimensions covered by FACT-G – secondary outcome
	SF-12 (not used in meta-analysis because only its first item was used)	
Nottelmann *et al.*[104] • 12 weeks • Cancer	EORTC QLQ-C30	The EORTC QLQ-C30 consists of 30 items in 15 scales. In this study, additional items measuring role functioning, cognitive functioning, social functioning, dyspnoea, pain, fatigue, insomnia, appetite loss, nausea/vomiting and constipation were added to the questionnaire to expand these scales to at least four items in each scale
O'Riordan *et al.*[161] • Not stated, but appeared to be 6 months; 6 months was used in meta-analysis • Heart failure	MLHF questionnaire	MLHF questionnaire measures heart failure-specific HRQoL. No further information provided
Ozcelik *et al.*[95] • On discharge • Cancer	EORTC QLQ-C30	The scale consists of two subscales: 'functional' and 'symptom'. The functional section is divided into six subsections: physical, role, cognitive, emotional, social and global quality of life. The symptom section includes the following symptoms: fatigue, nausea and vomiting, pain, dyspnoea, sleep disorders, loss of appetite, constipation, diarrhoea and financial impact – primary outcome

Study, primary end point, disease group	Scales used	Dimensions covered in scales
Rodin *et al.*[163] • 12 weeks • Cancer	FACIT-Sp	The scale covers physical, social/family, emotional, functional and spiritual well-being
Rogers *et al.*[165] • 6 months • Heart failure	FACIT-Pal (presented in meta-analysis)	Assesses QoL in several domains, including physical well-being, social/family well-being, emotional well-being, functional well-being, and palliative care – primary outcome
	KCCQ	The overall summary score is derived from the physical function, symptom, social function and Qp: domains
Sidebottom *et al.*[96] • Not stated. but data presented at 3 months used in meta-analysis • Heart failure	MLHF questionnaire	The MLHF questionnaire was created to be representative of the ways in which heart failure and treatments can affect key physical, emotional, social, and mental dimensions of QoL. It assesses how much a person's heart failure has affected many aspects of their life during the preceding month – primary outcome
Solari *et al.*[126] • 6 months	SEIQoL-DW questionnaire	The SEIQoL-DW is administered in an interview during which respondents nominate the five areas of life that are most important in determining their QoL, and rate the satisfaction/functioning and weight/importance in each of these areas. The SEIQoL-DW index can range from 0 to 100 (best)
Tattersall *et al.*[106] • 1 year • Cancer	MQOL	Physical symptoms, psychological symptoms, outlook on life, and meaningful existence – primary outcome
Temel *et al.*[35] • 12 weeks • Cancer	FACT-L (presented in meta-analysis) Lung Cancer Subscale Treatment Outcome Index	Assesses multiple dimensions of the QoL (physical, functional, emotional and social well-being) during the previous week. In addition, the Lung Cancer Subscale of the FACT-L scale evaluates seven symptoms specific to lung cancer – primary outcome
Temel *et al.*[167] • 12 weeks • Cancer	FACT-G	Assesses four dimensions of QoL (physical, functional, emotional and social well-being) – primary outcome
Vanbutsele *et al.*[168] • 12 weeks • Cancer	EORTC QLQ-C30 (presented in meta-analysis)	Global health status/QoL scale of the EORTC QLQ-C30, version 3
	MQOL	Single-item scale and overall summary score of the MQOL. The MQOL incorporates a Single Item Scale of global quality of life and four subscales, measuring four relevant domains of quality of life (i.e. physical, psychological, existential/spiritual, and social)
Woo *et al.*[116] • 4 weeks • Cancer	EORTC QLQ-C30 (Korean version)	EORTC QLQ-C30 (Korean version) assesses multiple dimensions of QoL (physical, functional, emotional and social well-being) during the previous week

FACIT-Sp, Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being Scale; FACT-BMT, Functional Assessment of Cancer Therapy – Bone Marrow Transplant; FACT-G, Functional Assessment of Cancer Therapy-General; KBILD, King's Brief Interstitial Lung Disease questionnaire; MLHF, Minnesota Living with Heart Failure; MQOL, McGill Quality of Life questionnaire; MSIS, Multiple Sclerosis Impact Scale; QoL, quality of life; SF-12, Short Form questionnaire-12 items; SF-36, Short Form questionnaire-36 items; SGRQ, St George's Respiratory Questionnaire.

Appendix 9 Studies that reported on mortality/survival

Author	Results for mortality/survival	*p*-value
Ahronheim *et al.*[81]	Number of deaths in the sample • Intervention: 12 (25%) • Control: 12 (25%)	0.96
Bajwah *et al.*[72]	Number of deaths in the sample • Intervention: 8 (32%) • Control: 13 (54%)	Not stated
Bakitas *et al.*[129]	Number of deaths in the sample • Intervention: 112 (69.6%) • Control: 119 (73.9%)	Cox proportional hazards model estimate demonstrated a reduced relative risk of death (HR 0.67, 95% CI 0.496 to 0.906; $p = 009$) in the HSPC group during the first year of the study and a greater relative risk after 1 year (HR 1.56, 95% CI 0.908 to 2.655)
	Survival time (months), median (95% CI) • Intervention: 14 (10.6 to 18.4) • Control: 8.5 (7 to 11.1)	*p*-value for survival time = 0.14
Bakitas *et al.*[73]	Number of deaths [authors stated that there were 109 deaths (52.7%)] • Intervention: numbers not provided • Control: numbers not provided Survival time (median) • Intervention: 18.3 months • Control: 11.8 months	Kaplan–Meier curves illustrate a 15% difference in survival at 1 year (HSPC 63% vs. control 48%; $p = 0.038$). However, for the overall log-rank test, $p = 0.18$, suggesting a convergence in overall survival after 12 months
Bekelman *et al.*[139]	Number of deaths in the sample • Intervention: 10 (6.4%) • Control: 13 (8.3%)	0.52
Brännström *et al.*[118]	Number of deaths in the sample • Intervention: 8 (22%) • Control: 4 (11.1%)	0.34
Brumley *et al.*[142]	Number of deaths (authors highlighted 75% death among participants) • Intervention: numbers not provided • Control: numbers not provided Survival time (days), mean (SD) • Intervention: 196 (164) • Control: 242 (200)	$p = 0.03$ However, results of the Kaplan–Meier survival analysis did not show differences in survival time between study groups ($p = 0.08$)
Carson *et al.*[82]	Survival time (days), median (IQR) • Intervention: 19 (12–37) • Control: 23 (12–39)	*p*-value for survival time = 0.51 90-day survival (HR 0.95, 95% CI 0.65 to 1.38; $p = 0.96$). Post hoc adjustment for baseline activities of daily living and study site did not alter the outcome (HR 1.01, 95% CI 0.69 to 1.47; $p = 0.96$)

Author	Results for mortality/survival	*p*-value
Cheung *et al.*[84]	Number of deaths in the sample • Intervention: 7 (70%) • Control: 9 (90%)	0.58
Edmonds *et al.*[74]	Number of deaths in the sample • Intervention: 1 (70%) • Control: 3 (11.5%)	Not stated
El-Jawahri *et al.*[85]	Number of deaths in the sample • Intervention: 3 (3.7%) • Control: 0	Not stated
Farquhar *et al.*[75]	Number of deaths in the sample • Intervention: 2 (5.7%) • Control: 0	Not stated
Farquhar *et al.*[76]	Number of deaths in the sample • Intervention: 1 (2.3%) • Control: 1 (2.3%)	Not stated
Franciosi *et al.*[147]	Number of deaths in the sample • Intervention: 52 (37.4%) • Control: 30 (36.6%)	Not stated
Gade *et al.*[88]	Number of deaths in the sample • Intervention: 173 (63%) • Control: 132 (56%) Survival time (days), median (IQR) • Intervention: 30 (6–104) • Control: 36 (13–106)	*p*-value for difference in number of deaths = 0.08 *p*-value for difference in survival time = 0.08
Groenvold *et al.*[148]	Number of deaths in the sample • Intervention: 25 (27%) • Control: 22 (23%) Survival time (median) • Intervention: 323 days • Control: 364 days	*p*-value for difference in survival time = 0.16, but in the adjusted analysis, *p* = 0.39
Grudzen *et al.*[89]	Number of deaths in the sample • Intervention: 41 (59.4%) • Control: 44 (65.7%) Survival time (days), median (95% CI) • Intervention: 289 (128 to 453) • Control: 132 (80 to 302)	The *p*-value for difference in median survival was 0.20 (log-rank test)
Higginson *et al.*[77]	Number of deaths in the sample • Intervention: 1 (3.8%) • Control: 3 (11.5%)	Not stated

Author	Results for mortality/survival	*p*-value
Higginson *et al.*[78]	Number of deaths in the sample • Intervention: 3 (5.7%) • Control: 13 (25%) Survival time (days), median (range) • Intervention: 745 (338–1075) • Control: 711 (345–1045)	The *p*-value for survival rate was 0.048. In subgroup analysis, this pattern was not recorded for patients with cancer ($p = 0.97$), but it became more marked for patients with diseases other than cancer ($p = 0.01$)
Hopp *et al.*[93]	Number of deaths in the sample (denominator unclear) • Intervention: 11 • Control: 8	0.47
Janssens *et al.*[123]	Number of deaths in the sample • Intervention: 4 (15.4%) • Control: 4 (17.4%) Survival time (days) [unclear if mean or median reported (95% CI)] • Intervention: 454 (382 to 525) • Control: 425 (339 to 509)	Survival did not differ between groups (log-rank test, $p = 0.913$)
Kane *et al.*[156]	One-third of the sample died within 45 days of enrolment, and the second third died within 120 days, but numbers were not provided for the intervention and control groups	Authors reported no difference in the survival patterns of HSPC and control patients
Lowther *et al.*[97]	Number of deaths in the sample • Intervention: 3 (5%) • Control: 0	Not stated
Ma *et al.*[70]	Number of deaths in the sample • Intervention: 34 (35.1%) • Control: 37 (36.3%)	0.87
McCaffrey *et al.*[160]	Number of deaths in the sample • Intervention: 16 (69.6%) • Control: 5 (62.5%)	Increment reported as 7 (95% CI −45.1 to 30.4)
McCorkle *et al.*[48]	Number of deaths in the sample • Intervention: 7 (10.6%) • Control: 3 (3.8%)	Not stated
McWhinney *et al.*[79]	Authors reported that 36 (24.7%) patients dies before 1 month, but did not provide numbers in the intervention and control groups	
O'Riordan *et al.*[161]	Number of deaths in the sample • Intervention: 1 (4.5%) • Control: 1 (5.6%)	Not stated
Rogers *et al.*[165]	Number of deaths in the sample • Intervention: 23 (30.7%) • Control: 20 (26.7%)	Not stated
Sidebottom *et al.*[96]	Number of deaths in the sample • Intervention: 14 (12.1%) • Control: 5 (4.3%)	Results of the survival analysis found no association between study group assignment and death within 6 months after adjustment for age, sex and marital status

Author	Results for mortality/survival	*p*-value
Solari *et al.*[126]	Number of deaths in the sample • Intervention: 3 (3%) • Control: 0	Not stated
Tattersall *et al.*[106]	Number of deaths in the sample • Intervention: 39 (65%) • Control: 31 (51.7%) Survival time (months), median (95% CI) • Intervention: 7 (5.2 to 9.8) • Control: 11.7 (9.8 to 18.8)	*p* (log rank) = 0.014 The estimated HR was 1.6 (95% CI 1.1 to 2.3; *p* = 0.015). This estimate changed to 1.5 (95% CI 0.99 to 2.2; *p* = 0.06) when adjusted for the oncologist's baseline estimate of likely survival, diagnosis, months since diagnosis and sex
Temel *et al.*[35]	Number of deaths [authors stated 105 participants (70%) had died by the time of analysis] • Intervention: numbers not provided • Control: numbers not provided Survival time (months), median (95% CI) • Intervention: 11.6 (6.4 to 16.9) • Control: 8.9 (6.3 to 11.4)	Log-rank *p* = 0.02 After adjustment for age, sex and baseline Eastern Cooperative Oncology Group performance status, the group assignment remained a predictor of survival (HR for death in the standard-care group 1.70, 95% CI 1.14 to 2.54; *p* = 0.01)
Temel *et al.*[167]	Number of deaths in the sample • Intervention: 33 (18.9%) • Control: 41 (23.4%)	Not stated
Vanbutsele *et al.*[168]	Number of deaths [authors stated that 121 (65%) participants had died by the end of the study] • Intervention: numbers not provided • Control: numbers not provided Survival time (days), median (95% CI) • Intervention: 312 (190 to 434) • Control: 343 (253 to 433)	0.97
Woo *et al.*[116]		Authors reported that there was no difference in survival between HSPC and usual care, but did not present any data

Appendix 10 Studies that reported adverse events in patients and/or caregivers

Studies	Participants	Adverse effects in patients/caregivers
Bajwah *et al.*[72]	Patients and caregivers	Authors reported no worsening of any outcome after receiving the intervention
Bekelman *et al.*[139]	Patients	There were no harmful adverse events attributed to the intervention
Groenvold *et al.*[148]	Patients	Authors did not observe any harmful effect of the intervention
Higginson *et al.*[78]	Patients (and caregivers if present)	Authors did not observe any harmful effect of the intervention
Lowther *et al.*[97]	Patients	Authors did not observe any harmful effect of the intervention
Rodin *et al.*[163]	Patients	Authors reported no adverse events during the study
Solari *et al.*[126]	Patients and caregivers	Authors reported 15 serious adverse events in 13 patients in the HSPC group and seven in seven patients in the control group ($p = 0.78$). Serious adverse events reported included aspiration pneumonia, generalised anxiety, breathing difficulty, urine retention/infection, anarthria, contact dermatitis, dysphagia, vomiting, bladder catheter malfunctioning, fever, arrhythmia, necrotising fasciitis, traumatic wound, macrohaematuria, constipation, abdominalgia and bronchitis. Three patients in the HSPC group died, but this was considered to be unrelated to the intervention
Tattersall *et al.*[106]	Patients	Authors reported that more patients in the HSPC group than in the control group had poorer appetite ($p = 0.04$)

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