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PALLIATIVE CARE SERVICES

**HEALTH TECHNOLOGY ASSESSMENT SECTION
MEDICAL DEVELOPMENT DIVISION
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DISCLOSURE

EXECUTIVE SUMMARY

Background

World Health Organization (WHO) defines palliative care (PC) as 'an approach that improves the quality of life (QOL) of patients (adults and children) and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, whether physical, psychosocial, and spiritual'. In 2014, the first ever global resolution on palliative care had called upon WHO and Member States to improve universal access to palliative care as a core component of health systems. The Health Assembly also asserted that integration of palliative care into public health care systems is essential for achievement of Sustainable Development Goal (SDG) 3.8 in universal health coverage. In the WHO Global Action Plan for the Prevention and Control of Non-communicable Diseases (NCDs) 2013-2020, palliative care was recognised as part of the comprehensive services required for the management of NCDs and access to opiate pain relief becomes one of the 25 indicators in the global monitoring framework for NCDs. In Malaysia, Ministry of Health (MOH) has recognised palliative care as a medical specialty and the provision of palliative care services has started in the hospitals. At present the strategic plan for palliative care in the Ministry of Health is to eventually develop specialized units in all state hospitals in the country with seamless care provided by the community palliative care services. This Technology Review was conducted following a request by the National Head of Palliative Care Services, Ministry of Health Malaysia to review the evidence on the effectiveness, safety, cost-effectiveness, organizational, ethical and cultural issues in improving QOL and symptoms control among chronic life-limiting illness patients.

Objective/aim

To assess the effectiveness, safety, economic implication as well as the organizational, ethical and cultural issues in palliative care interventions in improving QOL and symptoms control among patients with chronic life-limiting illness.

Results and conclusions

Effectiveness

Quality of life
There was sufficient, good level of retrievable evidence to suggest that;
  i.   Specialised palliative care in hospital-based, community-based and home-based settings improved QOL in patients with life-threatening diseases.
  ii. Specialised palliative care also has positive impact on survival

iii. Direct contact, comprehensive team-based model significantly improves patient QOL
iv. Early integration of PC multidisciplinary team concurrently with treatment resulted in improvement in QOL, better symptom control, less caregiver burden, improvement in continuity and coordination of care, fewer admissions, patients dying in their preferred place.

There was fair level of evidence to suggest technological-based interventions had potential in improving outcomes in terms of QOL as well as pain control and depression

Physical well-being
There was sufficient fair to good level of retrievable evidence that suggest;
i. Palliative care improved physical symptoms, specifically on pain.
ii. Oral morphine was an effective analgesic for cancer pain, with similar efficacy to other opioids. Both immediate-release and sustained-release formulations of oral morphine can be titrated to analgesic effect.
iii. Single fraction and multiple fraction radiation treatment regimens demonstrated similar outcomes in pain control and toxicities, but re-treatment was more common for single fraction treatment patients.

There was insufficient evidence retrieved on fatigue, weight loss and palliative pharmacological sedation on QOL or symptom control.

Psychosocial well-being
There was fair to good quality of retrievable evidence that suggest;
i. Psychosocial interventions improve QOL and emotional wellbeing
ii. Dignity therapy and therapeutic life review were potentially beneficial for people near the end of life

Spiritual well-being
There was fair level of retrievable evidence that suggest spiritual interventions had a moderate beneficial effect in terms of improving QOL of cancer patients

Paediatric Palliative Care
There was good quality of retrievable evidence that suggest home-based paediatric palliative care improved QOL of patients and their caregivers. However no conclusions can be drawn about efficacy or harm in the use of opioids to treat cancer-related pain in children and adolescents due to low quality of evidence retrieved.

Traditional and Complementary Medicine
There was good quality of retrievable evidence that suggest combined Chinese Herbal Medicine and conventional treatment significantly reduced pain and constipation. However, more research is warranted on the use of CHM for treating anorexia and fatigue.

Safety

There was fair level of retrievable of evidence that suggest most people will experience tolerable adverse events from using various types of opioids. Prevalence of adverse events related to morphine, fentanyl, oxycodone or codeine ranged from 5% for diarrhoea and insomnia to 25% for constipation and somnolence. No direct evidence that opioids affected patient consciousness, appetite or thirst when used to treat cancer pain.

Economic evaluation

There was sufficient retrievable evidence that suggest palliative care unit was cost saving. Hospital costs were lower for patients seen by a palliative care consultation team than for patients who not did not receive this care, especially was greater for those with a primary diagnosis of cancer and those with more comorbidities compared. Community-based specialist palliative care associated a reduction of inpatient averaged hospital costs of 9% (7%-10%) to A$1030 (MYR 2,994 per hospitalised decedent per day) across multiple life-limiting conditions. It was associated with reduced acute care admissions, bed days, and costs over the last year of life. Outpatient palliative care significantly reduced total health care costs among patients with terminal or advanced and complex illness. The delivery of early PC does not appear to increase overall medical care expenses for patients with metastatic cancer.
There was also retrievable evidence that suggest home-based palliative care for paediatric patients was cost-saving although results were somewhat mixed in the adults.

Organizational issues

There was retrievable evidence that community-based specialist palliative care teams were effective at reducing acute care use and hospital deaths at the end of life. Competencies identified as critical for the delivery of high-quality PC in critical care settings included; prognostication, conflict mediation, empathic communication as well as patient and family-centred aspects of care. Patient-centred communication intervention resulted in clinically and statistically significant improvements in the primary physician-patient communication end point.

Ethical and cultural considerations

Individuals have three primary goals with respect to making treatment decisions for them during periods of incapacity: involve their family, treat them consistently with their own treatment preferences, and reduce the burden on their family. Culture and religion influence lifestyle and shapes the experiences of illness, pain, and end-of- life care and cannot be generalized to all patients and families.

PALLIATIVE CARE SERVICES

1.0   BACKGROUND

World Health Organization (WHO) defines palliative care as 'an approach that improves the quality of life (QOL) of patients (adults and children) and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, whether physical, psychosocial, and spiritual'.[1] It is interdisciplinary and holistic in nature and treats the patient and family as the 'unit of care'. Palliative care for children is the active total care of the child's body, mind and spirit, and also involves giving support to the family. It begins when illness is diagnosed, and continues regardless of whether or not a child receives treatment directed at the disease.

Worldwide, over 20 million people are estimated to require palliative care at the end of life every year. [2] The majority (69%) are adults over 60 years old and only 6% are children. Although most palliative care is provided in high-income countries, almost 80% of the global need for palliative care is in low- and middle-income countries.[2] In 2014, the first ever global resolution on palliative care, World Health Assembly 67.19 had called upon WHO and Member States to improve universal access to palliative care as a core component of health systems.[3] The Health Assembly also asserted that integration of palliative care into public health care systems is essential for achievement of Sustainable Development Goal (SDG) 3.8 in universal health coverage. In WHO Global Action Plan for the Prevention and Control of Non-communicable Diseases (NCDs) 2013-2020, palliative care was recognised as part of the comprehensive services required for the management of NCDs and access to opiate pain relief becomes one of the 25 indicators in the global monitoring framework for NCDs.[4] In 2018, the ASTANA declaration has called for provision of palliative care in the primary healthcare setting.[5]

In Malaysia, the estimated number of Malaysians requiring palliative care is around 56,000 yearly.[6] Non-communicable diseases (NCDs) are the top causes of death in adults needing palliative care, with cardiovascular diseases (43.8%) overtaking cancer (32.7%) as the main cause. Others are chronic obstructive pulmonary diseases (COPD), diabetes mellitus, HIV/AIDS, kidney diseases and certain neurological diseases such as Parkinson's and Alzheimer's.[6]The number of children in need of palliative care is estimated to be 3.91% of total palliative care needs with the causes of death substantially different from adults, consisting mainly of congenital anomalies, hereditary disorders, and neonatal conditions and to a lesser degree cancer and infectious diseases.[6]

The first palliative care services in Malaysia were established in the 1990s by charitable organisations providing care in the community before they were formally introduced in the Ministry of Health (MOH) in 1995.[7] Since then, MOH

has recognised palliative care as a medical specialty and started to develop services in the hospitals. At present the strategic plan for palliative care in the Ministry of Health is to eventually develop specialized units in all state hospitals in the country with seamless care provided by the community palliative care services.

Therefore, this Technology Review was conducted following a request by the National Head of Palliative Care Services, Ministry of Health Malaysia to review the evidence on the effectiveness, safety, cost-effectiveness, organizational, ethical and cultural issues in improving QOL and symptoms control among chronic life-limiting illness patients.

2.0 OBJECTIVE / AIM

To assess and review the effectiveness, safety, economic implication as well as the organizational, ethical and cultural issues of palliative care interventions in improving QOL and symptoms control among patients with chronic life-limiting illness.

3.0 TECHNICAL FEATURES

3.1 Palliative care services

Palliative care integration in health care system has been strongly advocated to ensure access to good pain and symptom relief, practical support, and high-quality end-of-life care.[8] It should be applied as early as possible in the course of any chronic, ultimately fatal illness. In the presence of such an illness, there may be a gradual transition from curative care to the acceptance that palliation is the major goal of management (Figure 1).
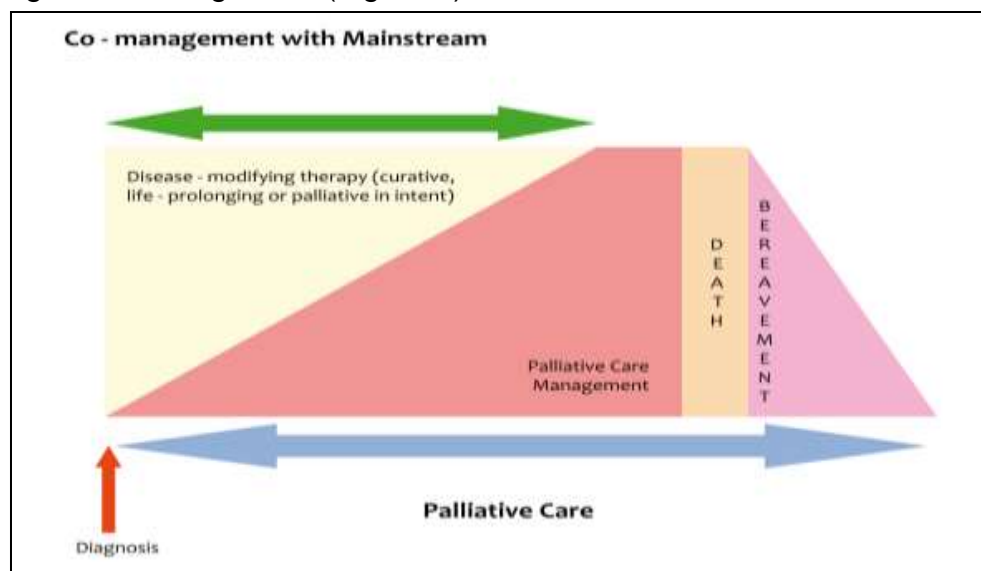

Figure 1: Integrated Model of Palliative Care (Adapted from Twycross, 2002)[7]

There is a difference in the way that some terms are defined and understood between the United States and most other countries (e.g, United Kingdom, Australia or Europe).[9] In Europe/Australia, the terms palliative care and hospice are often used interchangeably while in the United States, the term hospice refers to a primarily home care programme and palliative care tends to refer to hospital-based services.[9]

Healthcare providers involved in palliative care may include physicians, nurses, social workers, psychologists, spiritual counsellors, volunteers, pharmacists and traditional healers.[10] In Malaysia, a palliative care team is typically composed of a physician trained in palliative medicine, at least one clinical nurse and a part-time social worker, all supported by adequate administrative staff.[7] Such a team has no dedicated beds of its own but advises on every aspect of palliative care. This approach makes it possible to provide palliative care consultations to a large number of patients, in a hospital or nursing home. It is an ideal way of providing specialist care while at the same time training the large numbers of physicians and nurses with whom the team interacts.

The scope of service covers both cancer and non-cancer patients with progressive life threatening illness include:[7]

i. Medical management of chronic cancer pain and other distressing physical symptoms related to advanced cancer
ii. Medical management of pain and other distressing physical symptoms related to progressive life-threatening non-cancerous illnesses. Key areas where palliative medicine in non-cancerous conditions is rapidly developing includes:
   a) End stage cardiac disease with refractory symptoms.
   b) End stage renal disease where dialysis support is not feasible or being withdrawn.
   c) Progressive neurodegenerative disorders (e.g. Motor Neurone Disease, Multiple Sclerosis).
   d) Severe chronic airway limitation with deteriorating respiratory function and poor candidate for ventilator support.
   e) Life threatening paediatric conditions (to be managed by paediatric palliative medicine physician) including life threatening congenital disorders.
   f) HIV / AIDS not responding to anti-retroviral therapy or rapidly deteriorating due to overwhelming disease related complications (infections or malignancy).
   g) Frailty in the elderly with multiple progressive comorbidities (consider collaboration with geriatrician where available)
iii. Provision of psychosocial and spiritual supportive care to patients and families facing life-threatening illness.
iv. Provision of terminal care for patients at the end of life.
v. Provision of respite care for patients and families.
vi. Provision of a holistic management plan to optimize QOL throughout the course of patients' illness and to apply a multidisciplinary approach to care.

vii.   Provision of consultative advice and assistance to other medical colleagues regarding palliative management of patients with life threatening situations under their care.

Components of palliative care services in Malaysia include;[7]
i.   In-patient palliative care service
ii.   Out-patient palliative care service
iii.   Consultative palliative care service in general wards.
iv.   Consultative palliative care service in other hospitals without palliative care units.
v.   Community palliative care service.
vi.   Day palliative care service.

Ideally, each component of palliative care services (in-patient, consultative and community palliative care) should have its own dedicated specialist, medical officers and nursing staff. However due to lack of human resource, all three components of care may need to be managed by a single team playing interchangeable roles to fulfill each component of care. Figure 2 illustrated the components of palliative care services and their relationships.

In-patient palliative care services
In-patient, hospital-based team provides palliative care to patients requiring admission.

Consultative palliative care service
Palliative care team accept and review referrals from other specialty within the hospitals or in other hospital without palliative care units.

Community Palliative Care Service
The role of the community team is to review patients as and when necessary in their homes, so as to provide continuity of care after discharge from hospital. The community care team comprises of a specialist, preferably a family medicine specialist, a medical officer and a nurse coordinator. At present the majority of community palliative care services in Malaysia are run by Non-Governmental Organizations (NGOs) i.e hospice organisations, hence where such NGOs are available, this component of care need not be duplicated. If there is no NGO palliative care service available, then efforts should be made to develop a community service within the hospital palliative care service or within the public health sector in the MOH, i.e. clinics with resident family medicine specialist. The service may be managed through formal palliative care programmes, home health or hospice agencies, or other community-based clinicians, with support provided in person, by telephone, or by electronic correspondence; when linked with hospital-based palliative care services.

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Hospice care
A form of palliative care in which hospice agencies provides volunteer services, medical, psychosocial, spiritual care in synergy with the provision of medical interventions. These services are usually financed by an all-inclusive per-diem rate and may be provided either in the home or in a separate hospice facility.

Daycare services
This refer to a palliative daycare centre where patients come for respite during the day and engage in social activities and interact with other patients who are of relatively good performance status. Daycare activities may be jointly organized with the help of volunteer organizations who will provide the main human resource of this service.
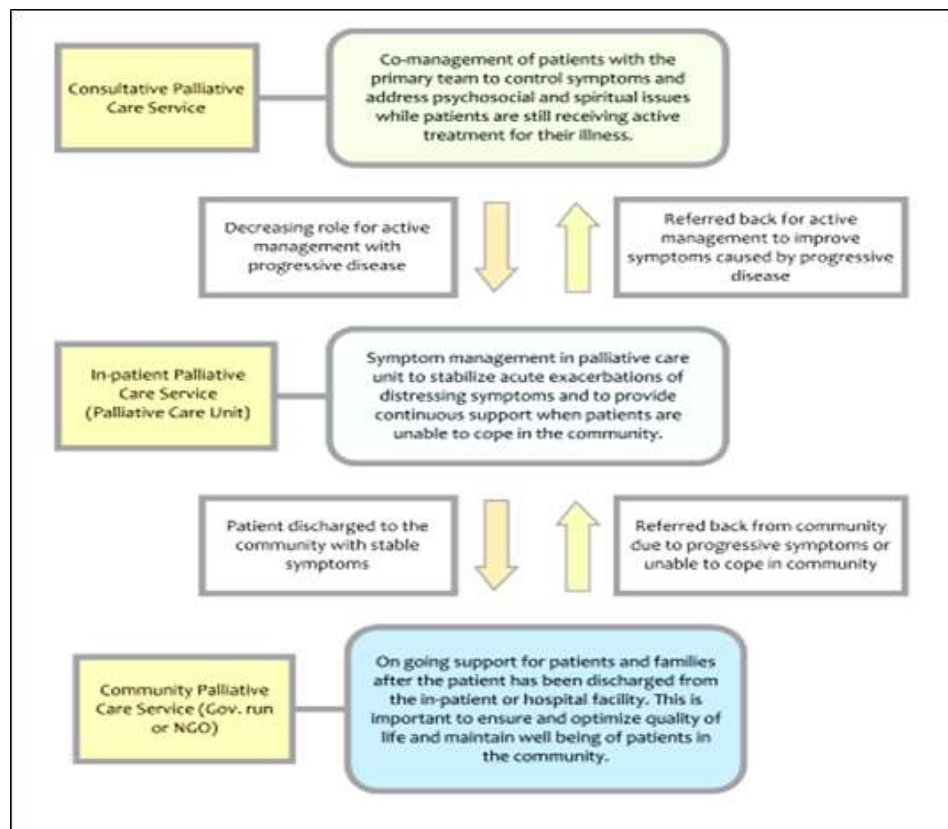

Figure 2: Components of palliative care services and their relationships[7]

Paediatric Palliative care (PPC) represents a special, albeit closely related field to adult palliative care. Health providers evaluate and manage child's physical, psychological, and social distress with the active involvement of the family in health care decisions.[3]

3.2 Palliative care interventions

A palliative care programme should deliver good quality basic services of physical (such as pain), psychosocial and spiritual symptom management, counselling, good nursing care, discharge planning and bereavement care, to all members of the target population in need, including patients, family members and caregivers.[10]

Management of physical well-being
Physical symptoms experienced by palliative care patients include pain (e.g. somatic, visceral pain), respiratory symptoms such as dyspnoea, gastrointestinal symptoms such as constipation, fatigue, weight loss and much more. Opioid analgesics, including codeine, play a significant role in major guidelines associated with the management of moderate to severe pain as well as dyspnoea for palliative care patients. Morphine and codeine are the two opioids included in the World Health Organization (WHO) essential drugs list[11]; other opioids are generally similar, but have differences in potency, lipophilicity (the ability of a chemical compound to dissolve in fats, oils, lipids), and routes of administration. Morphine has long been considered the preferred choice of opioid. It is widely available, although in some countries it is severely restricted, comparatively inexpensive, and is effective orally. Codeine is considerably less potent than morphine and recommended for mild to moderate cancer pain. The majority of opioids are administered orally, often in the form of modified-release formulations to reduce dosing to once or twice daily. Rectal administration is also possible. Fentanyl and buprenorphine can also be administered by transdermal patch.

Management of psychosocial well-being
Psychosocial symptom include symptoms of anxiety, depression, distress, worry, sadness, fear of being alone, difficulty talking about feelings, loss of independence, and loss of perspective. Interventions could include antidepressants, antipsychotic, counselling, relaxation techniques, dignity therapy as well as technology-based intervention. Dignity Therapy is a brief, individualized psychotherapy and aims to relieve psycho-emotional and existential distress and to improve the experiences of patients whose lives are threatened by illness. This therapy offers patients an opportunity to reflect on issues that are important to them or other things that they would like to recall or transmit to others[12]

Management of spiritual well-being
Spiritual interventions was defined as any approach involving two components, religious (i.e., achieving harmony with God) and existential aspects (i.e., finding meaning and purpose in one's life), based on Paloutzian and Ellison's (1982) conceptualization of spirituality. It is not only relates to one's faith, but it is to do with how we live, what we treasure and value, and peace of mind.

End of life (EoL) care

The terminal phase is defined as the period when day to day deterioration of strength, appetite and awareness are occurring in a patient with an incurable and progressive illness. Prognostication refers to the skill of predicting survival or outcome of a situation and communicating this sensitively to family and significant others. During this phase, the team individualise plan of care that explore needs of the dying person and family and decisions about treatment and preferences for care.

4.0   METHODS

4.1.   Searching

Electronic databases searched through the Ovid interface:

MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE (R) 1946 to present

EBM Reviews - Cochrane Central Registered of Controlled Trials – August 2018

EBM Reviews - Database of Abstracts of Review of Effects – 3rd Quarter 2018

EBM Reviews - Cochrane Database of Systematic Reviews - 2005 to August 2018

EBM Reviews - Health Technology Assessment – 3rd Quarter 2018

EBM Reviews - NHS Economic Evaluation Database – 3rd Quarter 2018

Other databases used:

- Embase
- PubMed
- Other websites: INAHTA

The keywords used were "palliative care", "terminal care", "terminally ill", "end of life care", "hospice", "life-limiting illness". Additional articles were identified from reviewing the references of retrieved articles. The search was limited to articles on human. There was no language limitation in the search. **Appendix 1** showed the detailed search strategies. The last search was conducted on 25 August 2018.

4.2.   Selection

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection. The inclusion and exclusion criteria were:

Inclusion criteria

Population	All age group life-limiting illness
Interventions	Palliative care interventions/services/ programmes/ systems/models/hospice care

	Setting •In-patient palliative care (hospital based) •Consultative palliative care (hospital based) •Out-patient care •Community palliative care (community-based) •Day palliative care **Treatment modalities** -Physical symptoms (pain, respiratory, GI, oral, skin) •Drugs – pain medication (opiods, NSAIDS, PCM), anti-emetics, laxatives, sedatives, adjuvant analgesics, corticosteroids, anticholinergic •Traditional & complementary medicine- acupuncture, massage -Psychological & social •Antidepressants, SSRI •Counselling •Relaxation -Spiritual
Comparators	Current standard treatment / usual care (on its own / adjunct)
Outcomes	Effectiveness: • Symptom control: Physical (e.g. pain), psychosocial, spiritual symptoms • Improvement in quality of life • Improvement in survival Safety Financial Implications: • Cost-effectiveness / cost utility analysis • Cost analysis Organizational issues Ethical and cultural issues
Study design	Systematic review (SR) with or without meta-analysis, health technology assessment (HTA), randomised controlled trial (RCT), non-randomised controlled trials, cohort, case control, cross-sectional
Language	English, full text articles

Exclusion criteria

Study design	Case report, case series, narrative review, anecdotal, animal studies
	Non-English articles

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) checklist and evidence graded according to the US/Canadian Preventive Services Task Force (**Appendix 2**).[13] Risk of bias of

RCTs was assessed using Cochrane Risk of Bias Assessment Tool. Data were extracted from included studies using a pre-designed data extraction form (Evidence Table as shown in **Appendix 3**) and presented in tabulated format with narrative summaries. The data were not pooled and only qualitative analysis was carried out.

5.0 RESULTS AND DISCUSSION

A total of 833 records were identified through the Ovid interface and PubMed, and 11 were identified from other sources (references of retrieved articles). After removal of five duplicates, 839 records were screened and 523 were excluded. Of these, 316 relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the full text articles, 43 full text articles were included while 273 full text articles were excluded. The articles were excluded due to the study was already included in systematic review and meta-analysis (n=199), studies not addressing pre-specified population, intervention, and comparison characteristics (n=16) and irrelevant outcomes (n=31).
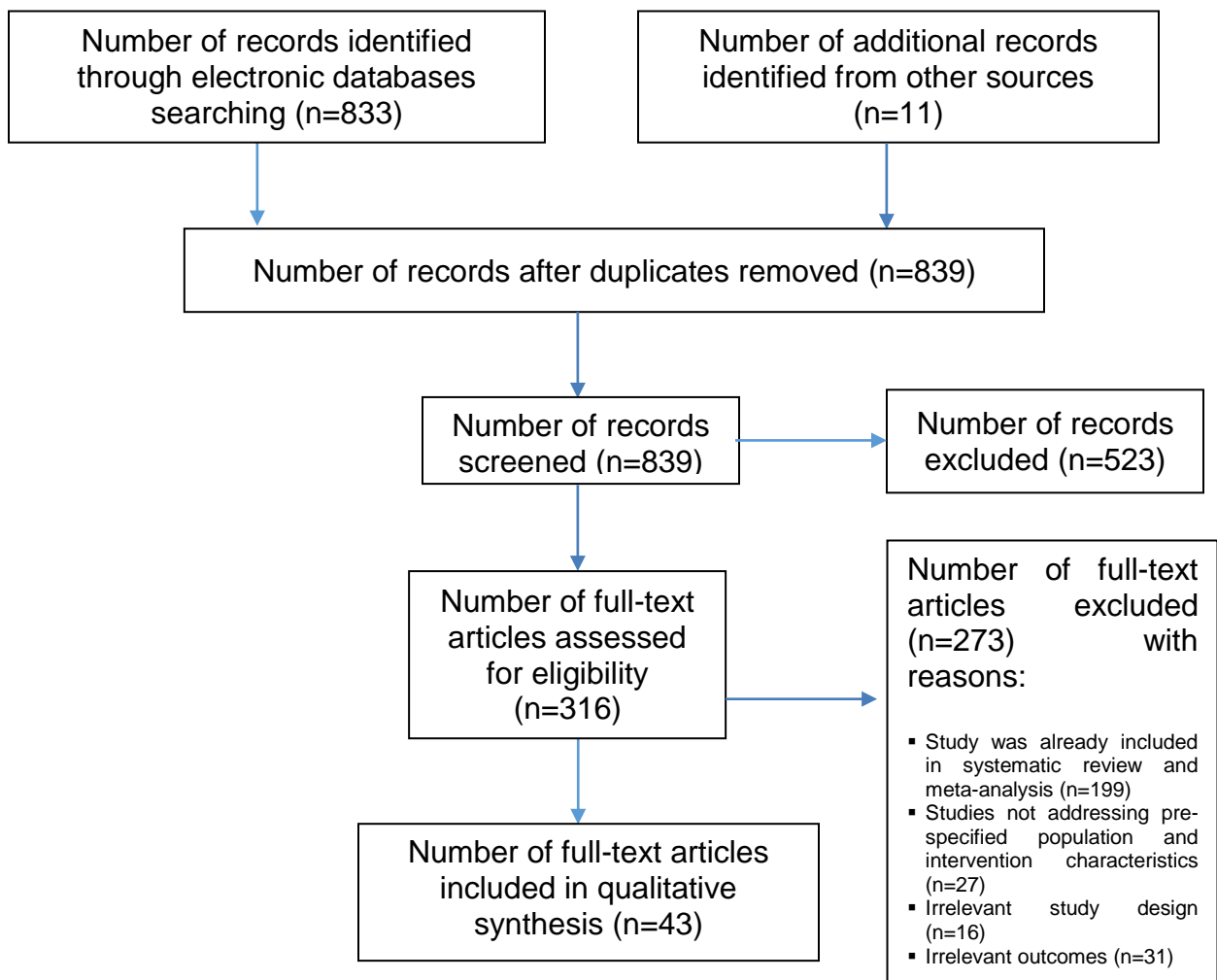
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┌─────────────────────────────┐   ┌─────────────────────────────┐
│  Number of records identified│   │ Number of additional records │
│  through electronic databases│   │  identified from other sources│
│       searching (n=833)      │   │            (n=11)            │
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          │                 (n=839)                     │
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              │   screened (n=839)  │        │  excluded (n=523)   │
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              │ Number of full-text │        │ Number of full-text articles │
              │  articles assessed  │───────▶│  excluded (n=273) with       │
              │   for eligibility   │        │  reasons:                    │
              │       (n=316)       │        │ ▪ Study was already included │
              └─────────────────────┘        │   in systematic review and   │
                             │               │   meta-analysis (n=199)      │
                             ▼               │ ▪ Studies not addressing pre-│
              ┌─────────────────────┐        │   specified population and   │
              │ Number of full-text │        │   intervention characteristics│
              │ articles included in│        │   (n=27)                     │
              │ qualitative synthesis│       │ ▪ Irrelevant study design    │
              │       (n=43)        │        │   (n=16)                     │
              └─────────────────────┘        │ ▪ Irrelevant outcomes (n=31) │
                                             └─────────────────────────────┘
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Figure 2: Flow chart of study selection

Study Design

Forty-three studies were included in this review. Thirty-three of the studies were systematic review with or without meta-analysis, two randomised controlled trials (RCT) which were not included in any of the systematic reviews, one pre-post intervention studies, four cohort studies and three economic analysis.

Quality assessment of included studies

Critical Appraisal (CASP) checklist was used to critically appraise the intervention studies which consist of eight critical appraisal tools designed for SR, RCT, cohort studies, case control studies and economic evaluations. This is achieved by answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias as either:

+	Indicates YES (low risk of bias)
?	indicates UNKNOWN risk of bias
-	Indicates NO (high risk of bias)

All except three SR with meta-analysis reported the risk of bias of the included studies. Three studies including Health Quality Ontario Study (2014), Wiffen et.al (2017) and Payne et al (2012) used The Assessment of Multiple Systematic Reviews (AMSTAR) measurement tool.[14,15,16] Twelve other studies utilised Cochrane Risk of Bias Tool [16,17,18,19,20,21,22,23,24,25,26,27] while one study adapted other quality checklists to assess risk of bias. [28]

Criteria assessed	Authors look for the right type of papers?	Selection of studies (all relevant studies	Assessment of quality of included	If the results of the review have been combined, is it reasonable to do so
Singer et al. 2016	+	+	+	?
Phongtankuel et al. 2018	+	+	-	+
Health Quality Ontario 2014	+	+	+	+
Gomes et al. 2013	+	+	+	+
Haun et al. 2017	+	+	+	+
Gaertner et al. 2017	+	+	+	+
Kassianos et al. 2017	+	+	+	+
Wiffen et al. 2017	+	+	+	+
Rich et al. 2018	+	+	-	+
Beller et al. 2017	+	+	+	+
Payne et al. 2012	+	+	+	+
Wang, Chow & Chan 2017	+	+	+	+
Parahoo et al. 2013	+	+	+	+
Galway et al. 2012	+	+	+	+
Larson et al. 2017	+	+	-	+

Study				
Agboola et al. 2015	+	+	+	+
Kruizinga et al. 2016	+	+	+	+
Oh Pok-Ja et al. 2014	+	+	+	+
Cunningham & Ollendorf 2017	+	+	+	+
Chung et al. 2016	+	+	+	+
Kelly et al. 2012	+	+	+	+
Weiner et al. 2013	+	+	+	+
Bravo et al. 2008	+	+	+	+
Schram et al. 2016	+	+	+	+

Figure 1: Critical appraisal of systematic review studies using CASP checklist

Criteria assessed	Adequate sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data addressed	Free of selective reporting	Free of other bias
Vanbutsele et al. 2018	+	+	-	+	+	+
Prescott et al. 2017	?	?	-	+	+	?
Eipstein et al. 2016	-	-	+	+	+	?

Figure 2: Assessment of risk of bias of RCT (Cochrane tool)

Criteria assessed	Selection of cohort	Exposure accurately measured	Outcome accurately measured	Confounding factors	Follow-up of subjects
Seow et al. 2014	+	+	+	?	+
Spilsbury & Rosenwax 2017	+	+	+	+	+
Chong et al. 2018	+	+	+	+	+
Widger et al. 2017	?	+	+	+	+
Youens & Moorin 2017	+	+	+	+	+

Figure 3: Critical appraisal of cohort studies using CASP checklist

Criteria assessed	Pham & Krahn 2014	Greer et al. 2016	Isenberg et al. 2017
A well-define question posed?	+	+	+
Comprehensive description of competing alternative given?	+	?	+
Effectiveness established?	+	+	+
Effects of intervention identified, measured and valued appropriately?	+	+	+
All important and relevant resources required and health outcome costs for each alternative identified, measured in appropriate units and valued	+	+	+

credibly?			
Costs and consequences adjusted for different times at which they occurred (discounting)?	+	+	+
Results of the evaluation?	+	+	+
Incremental analysis of the consequences and costs of alternatives performed?	+	+	+
Sensitivity analysis performed?	+	+	+

Figure 4: Critical appraisal of economic evaluation (CASP) using CASP checklist

Criteria assessed	Gans et al. 2016
Question or objective clearly stated?	+
Eligibility/selection criteria for study population clearly described?	?
Were participants representative for those who would be eligible for the test/ service/ intervention in the population of interest?	?
Were all eligible participants that met the pre-specified entry criteria enrolled?	+
Sample size sufficiently large to provide confidence in findings?	+
Test/service/intervention clearly described and delivered consistently?	+
Outcome measures prespecified, valid, reliable, and assessed consistently?	+
People assessing the outcome measures blinded to participants exposure/ interventions?	+
Loss to follow-up after baseline 20% or less? Loss to follow-up accounted for in the analysis?	?
Statistical methods examine changes in outcome measures from before to after intervention? p value?	+
Outcome measures taken multiple times before and after intervention? Use interrupted time-series design?	-
If intervention conducted at group level, did statistical analysis take into account of individual level data to determine effects at group level?	+

Figure 5: Quality assessment of pre-post studies with no control (NIH)

5.1 Efficacy/ Effectiveness

We identified 27 articles in which researchers measured patients' QOL, physical, psychosocial and spiritual well-beings as the outcomes of the studies as well as two articles on paediatric palliative care and one on traditional and complementary medicine.

5.1.1 Quality of Life

There were 12 articles in which researchers primarily measured patients' QOL. These include 11 systematic reviews with and without meta-analysis and one non-blinded RCT. In these studies, interventions included three systematic reviews that looked into community-based and hospital-based specialized

palliative care programmes, three on team-based or multicomponent model of care, three on early and integrated model of care, two on technology-based interventions and one on spiritual intervention.

Specialised palliative care
Gaertner et al. (2017) evaluated the effect of specialist palliative care services on QOL and symptom burden in adults with advanced incurable illness in hospital, hospice, or community settings in a systematic review and meta-analysis.[29,Level 1] Twelve articles included ten RCTs involving 2454 patients with 72% of them had cancer. Specialist palliative care was defined as service of health care professional from at least two different professions that provides or coordinates comprehensive care for patients. The intervention varied across studies. All ten studies included a nurse while nine studies (90%) included a physician. Social workers and chaplains were part of the multi-professional team in five of the 10 trials (50%). The study found small effect in favour of specialist palliative care (SMD 0.16, 95% CI 0.01, 0.31; QLQ-C30 global health/QOL 4.1, 95% CI 0.3, 8.2; n=1218, 6 trials). Sensitivity analysis showed an SMD of 0.57 (−0.02 to 1.15; global health/ QOL 14.6, −0.5 to 29.4; n=1385, seven trials). The effect was marginally larger for patients with cancer (0.20, 0.01 to 0.38; global health/QOL 5.1, 0.3 to 9.7; n=828, five trials) and especially for those who received specialist palliative care early (0.33, 0.05 to 0.61, global health/QOL 8.5, 1.3 to 15.6; n=388, two trials). The results for pain and other secondary outcomes were inconclusive. Specialist palliative care was associated with a small effect on QOL and might have most pronounced effects for patients with cancer who received such care early.[29,Level 1]

Kassianos et al. (2017) examined the impact of specialized palliative care (SPC) on cancer patients' health-related QOL (HRQOL) in a systematic review and meta-analysis.[28,Level 1] Eleven studies consisting of five RCTs and six prospective studies were included, making a total of 2939 patients (mean age ranged 52.6 to 68 years) with various types of cancer. The included RCTs were homogeneous to be analyzed with fixed-effects models (Q =8.22, p =0.084, I^2 = 51.3%) but there was heterogeneity in non-RCTs (Q = 34.89, p <0.001, I^2 = 85.6%). All studies with the exception of one RCT, showed some evidence of improvement of HRQOL in the specialised palliative care group compared to the control arm. There was a positive moderate impact of SPC in HRQOL (SMD, 0.28; 95% CI 0.16, 0.41; p < 0.001). They also reported having lower symptom intensity overall, specifically on pain, fatigue and nausea, improvements in symptoms of depression, mood, anxiety and spiritual well-beings. Those who received SPC were more likely to die at home and be more satisfied with care. Two studies also reporting a positive impact on survival. There were non-significant differences on the impact of SPC on HRQOL between RCTs and non-RCTs (p =0.990), types of cancer (p = 0.627), and between inpatients, outpatients, and both (p = 0.172). However, mixed-effects analysis showed that SPC had a positive impact in studies using in-patients (SMD, 0.55; 95% CI 0.17, 0.92; p = 0.004) or both (SMD, 0.18; 95% CI 0.08,0.27; p < 0.001) but non-significant effect for

outpatients (SMD, 0.20; 95% CI − 0.03,0.44; p =0.89). The methodological problems and publication bias call for higher-quality studies to be designed, funded, and published. However, there is a clear message that SPC is multi-disciplinary and aims at palliation of symptoms and burden in line with current recommendations.[28,Level 1]

A systematic review and meta-analysis was conducted by Kavalieratos et al. (2016) to determine the association between palliative care and patient QOL, symptom burden, and survival.[30,Level 1] Randomised controlled clinical trials of palliative care interventions in adults with life-threatening illnesses were reviewed, and 43 trials involving 12,731 patients and 2,479 care-givers were included in the analysis. Of these, 14 trials took place in the ambulatory setting, 18 were home-based, and 11 were hospital-based. As measured by a variety of standardised scales, palliative care was associated with statistically significant and clinically meaningful improvements in patient QOL (standardised mean difference SMD= 0.46; 95% CI 0.08,0.83) and symptom burden (SMD= −0.66; 95% CI −1.25,−0.07) at one-to-three-month follow-up but not with improved survival (hazard ratio, 0.90; 95% CI 0.69,1.17). Palliative care was associated consistently with improvements in advance care planning, patient and caregiver satisfaction, and lower health care utilisation. When only trials with a low risk of bias were analysed, the association between palliative care and symptom burden was no longer statistically significant (SMD −0.21; 95% CI −0.42, 0.00), and the association between palliative care and QOL remained statistically significant but was not clinically meaningful (SMD 0.20; 95% CI 0.06,0.34). Evidence was mixed regarding the association between palliative care and other outcomes, including caregiver outcomes such as caregiver QOL, mood, and burden. These findings should be interpreted with caution, because there is wide variation in the condition of patients with life-limiting illnesses.[30,Level 1]

Model of care
Health Quality Ontario (2014) conducted a health technology assessment to determine whether an optimal team-based model of care exists for service delivery at end of life.[14,Level 1] The four core elements of team-based care deliver included team membership, services provided, setting, and mode of patient contact. Six team-based models of care were identified; hospital-based care, direct contact home-based care, indirect contact home-based care, indirect contact comprehensive care, direct contact comprehensive care, direct, and early contact. Direct contact was defined as when team members see the patient while indirect contact was when they advise another health care practitioner (e.g., a family doctor) to see the patient. Comprehensive Team-Based Model (CTM) provides continuity of service across inpatient and outpatient settings, e.g. in hospital and then at home. The main outcome measures included patient QOL, symptom management and patient satisfaction. Twelve studies encompassing two SR and ten RCTs were included in the review. Team membership includes at minimum a physician and nurse, with at least one having specialist training and/or experience in end-of-life care. Team services include symptom

management, psychosocial care, development of patient care plans, end- of-life care planning, and coordination of care. Comparison group included patients who received multidisciplinary care mostly on an ad hoc basis, uncoordinated, without end of life care consultations. (e.g ICU care). The study found fair quality evidence that direct contact CTM significantly improves patient QOL, with an estimated survival of up to nine months, symptom management, and patient and informal caregiver satisfaction; increases the patient's likelihood of dying at home; decreases the patient's likelihood of dying in a nursing home but had no impact on hospital admissions or hospital length of stay. Similarly, moderate-quality evidence indicated that a hospital team-based model with direct patient contact has no impact on length of hospital stay. There was however low-quality evidence that this model significantly reduces ICU admissions. In regards to home team-based model, low-quality evidence indicated that this model significantly increases patient satisfaction, and increases the patient's likelihood of dying at home. It was found to also significantly decrease emergency department visits and hospital admissions.[14,Level 1]

Singer et al. conducted a systematic review to identify individuals appropriate for palliative care, elements of health service interventions (personnel involved, use of multidisciplinary teams, and settings of care) effective in achieving better outcomes (QOL, symptom control) for patients, caregivers, and the healthcare system.[18,Level 1] The review included 124 RCTs with majority of these studies demonstrated statistically significant relationship between palliative care interventions and patient or caregiver outcomes; in patients with cancer (49% studies), congestive heart failure (CHF; 62%), chronic obstructive pulmonary disease (COPD; 58%), and dementia (60%). Most interventions included a nurse (70%), and many were nurse-only (39%). Social workers were well represented, and home-based approaches were common (56%). Home interventions with visits were more effective than those without (64% versus. 46%). Interventions improved communication and care planning (70%), psychosocial health (36% for depressive symptoms; 41% for anxiety), and patient (40%) and caregiver experiences (63%). Many interventions reduced hospital use (65%), but most other economic outcomes, including costs, were poorly characterized. Palliative care teams did not reliably lower healthcare costs. The author concluded that palliative care improves cancer, CHF, COPD, and dementia outcomes. Effective models include nurses, social workers, and home-based components, and a focus on communication, psychosocial support, and the patient or caregiver experience. High quality research on intervention costs and cost outcomes in palliative care is limited.[18,Level 1]

Phongtankuel et al. conducted a systematic review looking at the multicomponent palliative care interventions in advanced chronic diseases.[31,Level1] Apart from studying the delivery of multicomponent palliative care (PC) interventions, the authors analysed whether the number of disciplines or components being implemented were associated with positive outcomes in terms of QOL or symptom control. Seventy one studies (consisting of mostly RCTs and

observational studies) conducted either in the US or in Europe were included. Mean age of participants in these studies was 65.4 years (range: 51-81). Multicomponent intervention included two or more of the following domains; symptom management, psychological support/ counseling, spiritual/ existential support, advanced care planning, education of illness or disease, care coordination and bereavement services. Interventions were conducted in various settings, including outpatient (33%), inpatient (17%), home (16%), and mixed (34%) venues. Of the 64 interventions, 24 (38%) incorporated caregivers and/ or families and 24 (38%) explicitly reported communication between the palliative care provider and the primary physician/ team. Nurses (88%) were most often involved in delivering care, followed by physicians (67%), social workers (52%), and chaplains (30%). The most common palliative care components patients received were symptom management (88%), psychological support / counselling (81%), and disease education (75%), care coordination (50%), advanced care planning (45%), spiritual/existential support (33%), and bereavement services (9%). The regression of QOL on number of disciplines was significant (p<0.05), adjusting for number of components. This result owed solely to the involvement of a physician and or a physical/occupational therapist.[31,Level 1]

Palliative care integration
In a systematic review and meta-analysis, Siouta et al. looked at the empirically-tested models of PC integration in treating cancer and chronic diseases in the Europe.[32,Level 1] From the 14 studies included, there was strong agreement on the benefits of the integration of PC multidisciplinary team concurrently with treatment in terms of better symptom control, less caregiver burden, improvement in continuity and coordination of care, fewer admissions, cost effectiveness and patients dying in their preferred place. [32,Level 1]

Vanbutsele et al. (2018) conducted non-blinded RCT in Belgium to determine the effect of early and systematic integration of palliative care alongside standard psychosocial oncological care in patients with advanced cancer.[33,Level II-1] Patients were randomly assigned either to early (within three weeks of enrolment) and systematic integration of palliative care into oncological care, or standard oncological care alone in a setting where all patients are offered multidisciplinary oncology care by medical specialists, psychologists, social workers, dieticians, and specialist nurses. A total of 468 patients participated in the study with overall QOL at 12 weeks were significantly higher in the early and systematic palliative care group EORTC QLQ C30 score of 61.98 (95% CI 57.02,66.95) than in control group [54.39 (95% CI 49.23,59.56)] p=0.03). The authors concluded that a model of early and systematic integration of palliative care in oncological care increases the QOL of patients with advanced cancer than palliative care consultations offered on demand, even when psychosocial support has already been offered.[33,Level II-1]

Similarly, Haun et al. also looked at early palliative care for adults with advanced cancer in a systematic review and meta-analysis.[17,Level II-1] The outcome

measures include HRQOL, depression, symptom intensity, and survival. Seven randomised and cluster-RCTs were included with total of 1614 participants. Four studies evaluated interventions delivered by specialised palliative care teams, and the remaining studies assessed models of co-ordinated care. Early palliative care significantly improved HRQOL at a small effect size (SMD 0.27, 95% CI 0.15,0.38; participants analysed at post treatment = 1028; evidence of low certainty). When re-expressed in natural units (absolute change in Functional Assessment of Cancer Therapy-General (FACT-G) score), health-related QOL scores increased on average by 4.59 (95% CI 2.55,6.46) points more among participants given early palliative care than among control participants. In terms of survival, four studies enrolling a total of 800 participants, did not indicate differences in efficacy (death hazard ratio 0.85, 95% CI 0.56,1.28; evidence of very low certainty). Levels of depressive symptoms among those receiving early palliative care did not differ significantly from levels among those receiving usual/standard cancer care (five studies; SMD -0.11, 95% CI -0.26,0.03; participants analysed at post treatment = 762; evidence of very low certainty).[17,Level II-1]

Technology-based interventions

Agboola et al. (2015) studied the effect of technology-based interventions on pain, depression, and QOL in patients with cancer in a systematic review of RCTs.[24,Level II-1] Twenty RCTs were included using telehealth interventions such as telephone based, web based systems, store-and-forward video-recorded sessions. These interventions involved professional interventionist (nurses, psychologists, or counsellors) trained to provide counselling, or peer counsellors who are cancer survivors, or utilized automated voice response in conjunction with life-support personnel. The comparison groups included those receiving standard care for cancer, wait-listed controls, received oral and written education materials, standard internet standard group (ISG) and internet training and access. Studies were largely heterogeneous in the type and duration of the intervention as well as in outcome assessments. Majority of the studies were telephone-based interventions that remotely connected patients with their health care provider or health coach. Most of the studies had low risk of bias but had insufficient information about the allocation concealment domain. This study found that telehealth interventions had potential in improving outcomes in terms of pain control, depression and QOL in cancer care. However, more high-quality large-sized trials are needed to demonstrate evidence of its effectiveness. [24,Level II-1]

In a more recent systematic review, Larson et al. (2017) studied the effect of telehealth interventions on QOL of cancer patients.[34,Level II-1] Five of nine articles used telephone-based interventions, three studies used Web-based designs while one utilized video-conferencing. Mean age of the patients ranged from 53 to 67 years of age. Both telehealth (Hedges g = 0.211, p=0.016) and standard of care (Hedges g = 0.217, p < 0.001) cancer treatment delivery methods demonstrated small, but statistically significant improvements in QOL measures.

However, there were no statistically significant differences in effectiveness between the telehealth interventions and usual care (p =0.76). [34,Level II-1]

Spiritual interventions
Kruizinga et al. studied the effect of spiritual interventions in addressing existential themes using a narrative approach on QOL of cancer patients in a systematic review and meta-analysis.[25,Level 1] Outcomes measures were mean difference in QOL between the control group and intervention group 0–2 weeks after the intervention and secondary outcome included mean difference in QOL 3–6 months after the intervention. Fourteen clinical trials were included involving mostly advanced cancer patients, cancer patients with at least one month diagnosed, cancer patients with depressive disorder and advanced ovarian cancer patients. Types of interventions ranged from only spiritual interventions (that addressed existential themes using a narrative approach) to multidisciplinary interventions with spiritual components. These were performed by various trained people, mostly psychologists/psychiatrists and oncology professionals or general healthcare professionals or by spiritual healers or chaplain. Overall risk of bias was high. When combined, all studies showed a moderate effect d= 0.50 (95% CI 0.20,0.79), 0–2 weeks after the intervention on overall QOL in favour of the spiritual interventions. Heterogeneity was very high (I^2 =84%.). Overall effect size of the five studies that assessed QOL 3–6 months after intervention was d=0.11 (95% CI -0.08,0.35), a small and insignificant effect (p=0.21). Heterogeneity was low (I^2 =0%). Meta-analysis with the interventions grouped into three subgroups as follows: (i) life reviewing interventions; (ii) multidisciplinary interventions; and (iii) meaning-making interventions. All studies showed a trend towards a positive outcome on QOL of cancer patients in favour of the intervention. The strongest effect was seen in subgroup meaning-making interventions (d=0.63; 95% CI 0.01,1.26, p=0.05). The authors concluded that directly after the intervention, spiritual interventions had a moderate beneficial effect in terms of improving QOL of cancer patients compared with that of a control group. No evidence was found that the interventions maintained this effect up to 3–6 months after the intervention. [25,Level 1]

5.1.2 Physical well-being

Six systematic reviews evaluated the effect of various palliative care interventions on alleviating the physical symptoms. These physical symptoms include pain, fatigue, weight loss, nausea, vomiting, diarrhoea, and dyspnoea and many more.

Home-based palliative care
In a systematic review and meta-analysis, Gomes et al. (2013) evaluated the effectiveness and cost-effectiveness of home palliative care services for adults with advanced illness and their caregivers.[35,Level 1] The outcome measures for effectiveness include patients' odds of dying at home, symptom control, QOL, caregiver distress and satisfaction with care. Twenty three studies consisting of

16 RCTs, (6 of high quality), with a total of 37,561 participants and 4042 family caregivers were included. Majority of patients had advanced cancer, others include congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), HIV/AIDS and multiple sclerosis. The interventions include specialist palliative or hospice care provided by doctors or nurses who have undergone higher specialist training in palliative medicine, and professionals from differing clinical disciplines working full - time or most of the time in palliative/hospice care, who have not undergone any higher specialist training. The comparison groups were community care (primary or specialist care at home and in nursing homes), hospital care (inpatient and outpatient) and in some instances palliative or hospice care (or both). Four studies found significantly better outcomes with the intervention (increased probability of death at home and participant's ability to stay at home as long as wanted, reduced probability of death in hospital, decreased symptom burden, pain and caregiver burden, higher satisfaction with care and better quality of death). Meta-analysis showed increased odds of dying at home [odds ratio (OR) 2.21, 95% CI 1.31,3.71; Z = 2.98, p value = 0.003; x^2 = 20.57, degrees of freedom (df) = 6, p value = 0.002; I^2 = 71%; Number needed to benefit (NNTB) = 5, 95% CI 3,14]. Small but statistically significant beneficial effects of home palliative care services were found compared to usual care on reducing symptom burden for patients and of no effect on caregiver grief. It was concluded that the results provide clear and reliable evidence that home palliative care increases the chance of dying at home and reduces symptom burden in particular for patients with cancer, without impacting on caregiver grief.[35,Level 1]

Opioids

A Cochrane review by Wiffen et al. (2013) assessed oral morphine for cancer pain among both adults and children[36,Level II-1] A total of 62 RCTs examining oral morphine versus placebo, non-oral morphine, or active control were identified (n=4241). Daily doses in studies ranged from 25 to 2000 mg (average 100–250 mg). However, due to high heterogeneity, data could not be meta-analysed. The outcome measures was pain defined as 'no worse than mild pain' equated to a score of ≤30/100 mm on a visual analogue pain intensity scale, or its equivalent on other pain scales. An average level of 'no worse than mild pain' was achieved in 18 studies, and no study reported average pain levels above this threshold in patients receiving oral morphine. In the 17 studies reporting results for individual patients, 96% of patients had 'no worse than mild pain', and an outcome equivalent to treatment success (or successful pain control, or participant global evaluation of 'very good' or 'excellent') was deemed to have been achieved in 63% of patients. Pain relief did not differ between modified and immediate release morphine, and the authors noted that dose titration to analgesic effect was achieved with both these formulations. In 24 studies reporting data on patient withdrawal because of adverse effects, the dropout rate was 7%. Among 9 studies reporting patient withdrawals because of ineffective analgesia, the dropout rate was also 7%. Evidence was limited as only 13 of the 62 studies adequately reported randomisation methods, few reported on allocation

concealment, and some were not double blind. Most studies were considered by the authors to be at high risk of bias because of their size (only 11 studies included at least 100 participants and most had fewer than 50). Patient-reported outcomes such as a good level of pain relief were reported in only 9 of 62 studies. The authors concluded that oral morphine is an effective analgesic for cancer pain, with similar efficacy to other opioids. Titration to analgesic effect appears to be possible for both immediate-release and sustained-release formulations of oral morphine. [35,Level II-1]

In a more recent Cochrane review, Wiffen et al. (2017) examined the analgesic efficacy of various opioids for cancer pain.[15,Level II-1] All eligible Cochrane Reviews of randomised, controlled trials (RCTs) of opioid drugs for the treatment of cancer pain in adults were included. The outcomes measures were proportion of participants reporting no worse than mild pain on treatment by 14 days after start of treatment, Patient Global Impression of Change (PGIC) of much or very much improved and withdrawals due to adverse events. Nine Cochrane Review studies were included (152 included studies and 13,524 adults participants) looking at various types of opioids including hydromorphone, methadone, oxycodone, buprenorphine, codeine, tapentadol, tramadol, fentanyl, morphine in comparison to either a different formulation of the same opioid, or a different opioid; or placebo control. Various routes of administration of opioids were considered including oral with most opioids, transdermal administration with fentanyl, and buprenorphine but not subcutaneous opioid administration. The reported pain outcomes were varied and inconsistent. Reviews on buprenorphine, codeine with or without paracetamol, hydromorphone, methadone, tramadol with or without paracetamol, tapentadol, and oxycodone did not have information about the primary outcome of mild or no pain at 14 days, although that on oxycodone indicated that average pain scores were within that range. The authors concluded that the amount and quality of evidence around the use of opioids for treating cancer pain was low. Oral morphine remains the gold standard for treating moderate to severe cancer pain while oxycodone as major opioid in the USA offers similar levels of pain relief and overall adverse events to other strong opioids including morphine. Fentanyl as a transdermal patch is widely used in higher income countries and may cause less constipation than oral opioids. Codeine has no proven role from clinical trial data in treating cancer pain. Most people will experience adverse events, and help may be needed to manage the more common undesirable adverse effects such as constipation and nausea. [15,Level II-1]

Palliative radiotherapy
Rich et al. (2018) conducted an update of previous meta-analysis of randomised trials comparing single fraction to multiple fractions of radiation therapy in patients with uncomplicated bone metastases.[37,Level 1] Ten new randomised trials were identified since 2010, five with adequate and appropriate data for inclusion, resulting in a total of 29 trials that were analysed. Search terms used were similar to prior meta-analysis. Primary outcomes were complete response and overall

response rates as reported and defined by the identified trials. In total, 26 randomised trials about bone metastases were included in the calculation of overall response rates while only five were included in the meta-analysis. Majority of patients had prostate or breast cancer in most of the trials studied. In intention-to-treat analysis, 3059 patients were included in the single fraction arm and 3040 patients in the multiple fraction arm. Overall response rate was similar in patients for single fraction treatments (61%) and those for multiple fraction treatments (62%). For each study, odds ratios ranged from 0.84 to 1.08 with a pooled odds ratio of 0.98 (95% confidence interval 0.95–1.01). A total of 2802 patients in the single fraction arm and 2783 patients in the multiple fraction arm, 23% and 24% of patients in these arms had a complete response, respectively. Odds ratios were varied 0.52–1.86 and the pooled odds ratio was 0.97 (95% confidence interval 0.89,1.06). Re-treatment was significantly more frequent in the single fraction treatment arm, with 20% receiving additional treatment to the same site versus 8% in the multiple fraction treatment arm (p < 0.01). No significant difference was seen in the risk of pathological fracture at the treatment site, rate of spinal cord compression at the index site, or in the rate of acute toxicity. The authors concluded that single fraction and multiple fraction radiation treatment regimens continued to demonstrate similar outcomes in pain control and toxicities, but re-treatment was more common for single fraction treatment patients. [37,Level 1]

Palliative pharmacological sedation
In a systematic review, Beller, van Driel and Mitchell (2017) looked at the evidence for the benefit of palliative pharmacological sedation on QOL, survival, and symptoms in terminally ill adults during their last few days of life.[20,Level II-1] Settings of the studies included hospices, palliative care units, hospital oncology wards, and home-based palliative care. Fourteen studies, involving 4167 adults, of whom, 1,137 received palliative sedation (e.g. benzodiazepines, barbiturates, anaesthesia, opioids, antipsychotics, antihistamines, or other hypnotics) were included. All studies were consecutive case series, with only three having prospective data collection. Majority of studies involved patients with cancer and all studies had used midazolam to achieve palliative sedation. Other drugs were haloperidol (eight studies) and chlorpromazine (five studies). A small proportion of people received only opioids (morphine, fentanyl, and methadone), or propofol, other benzodiazepines (e.g. lorazepam), antihistamines (promethazine and chlorphenamine), phenobarbital, scopolamine hydrobromide, or ketamine hydrochloride. Five studies measured symptom control, using four different methods, thus pooling was not possible while none measured QOL. Control of other symptoms appeared to be similar in sedated and non-sedated people. Despite sedation, delirium and dyspnoea were still troublesome symptoms in these people in the last few days of life. Only one study measured unintended adverse effects of sedative drugs and found no major events. Studies which measured survival time from admission or referral to death, demonstrated no statistically significant difference between sedated and non-sedated groups. The authors concluded that there was insufficient evidence about the efficacy of

palliative sedation in terms of a person's QOL or symptom control. There was evidence that palliative sedation did not hasten death, which has been a concern of physicians and families in prescribing this treatment. However, this evidence comes from low quality studies, so should be interpreted with caution. [20,Level II-1]

Interventions for fatigue and weight loss
Payne, Wiffen and Martin (2012) assessed evidence on the interventions for fatigue and weight loss in adults with advanced progressive illness in a systematic review.[37,Level 1] Twenty seven systematic reviews (302 studies with 31,833 participants) were included. Interventions included pharmacological interventions, exercise, behavioural management, use of assistive devices, lifestyle management, nutritional support, complementary or alternative therapy and counselling. None of the included systematic reviews reported quantitative data on the efficacy of interventions to manage fatigue or weight loss specific to people with advanced progressive illness. All of the included reviews apart from one were deemed of high methodological quality. For cancer-related fatigue, five systematic reviews (116 studies with 17,342 patients) evaluated pharmacological interventions [eicosapentaenoic acid (EPA) and any drug therapy] and non-pharmacological interventions (exercise, psychosocial interventions). One SR found a small but significant improvement in fatigue over placebo with the psychostimulant drug methylphenidate, and another SR supported the benefit of exercise. There was insufficient evidence found on benefit of EPA, antidepressant drug paroxetine, progestational steroids or psychosocial interventions. For chronic obstructive pulmonary disease (COPD)-related fatigue, one meta-analysis showed a significant improvement in fatigue scores, functional and exercise capacity in those who received respiratory rehabilitation compared with conventional community care. One RCT (135 participants) showed a statistically significant improvement in fatigue at 12 months follow-up with a GP practice-based self-management education programme compared to usual care. Other studies on patients with amyotrophic lateral sclerosis/motor neuron disease (ALS/MND), cyctic fibrosis, HIV/AIDS, multiple sclerosis and others were either limited by small samples or no evidence found. In terms of cancer-related weight loss, one systematic review (27 studies, 4148 participants) found small, statistically significant weight gain for treating people with palliative anorexia-cachexia syndrome using megestrol acetate versus placebo in six studies conducted over at least six weeks with 856 participants [risk ratio (RR) 1.86, 95% CI 1.31,2.63]. Another included study of 96 people with non-small cell lung cancer receiving chemotherapy, found nutritional intervention was effective in increasing caloric intake but had a limited effect on weight. For COPD-related weight loss, one systematic review (59 studies and 4048 participants) found nutritional support: no statistically significant differences in weight between those receiving nutritional support and controls receiving a placebo, other active therapy or usual care. In HIV/AIDS patients, four systematic reviews (42 studies and 2071 participants) evaluated the interventions to manage weight loss. One study found significant small increase in both lean body mass and body weight with anabolic steroids compared to placebo interventions. Macronutrient

supplementation had a statistically significant impact on calorie intake but did not result in a significant body weight increase. A meta-analysis showed a statistically significant increase in body weight compared to non-exercising controls and also when the resistive exercise was combined with aerobic exercise interventions. In other diseases, there was lack of robust evidence for interventions to manage fatigue and/or unintentional weight loss. [37,Level 1]

5.1.3 Psychosocial well-being

Psychosocial interventions
Parahoo et al. conducted a systematic review and meta-analysis on the effectiveness of psychosocial interventions for men with prostate cancer in improving QOL, self-efficacy and knowledge and in reducing distress, uncertainty and depression.[38,Level 1] Psychosocial interventions that explicitly used one or a combination of the following approaches were included; cognitive behavioural, psychoeducational, supportive and counselling as well as those interventions designed to provide information, physical exercise, relaxation, or art and music therapies. Nineteen studies with a total of 3,204 men with prostate cancer were included. These men were randomly assigned to psychosocial intervention or control groups. Psychosocial interventions can be delivered face-to-face, online, by telephone or through a combination of these approaches. Up to 12 months post intervention, men in the psychosocial intervention group had a small, statistically significant improvement in the physical component of general health-related QOL (GHQOL) at end of intervention (1414 participants, SMD 0.12, 95% CI 0.01,0.22) based on low- quality evidence. A small improvement in favour of psychosocial interventions (SMD 0.24, 95% CI 0.02,0.47) was also seen in the physical component of GHQOL at end of intervention for group-based interventions. However, there was no clear evidence suggested that psychosocial interventions were beneficial in improving the physical component of GHQOL at four to six and at eight to 12 months post-intervention. In addition, no clear evidence showed benefit associated with psychosocial interventions for the mental component of GHQOL at end of intervention. At end of intervention, cancer-related QOL showed a small improvement following psychosocial interventions (SMD 0.21, 95% CI 0.04, 0.39). For prostate cancer- specific and symptom-related QOL, the differences between groups were not significant. No clear evidence indicated that psychosocial interventions were beneficial in improving self-efficacy at end of intervention (337 participants, SMD 0.16, 95% CI -0.05,0.38) based on very low-quality evidence in three studies that assessed individual-based interventions. The results for self-efficacy at six to eight and at 12 months post-intervention were compatible with benefit and harm. The authors concluded that psychosocial interventions may have small, short-term beneficial effects on certain domains of well- being, as measured by the physical component of GHQOL and cancer-related QOL when compared with usual care. The review however, failed to demonstrate a statistically significant effect on other domains such as symptom-related QOL, self-efficacy, uncertainty, distress or depression. [38,Level 1]

In another systematic review by Galway et al., the effects of psychosocial interventions to improve emotional wellbeing and QOL for recently diagnosed cancer patients were examined.[23,Level 1] Thirty studies majority focused on patients with a single site malignancy were included. Psychosocial interventions involving interpersonal dialogue between a 'trained helper' and individual newly diagnosed cancer patients were compared to those received standard care only. No significant effects were observed for QOL at 6-month follow up (in nine studies, SMD 0.11; 95% CI -0.00,0.22); However, a small improvement in QOL was observed when QOL was measured using cancer-specific measures (in six studies, SMD 0.16; 95% CI 0.02,0.30). General psychological distress as assessed by 'mood measures' improved also (in eight studies, SMD - 0.81; 95% CI -1.44, -0.18), but no significant effect was observed when measures of depression or anxiety were used to assess distress (in six studies, depression SMD 0.12; 95% CI -0.07,0.31; in four studies, anxiety SMD 0.05; 95% CI - 0.13,0.22). Psychoeducational and nurse-delivered interventions that were administered face to face and by telephone with breast cancer patients produced small positive significant effects on QOL (in two studies, SMD 0.23; 95% CI 0.04,0.43). The authors concluded that due to significant variation that was observed across participants, mode of delivery, discipline of 'trained helper' and intervention content, conclusion was deemed inconclusive. [23,Level 1]

Prescott et al. (2017) examined the role of a palliative care intervention in moderating the relationship between depression and survival among individuals with advanced cancer.[39,Level II-1]The authors combined data set from the two RCTs ENABLE ((Educate, Nurture, Advise, Before Life Ends) studies (Bakitas et al., 2009, 2015). Intervention included psychoeducational approach in which after an initial in-person palliative care consult, advanced practice nurses specializing in palliative care facilitated semi-structured psychoeducational telephone coaching sessions with patients, followed by monthly check-in calls until the patient died or the study ended. Topics discussed during sessions included problem-solving, coping, self-care, symptom management, building a support system, communication skills, decision-making, advance care planning, and life review. In Bakita (2009), participants were randomly assigned upon enrolment to either (a) an intervention condition or (b) a usual cancer care control condition. In Bakita (2015) a wait-list control design was employed wherein all participants received the intervention but were randomly assigned to receive it either (a) early (upon enrolment) or (b) after a delay of 12 weeks. A total of 529 patients, of whom 161 received usual care (Bakita 2009 only), 265 received the early intervention (161 from Bakita 2009; 104 from Bakita 2015), and 103 received the delayed intervention (Bakita 2015 only). Cox analysis confirmed an effect of depression (Wald = 12.377, HR = 1.038, CI: 1.017–1.060, $p < 0.001$) such that higher depression at baseline was associated with shorter survival. In addition, there was a significant interaction between depression and the intervention (Wald = 4.451, HR = 0.973, CI: 0.949–0.998, $p = 0.035$), such that depression was more strongly associated with shorter survival among participants receiving usual

cancer care than among those receiving the intervention. In a full model, depression remained associated with shorter survival (Wald = 10.869, HR = 1.042, CI: 1.017–1.067, p = 0.001) and the depression by intervention interaction again remained significant (Wald = 5.636, HR = 0.963, CI: 0.933–0.993, p = 0.018) despite inclusion of the 19 covariates. The authors concluded that the intervention had a greater impact on survival for individuals with higher baseline depression, and this moderation effect remained significant independent of demographics, cancer site, and illness severity. Early palliative care moderates the relationship between depression and survival among individuals newly diagnosed with advanced cancer. Although depression was associated with higher mortality risk in the sample overall, this relationship was diminished among individuals who received the ENABLE palliative care intervention. From a clinical perspective, programmes should prioritize such patients when offering early palliative care services, because these individuals are most likely to benefit from these types of interventions. [39,Level II-1]

Life review intervention
Wang et al. (2017) examined the effects of life review interventions on spiritual well-being, psychological distress, and QOL in patients with terminal or advanced cancer in a systematic review and meta-analysis of RCTs.[22,Level II-1] Eight studies were included and they were conducted in Canada, Hong Kong, Japan, Mainland China, Portugal, United Kingdom, and United States. A total of 955 participants, including 427 in the intervention groups and 528 in the control groups, respectively. The pooled results suggested a desirable effect of therapeutic life review on; (when compared to usual care only) the meaning of life domain of spiritual well-being (SMD = 0.33; 95% confidence interval, 0.12, 0.53), general distress (SMD = −0.32; 95% confidence interval, −0.55,−0.09), overall QOL (SMD = 0.35; 95% confidence interval, 0.15,0.56). Only the pooled effect on overall QOL remained statistically significant at follow-ups up to three months after the intervention (SMD = 0.82; 95% confidence interval, 0.47,1.18). The authors concluded that therapeutic life review was potentially beneficial for people near the end of life. However, the results should be interpreted with caution due to the limited number of RCTs and associated methodological weaknesses. [22,Level II-1]

Dignity therapy
Martínez et al. conducted a systematic review to analyse the outcomes of dignity therapy in patients with advanced life-threatening diseases.[37,Level 1] Dignity therapy is a type of psychotherapy to relieve psychological and existential distress in patients at the end of life while client-centred care (CCC) is a type of psychotherapeutic support approach that focuses on non-generativity themes, that is, on here-and-now issues. Outcomes measures include reduction in psychological, existential, and spiritual distress. Twenty eight studies which were conducted in the UK, USA, Canada, Australia, Denmark, Portugal, Sweden, Japan and Spain were included and they were of high quality. One RCT showed statistically significant decrease on patients' anxiety and depression scores over

time. The other showed statistical decrease on anxiety scores pre–post dignity therapy, not on depression. Non-randomised studies suggested statistically significant improvements in existential and psychosocial measurements. Other design studies report beneficial outcomes in terms of end-of-life experience.

5.1.4 Spiritual well-being

Spiritual interventions
Oh and Kim (2014) conducted a meta-analysis on the effects of spiritual interventions in patients with cancer in Korea.[26,Level II-1] It involved 14 controlled trials (seven randomised and seven non-randomised) with 889 patients with cancer. A total of 889 adult participants who had been diagnosed with cancer of any type (solid or hematologic), at any tumour stage, with any kind of treatment mode, and at any time since diagnosis were included. Of the included studies, ten applied religious interventions, including spiritual nursing care, spiritual counselling, oncologist-assisted spiritual intervention, and spiritually focused meditation. Five studies used existential intervention, specifically meaning-centered psychotherapy, a meaning-of-life intervention, a meaning-making intervention, and a logo therapy-based resilience promotion programme. These interventions were provided either individually, in group, via telephone, or internet-based modalities. Nurses were the most frequent intervention providers, followed by clinical psychologists, dietitians, and oncologists. Weighted average effect size across studies was –0.48 (p = 0.006, I^2= 65%) for spiritual well-being, –0.58 (p = 0.02, I^2= 70%) for meaning of life, –0.87 (p = 0.02, I^2 = 87%) for anxiety, and –0.62 (p = 0.001, I^2 = 73%) for depression. When studies were grouped by study design, significant large effects on spiritual well-being (d = –0.78, 95% CI [–1.3, –0.27], I^2 = 59%), anxiety (d = –1.23, 95% CI [–1.76, –0.7], I^2= 24%), and depression (d = –1.36, 95% CI [–1.84, –0.88], I^2= 45%) were found in non-RCT studies. In the subgroup analysis by intervention type, existential intervention yielded significant moderate effects on meaning of life (d = –0.59, 95% CI [–0.87, –0.31], I^2= 0%) and significant small effect on anxiety (d = –0.35, 95% CI [–0.67, –0.03], I^2= 0%). In contrast, studies that applied religious intervention demonstrated a significant moderate-to-large effect on spiritual well-being (d = –0.54, 95% CI [–1, –0.08], I^2=71%) and depression (d = –0.79, 95% CI [–1.33, –0.25], I^2= 79%). However, this subgroup is substantially heterogeneous. The authors concluded that spiritual interventions had significant but moderate effects on spiritual well-being, meaning of life, and depression. However, the evidence remains weak because of the mixed study design and substantial heterogeneity. [26,Level II-1]

5.1.5 Paediatric Palliative Care

Home-based palliative care
Chong et al. (2018) evaluated whether Singaporean home-based paediatric palliative care improves patient outcomes and reduces healthcare costs in a mixed retrospective and prospective cohort study.[40,Level II-2] A structured impact

and cost evaluation of Singapore-based HCA Hospice Care's Star PALS (Paediatric Advance Life Support) programme was conducted. Retrospective cohort consisted of two groups of deceased patients: those enrolled in paediatric PC and those who were not enrolled in the programme (control group) and had died in hospital. Single-group prospective design for patients who had received PPC at home was employed. For the latter cohort study, Health-Related QOL (HRQL) of both patients and caregivers enrolled in the PPC group was assessed at 0, 3, 6, and 12 months. A total of 71 patients and 67 in control group with mean age at death were 12 years and six years, respectively. Males dominated both groups. More than half of causes of death were due to other causes compared to 45% due to cancers. Compared to the control group (n = 67), patients receiving home-based paediatric palliative care (n =71) spent more time at home than in hospital in the last year of life by 52 days (OR = 52.30, 95% CI 25.44,79.17) with at least two fewer hospital admissions (OR = 2.46, 95% CI 0.43,4.48); and five times more likely to have an advance care plan formulated (OR = 5.51, 95% CI 1.55,19.67). Both patients' QOL (in terms of pain and emotion), and caregiver burden showed improvement within the first year of enrolment into the programme. They reported improvement in emotion and reduction in pain with odds of being pain-free at three months (OR = 2.58, 95% CI 1.12,5.95) were significantly higher than at baseline (p < 0.05). In terms of effectiveness, home-based paediatric palliative care improved QOL of patients and their caregivers. Cost evaluation will be reported in other section of the report. [40,Level II-2]

Opioids

Wiffen et al. (2017) conducted a systematic review on opioids for cancer-related pain in children and adolescents, aged between birth and 17 years.[37,Level II-1] Three studies that were retrieved were not RCTs and of very low quality. No conclusions can be drawn about efficacy or harm in the use of opioids to treat cancer-related pain in children and adolescents. This means that at present, treatment is based on clinical experience and advice from respected authorities. [37,Level II-1]

5.1.6 Traditional and Complementary Medicine

Chinese Herbal Medicine

In a systematic review and meta-analysis, Chung et al. 2016 evaluated Chinese herbal medicine (CHM) for symptom management (e.g. pain, fatigue, constipation) in palliative care patients with cancer.[27,Level 1] Fourteen RCTs were included and they were all conducted in mainland China. Chinese herbal medicines used in the studies were indexed in the 2010 China Pharmacopeia Chinese Herbal Medicine Index, either in the form of single herbs, herbal formulations, or Chinese proprietary medicines. Compared with conventional palliative care intervention alone, meta-analysis showed that combined CHM and conventional treatment significantly reduced pain (three studies, pooled WMD: -0.90, 95% CI -1.69,-0.11). Six trials comparing CHM with conventional

medications demonstrated similar effect in reducing constipation. One RCT showed significant positive effect of CHM plus chemotherapy for managing fatigue, but not in the remaining three RCTs. The additional use of CHM to chemotherapy does not improve anorexia when compared to chemotherapy alone, but the result was concluded from two small trials only. Adverse events were infrequent and mild. CHM may be considered as an add-on to conventional care in the management of pain in cancer patients. It could also be considered as an alternative to conventional care for reducing constipation. However, more research is warranted on the use of CHM for treating anorexia and fatigue in cancer patients. [27,Level I]

5.2   Safety

A systematic review by Wiffen et al. (2017) that was mentioned previously, looked at the adverse events associated with opioid use for cancer pain.[15,Level II-1] The study included nine Cochrane studies included (152 included studies and 13,524 adults participants) which were all of good quality. Various routes of administration of opioids were considered (except subcutaneous administration); oral with most opioids, transdermal administration with fentanyl, and buprenorphine. Adverse event withdrawal was reported by five reviews, at rates of between 6% (oral morphine) and 19% (oral oxycodone). Participants with at least 1 adverse event were reported by three reviews, at rates of between 11% and 77%. The authors concluded that the amount and quality of evidence around the use of opioids for treating cancer pain is low. Most people will experience adverse events, and help may be needed to manage the more common undesirable adverse effects such as constipation and nausea. Perhaps between 1 in 10 and 2 in 10 people treated with opioids will find these adverse events intolerable.[15, Level II-1]

In a systematic review, Wiffen et al. (2014) determined the impact of opioid treatment on patient consciousness, appetite and thirst in RCTs of morphine, fentanyl, oxycodone or codeine for treating cancer pain.[41,Level II-1] The study found incidence rates of adverse events of opioids to be 25% for constipation, 23% for somnolence, 21% for nausea, 17% for dry mouth, and 13% for vomiting, anorexia, and dizziness, 5% and below for asthenia, diarrhoea, insomnia, mood change, hallucinations and dehydration. No direct evidence that opioids affected patient consciousness, appetite or thirst when used to treat cancer pain. The authors concluded that somnolence, dry mouth, and anorexia were common adverse events in people with cancer pain treated with morphine, fentanyl, oxycodone or codeine. [41,Level II-1]

5.3   Economic evaluation

Twelve articles on economic impact of various types of palliative care were included. These encompassed hospital-based palliative care, out-patient care,

community-based palliative care, home-based palliative care and paediatric palliative care.

Hospital-based palliative care

May et al. (2018) conducted a meta-analysis to estimate the association of palliative care consultation (PCC) within three days of admission with direct hospital costs for adults with serious illness.[42] In this meta-analysis of six studies, a total 133,118 patients, of whom 40.8% had a primary diagnosis of cancer and 3.6% received a PCC. The authors used ICD codes to generate 2 comorbidity measures: the Elixhauser index as an additive count of the presence of 31 serious conditions to act as a measure of illness burden, and the van Walraven index, a weighted count designed specifically to predict in-hospital mortality. Mean Elixhauser index scores ranged from 2.2 to 3.5 among the studies. When patients were pooled irrespective of diagnosis, there was a statistically significant reduction in costs (−USD3237; 95% CI −USD3581,−USD2893; p < 0.001). In the stratified analyses, there was a reduction in costs for the cancer (−USD4251; 95% CI, −USD4664,−USD3837; p<0.001) and non-cancer (−USD2105; 95% CI −USD2698,−USD1511; p<0.001) subsamples. The reduction in cost was greater in those with four or more comorbidities than for those with two or fewer. Hospital costs were lower for patients seen by a palliative care consultation team than for patients who did not receive this care. The estimated association was greater for those with a primary diagnosis of cancer and those with more comorbidities compared with those with a non-cancer diagnosis and those with fewer comorbidities. The authors concluded that the estimated association of palliative care consultation with hospital costs varies according to baseline clinical factors; prioritizing current staff to patients with a high illness burden and increasing capacity may reduce hospital costs for a population with high policy importance.[41]

Isenberg et al. (2017) conducted an economic evaluation study to establish costs of an inpatient palliative care unit (PCU) in John Hopkins Medicine and conduct a threshold analysis to estimate the maximum possible costs for the PCU to be considered as cost-effective.[43] Health provider's perspective was used that incorporated two cost standpoints: variable cost and contribution margin. The total costs of the PCU and cost per patient encounter (PE) were calculated, by considering PE as each distinct stay of a patient in the unit (ie, if a patient was in the unit twice, there were two separate PEs). Three categories of costs considered were palliative direct (i.e patients transferred from ED and clinics), palliative transfers (i.e patients transferred to the PCU from other departments, pre-PCU) and professional fees for physician services. Fixed costs were excluded from the calculation of costs because they do not vary on the basis of patient volume and are incurred regardless of where the patient received care in the hospital. Using threshold analysis, the intervention was deemed cost saving when the costs were lower for the new service, and cost-effective when the additional cost is offset by the additional gain in life or QALYs [cost-effectiveness ratio of USD180,000 (MYR 732,600) per QALY was taken as cost-effective]. Active management include (e.g; transfusions, epidural pain therapy, radiation

therapy, physical therapy) and specialized support (e.g, chaplaincy and social work). There were 153 PEs, a contribution margin of USD318,413 (MYR 1,295,940.91 or MYR1656.49 per PE per day), and variable costs of USD1,050,031 (MYR 4,273,626.17 or MYR 5466 per PE per day). PCU saved the hospital (cost - minimization analysis result) USD 353,645 (MYR 1,439,511 or MYR 1,839 per PE per day), a 25% cost reduction, compared to pre-PCU. The programme was estimated to generate 3.11 quality-adjusted life years (QALYs) from patients (0.05 QALY) and caregivers (3.06 QALYs). The threshold analysis determined that the PCU could cost up to USD 559,800 (MYR 2,278,665) more than standard care (i.e, the PCU could spend an additional MYR 2,914 per PE per day) and still be considered cost effective. The authors concluded that according to variable costs, the PCU was not cost effective; however, when considering savings of the PCU compared with usual care, the PCU was cost saving. The contribution margin showed that the PCU was cost saving. This study supports efforts to expand PCUs, which enhance care for patients and their caregivers and can generate hospital savings. (1USD=MYR4.07).[42]

Outpatient palliative care
Cunningham et al. (2017) conducted a systematic review to synthesize evidence describing the relative effectiveness of outpatient palliative care delivered in the United States or Canada relative to usual care, its drivers, and associated costs.[44] The care encompassed a multidisciplinary care team, palliative care specialist, patient and family education, advanced care planning, and monthly in-person office visits. Thirteen fair- to good-quality studies including eight RCTs were included comparing a palliative care intervention to usual or standard treatment for advanced or serious disease. All studies documented statistically significant QOL improvements over three to 13 months of follow-up with mean differences exceeding the minimum clinically important change measurable. One RCT reported a two-fold increase in the likelihood of death at home in the palliative care group (OR=2.20) versus usual care; 95%CI, 1.3 - 3.7; p < 0.001) while another recorded more than 50% reduction in the risk of dying in hospital (relative risk, 0.46; 95% CI 0.40,0.52). In contrast, evidence was mixed regarding the effects of palliative care on the use of emergency department and hospital care. One RCT of early palliative care in patients with cancer documented a three-month improvement in survival (11.6 versus 8.9 months for usual care; p = 0.02); another cancer RCT described a 30% reduction in the risk of death during the first year of follow-up (hazard ratio, 0.67; 95% CI 0.50,0.91; p = 0.01). Outpatient palliative care significantly reduced total health care costs among patients with terminal or advanced and complex illness. One RCT reported a significantly lower adjusted mean cost of care associated with outpatient care compared with usual care (USD12 670 versus USD20 222; p=0.03). Significant reductions in cost of 18 months of care after outpatient palliative care enrolment compared with pre-enrolment costs were also reported in a retrospective study set in the mid-Atlantic region (USD16,467 versus USD23,386; p < 0.001). Budget impact analysis suggested that even if only 10% of patients with advanced illness

enrolled in palliative care programmes in the last year of life, reductions in direct medical costs would exceed USD4 billion in the US.[43]

Greer et al. (2016) studied the financial impact of early involvement of palliative care (PC) in the outpatient setting based on data from a trial of 151 patients with metastatic non-small-cell lung cancer (NSCLC) who were randomised to early PC integrated with standard oncology care (SC) or SC alone.[45] Costs were calculated based on the visit type, including inpatient care, outpatient care, chemotherapy administration, or hospice care. Oral chemotherapy costs were estimated based on actual drug costs. Medicare reimbursement rate was used to estimate hospice costs. Of these, 70 were in the standard care group and 68 were in the early PC group. Early PC was associated with a lower mean total cost per day of USD117 (MYR 476, p = 0.13) compared to SC. In the final 30 days of life, patients in the early PC group incurred higher hospice care costs (mean difference = USD1,053; p = 0.07), while expenses for chemotherapy were less (mean difference = USD757; p = 0.03). Costs for emergency department visits and hospitalisations did not differ significantly between groups over the course of the study or at the end of life. Using hospital costs, rather than insurance reimbursements, as a measure of resource use, the authors found that randomisation to early PC was associated with a cost-effectiveness ratio of USD41,938/life year saved (MYR 170,708/LYS), compared to standard care. The authors concluded that the delivery of early PC does not appear to increase overall medical care expenses for patients with metastatic NSCLC.[44]

Community-based palliative care
Spilsbury and Rosenwax (2017) conducted a retrospective cohort in Western Australia (WA) to determine if community-based palliative care provided to people dying from non-cancer conditions was associated with reduced hospital costs in the last year of life and how this compared with people dying from cancer.[46] Hospital costs were assigned to each day of the last year of life for each decedent with a zero cost applied to days not in hospital. Day-specific hospital costs averaged over all decedents (cohort averaged; CA) and decedents in hospital only (inpatient averaged) were estimated. Two-part models and generalised linear models were used. A total of 12,817 people who died of one or more of ten disease conditions considered amenable for palliative care during the two year study period. The community-based palliative care was provided by Silver Chain WA which supplied over 90% of referred community-based specialist palliative care in WA. It encompassed multidisciplinary team of palliative care clinicians and nurses, allied health professionals and volunteers provide home nursing care, counselling, respite options, practical support and links to other services with the aim of enabling people with a life limiting illness to remain at home. Overall, periods of time receiving community-based specialist palliative care were associated with a 27% decrease from A$112 (MYR 456) per decedent per day to $A82 (MYR 238) per decedent per day of CA hospital costs. (1A$=MYR2.91). Community-based specialist palliative care was also associated a reduction of inpatient averaged hospital costs of 9% (7%-10%) to A$1030

(MYR 2,994 per hospitalised decedent per day. Cost reductions associated with community-based specialist palliative care were evident four months before death for decedents with cancer and by one to two months before death for decedents dying from other conditions. The authors concluded that community-based specialist palliative care was associated with hospital cost reductions across multiple life-limiting conditions.[45]

Youens et al. (2017) compared place of death, acute care hospital use and cumulative cost of hospital admissions in the last year of life between cancer decedents who did and did not access a community-based palliative care service.[47] A total of 28,561 West Australian cancer decedents were included in this retrospective cohort study. Decedents who accessed the community-based palliative care service (n = 16,530) were found to have triple (adjusted odds ratio 3.19 [3.01–3.38]) the odds of dying out of hospital compared with those who did not. Unplanned hospitalizations were reduced in the last year (adjusted incidence rate ratio [IRR] 0.94 [0.91–0.97]) and last week of life (adjusted [IRR] 0.35 [0.33–0.38]), as were ED presentations (adjusted RR 0.92 [0.98–0.95], adjusted RR 0.26 [0.23–0.28]) in the last year and last week of life, respectively. There were significant reductions in average total bed days [-7.60 (-8.34 to -6.87)] and acute care costs [-A$5,491 (-A$17,911.05, -A$4,827)] or MYR15,978.81 (-MYR 52121.15, -MYR14,046.57) over the last year of life (1A$=MYR2.91). Community-based palliative care was associated with reduced acute care admissions, bed days, and costs over the last year of life as well as supporting people to die out of hospital.[47]

Home-based palliative care
Gomes et al. (2013) conducted a systematic review and meta-analysis to evaluate economic impact of home-based palliative care.[35]There were six studies on economic evaluation included in the review. Evidence on cost-effectiveness (six studies) was inconclusive. Six studies (five RCTs and one CBA including 2047 patients and 1678 caregivers, all considered high quality economic evaluations) compared the impact on the total care costs of receiving home palliative care as opposed to usual care, alongside an evaluation of clinical effectiveness. Together, the RCTs analysed data related to 590 patients (samples ranged from 33 to 297 patients), adding to 1754 patients in Greer 1986. All studies measured institutional and non-institutional costs, three included medication costs and one calculated the costs associated with informal care. Studies reported lower costs in the intervention groups with differences ranging from 18% to 35% except Greer 1986 where the costs under the hospital-based intervention were 2% lower than conventional care as opposed to 32% lower under the community-based intervention. Notwithstanding, differences were statistically significant only in Brumley 2007. More work is needed to study cost-effectiveness especially for people with non-malignant conditions, assessing place of death and appropriate outcomes that are sensitive to change and valid in these populations, and to compare different models of home palliative care, in powered studies.

Cassel et al. (2016) conducted a retrospective study to evaluate the non-clinical outcomes of a proactive palliative care programme funded and operated by a health system for Medicare Advantage plan beneficiaries.[48] Transitions® is a concurrent care home-based programme designed for individuals with advanced chronic illness who would benefit from support provided by a trained specialty PC team comprising doctors, nurses, spiritual care providers, and social workers. The programme had four components: in-home medical consultation, ongoing evidence-based prognostication of further survival, caregiver support, and advance healthcare planning. The outcomes include hospital costs, other healthcare costs, readmission rates, hospital admissions and bed days, intensive care unit use in final 30 days of life, and death within 30 days of an admission). Costs were analysed from the perspective of the health system. Individuals who received the intervention (n = 368) were matched with 1,075 comparison individuals within each of four disease groups: cancer, chronic obstructive pulmonary disease (COPD), heart failure (HF), and dementia. Median age at death for each disease group was older than 80. For each disease, hospital costs and total costs per month were lower for Transitions® participants (all p ≤ 0.002). For three of the four disease groups, there was not a significant difference in non-hospital costs (p = 0.32 for cancer, p = 0.08 for COPD, p = 0.09 for HF). For each disease, the percentage of participants hospitalized, number of hospital days, admisssion in the final 30 days of life, using the intensive care unit in the final 30 days of life were lower for Transitions® than for controls (all p ≤ 0.001). Mean 30-day readmission rate was also lower for Transitions® participants with COPD, HF and dementia (p<0.01), but not those with cancer (p = 0.08). Transitions® participants' costs increased only slightly in the final months of life (from USD1,550 4 months before death to USD3,711 in final month), whereas comparison participants' costs increased dramatically (from USD2,631 four months before death to USD17,006 in final month). Adding the USD642 in costs per month for Transitions services to the Transitions® group, the net savings per participant per month were USD4,258 for cancer, USD4,017 for COPD, USD3,447 for HF, and USD2,690 for dementia. The return on investment (net cost reduction divided by programme costs) thus ranged from 4.2 for dementia to 6.6 for cancer. The authors concluded that intervention participants in all four disease groups had less hospital use and lower hospital costs compared to non-intervention participants, which drove lower overall healthcare costs. In the final six months of life, healthcare costs for the intervention groups stayed largely the same from month to month, whereas costs for comparison participants increased dramatically.[47]

*** End of life care intervention***
Pham and Krahn (2014) conducted an economic analysis to evaluate the cost-effectiveness of end-of-life (EoL) care interventions included in the EoL care mega-analysis.[49] The authors conducted primary economic analysis and budget impact analysis for an Ontario cohort of decedents and their families and included interventions pertaining to team-based models of care, patient care

planning discussions, educational interventions for patients and caregivers, and supportive interventions for informal caregivers. The analysis was conducted from the perspective of the Ontario Ministry of Health. According to Markov model home-based palliative care team was cost-effective; it increased the chance of dying at home by 10%, increased the average number of days at home (six days) and quality-adjusted life-days (0.5 days), and it reduced costs by approximately C$4,400 (MYR 13,630) per patient (1 Canadian dollar=MYR 3.09). Expanding home-based palliative team care to those currently not receiving such services (approximately 45,000 per year, at an annual cost of C$76–108 million) is likely to improve QOL, reduce the use of acute care resources, and save C$191–C$385 million in health care costs. However, results for the other interventions were uncertain.[48]

Specialist versus generalist

Gardiner et al. (2018) conducted a systematic review to review evidence on the costs of specialist and generalist palliative care in the UK, and to explore different approaches used for capturing activity and unit cost data.[50] Ten studies were included (five cross-sectional/ cohort, four modelling studies, one secondary analysis of trial data) involving patients with cancer, advanced disease and refractory breathlessness, any non-curative, heart failure, advanced melanoma, receiving any palliative care. Specialist palliative care was provided by professionals who have undergone recognised specialist palliative care training and generalist palliative care was provided as part of standard clinical practice by any healthcare professional that is not part of a specialist palliative care team. There was significant variation in cost estimates of end-of-life care, ranging from £4140 (MYR 22,023.71) for one week of life to £38,377 (MYR 204,155.54) for the last year of life, therefore it was not possible to present an accurate aggregate cost of palliative care in the UK. The majority of studies explored costs from a National Health Service perspective and only two studies included informal care costs. The latter found informal care to represent a significant percentage of the total cost of care (33% and 72%, respectively). Approaches to estimating activity and costs varied and challenging particularly for hospice and informal care and these were often neglected in economic studies.[50]

Paediatric home based palliative care

As previously mentioned, Chong et al. (2018) found that home-based paediatric palliative care (PPC) improved QOL of patients and their caregivers.[40] In the same study, they have also calculated the economic impact of home - based palliative care from the healthcare system perspective. Costs associated with hospitalization, ED visits and outpatient visits were estimated through total medical bill before any deduction for government subsidies and insurance claims. Cost of care for control group at the end of life was SGD $253,168 per year (MYR 763,320; SGD1=MYR3.02) with 32% incurred within the final month of life. Cost of care per year was significantly lower (SGD$74,683 =MYR225, 174) in the PPC group (p <0.05). At 12 months prior to death, medical costs for PPC group

were 70% lower than the control group. Cost savings increased to 87% (SGD$ 72 K) at one month prior to death.[39]

Gans et al. (2016) conducted a pre-post study to assess the healthcare costs associated with paediatric palliative care programme, Partners for Children (PFC) in California.[51] This programme provided comprehensive care coordination, expressive therapies, including art and play for the child, family education, respite care in and out of the home to provide needed rest for the primary caregivers, family and bereavement counselling as well as pain and symptom management and on-call nursing support services. A total of 151 children enrolled in the PFC pilot were included in the cost analyses with majority aged 0-10 years old (64%), 10-20 years old (36%). Most frequent primary diagnosis was a neurologic condition (30%), followed by cancers (20%) and pulmonary and neuromuscular conditions (11% each). Mean health care costs per enrolees per month (PEPM) of children in PFC decreased significantly from USD15,643 (MYR 63,698) before their participation in the programme to USD12,312 (MYR 50,134) while enrolled, a pre-post difference of USD3331 (MYR 13,563). Most of the savings were realized through a reduction in inpatient costs of USD4897 (MYR 19,940) PEPM, which was slightly modified by increases in outpatient and pharmacy services. Reductions in inpatient costs were consistent across nearly all of the disease categories studied. In terms of health service utilisation, PFC enrollees experienced a nearly 50% significant reduction in the average number of inpatient days per month, from 4.2 to 2.3. Average length of stay per hospitalization dropped significantly from an average of 16.7 days before enrolment to 6.5 days while in the programme. Similarly, the 30-day readmission rate was reduced from 45% of admissions to 37% of admissions, although not statistically significant.[50]

5.4   Organizational

Resource utilisation
Seow et al. (2014) conducted a pooled analysis of retrospective cohort to assess the impact of community-based, specialist palliative care teams on hospitalisations and emergency department visits late in life and hospital deaths.[52] The Study estimated the relative risk of using acute care in the last two weeks of life and dying in hospital in each of the 11 teams separately and also the overall pooled effect (weighted). The outcome measures include being in hospital in the last two weeks of life; having an emergency department visit in the last two weeks of life; or dying in hospital. A total of 3109 patients who received care from specialist palliative care teams in 2009-2011 (exposed) matched by propensity score to 3109 patients who received usual care (unexposed). Palliative care teams studied despite being varied in team composition and sizes, had the same core team members; a core group of palliative care physicians, nurses, and family physicians who provide integrated palliative care to patients in their homes. The teams' role was to manage symptoms, provide education and care, coordinate services, and be available without interruption regardless of time

or day. In both exposed and unexposed groups, about 80% had cancer and 78% received end of life homecare services for the same average duration. Across all palliative care teams, 970 (31.2%) of the exposed group were in hospital and 896 (28.9%) had an emergency department visit in the last two weeks of life respectively, compared with 1219 (39.3%) and 1070 (34.5%) of the unexposed group (p<0.001). The pooled relative risks of being in hospital and having an emergency department visit in late life comparing exposed versus unexposed were 0.68 (95% confidence interval 0.61 to 0.76) and 0.77 (0.69 to 0.86) respectively. Fewer exposed than unexposed patients died in hospital (503 (16.2%) v 887 (28.6%), p<0.001), and the pooled relative risk of dying in hospital was 0.46 (0.40 to 0.52). The authors concluded that community-based specialist palliative care teams, despite variation in team composition and geographies, were effective at reducing acute care use and hospital deaths at the end of life.[52]

Communication competency

Schram et al. (2016) evaluated communication- based competencies in palliative care in critical care settings.[53] There were 15 studies (five qualitative and ten quantitative) included. The competencies identified as critical for the delivery of high-quality PC in critical care settings included; prognostication (the ability to effectively communicate prognostic information to patients and family members), conflict mediation (the ability to detect and mediate disagreement between family members and clinicians), empathic communication (the ability to provide support to patients and family members during conversation using both specific statements and nonverbal cues) as well as patient and family-centred aspects of care (the ability to respect families and respond to their needs and wishes to facilitate shared decision-making, particularly when the patient cannot communicate). [52]

Communication training

Epstein et al. (2016) studied the effect of a patient-centred communication intervention on oncologist-patient communication, QOL, and health care utilisation.[54] They conducted multisite, cluster RCTs at community- and hospital-based cancer clinics in Western New York and Northern California. This Values and Options in Cancer Care (VOICE) study combined two interventions, a brief individualized oncologist skill-based training, and individualized patient and caregiver coaching incorporating a question prompt lists (QPL). The control group consist of those who received no training. The primary outcome was patient-centred communication in these domains: engaging patients to participate in the consultation, responding to patients' emotions, informing patients about prognosis and treatment choices, and framing information in a balanced manner. Secondary outcomes include shared understanding, patient-physician relationships, QOL, and health care utilisation in the last 30 days of life. A total of 38 medical oncologists (mean age 44.6 years) and 265 community-dwelling adult patients with advanced non-haematologic cancer (mean age 64.4 years) participated and followed for three years. In fully adjusted models, the intervention resulted in clinically and statistically significant improvements in the

primary physician-patient communication end point (adjusted intervention effect, 0.34; 95% CI 0.06,0.62; p=0.02). Of the individual communication component measures, only the engaging measure was statistically significant. Differences in other secondary outcomes were not statistically significant. Overall, QOL and health care utilisation differences between intervention and control were not statistically significant.[53]

5.5 Ethical and cultural considerations

Surrogate decision making

Kelly, Rid and Wendler (2012) conducted a systematic review to determine to what extent current practice promotes how adults want treatment decisions to be made for them during periods of incapacity.[55] Fourteen qualitative articles and 26 quantitative articles, providing data on the views of 22,828 individuals from the US, Canada, France, Japan, Sweden, Australia, and Singapore, were included. Most of the respondents were elderly or seriously ill. The majority wanted close family members to act as their surrogate. The most common reason for preferring family members was the belief that they know which treatments the patient would want. Individuals also wanted to reduce the burden on their families. Of the 17 articles that looked into whether respondents had any discussion with someone else regarding end-of-life decision-making; only one reported discussion rates higher than 70% while others reported discussion rates lower than 70%. There was significant variation in the extent to which respondents wanted their surrogates to have leeway when making treatment decisions. Another quantitative article found that 63% of respondents wanted their surrogates to follow their advance directives strictly or as much as possible, whereas 33% wanted their surrogates to use their advance directives as a reference only, and 3% did not care if their wishes were followed. The authors concluded that individuals have three primary goals with respect to making treatment decisions for them during periods of incapacity: involve their family, treat them consistently with their own treatment preferences, and reduce the burden on their family. Unfortunately, prior systematic reviews have found that family members often are not able to determine which treatment patients want, and family members frequently experience substantial distress when acting as surrogates. These findings suggest that current practice frequently fails to promote individuals' primary goals for treatment decision-making. Encouraging patients to document their own goals, including their treatment preferences and their preferences regarding how they want decisions to be made for them during periods of decisional incapacity could help patients achieve those goals.[54]

Cultural & religious considerations

In a systematic review, Weiner et al. (2013) examined the influence of religion and cultures in paediatric palliative care.[56] A total of 37 studies included involving participants from variety of cultural/religious groups; Chinese, Japanese, Korean, South Asian (India, Bangladesh, Nepal, Pakistan, Maldives, Sri Lanka), Latino, Filipino, Vietnamese, African- American, Native American, Caribbean-American

and Russian-American. The study found seven distinct themes emerged that have implications for paediatric palliative care including role of culture norms and customs in decision- making, faith and the involvement of clergy, communication (spoken and unspoken language), communicating to children about death, the meaning of pain and suffering, the meaning of death and dying, location of end-of-life care. This study provides insight into the influence of religion and how culture informs lifestyle and shapes the experiences of illness, pain, and end-of-life care. Cultural traditions are unique and cannot be generalized to all families. Health providers are encouraged to define these important differences for each family under their care.[55]

5.6   Limitation

Our review has several limitations and these should be considered when interpreting the results. The selection of the studies and appraisal was done by one reviewer. Although there was no restriction in language during the search, only the full text articles in English published in peer-reviewed journals were included in the report, which may have excluded some relevant articles and further limited our study numbers.

One of the important limitations was the methodological quality of the included studies, particularly in terms of heterogeneity and risk of bias. Small number of studies were included in several meta-analysis, which may have limit its power to ascertain differences in effect measures. This is probably due to the fact that palliative care researchers face particular challenges of attrition and missing data related to progressive illness and death. There is heterogeneity among the different intervention studies, for instance, the variety of instruments used to measure patients' QOL and the timing of the assessments as well as diversity of settings and mechanisms for delivering palliative care services. One of the difficulties inherent in palliative care research is the complexity of the care approach, with care commonly provided in a range of settings with different funding arrangements. This complexity means it is practically and methodologically difficult to collect accurate and comprehensive cost data.

6.0 CONCLUSION

6.1 Effectiveness

Quality of life
There was sufficient, good level of retrievable evidence to suggest that;
  i. Specialised palliative care in hospital-based, community-based and home-based settings improved QOL in patients with life-threatening diseases.
  ii. Specialised palliative care also has positive impact on survival
  iii. Direct contact, comprehensive team-based model significantly improves patient QOL
  iv. Early integration of PC multidisciplinary team concurrently with treatment resulted in improvement in QOL, better symptom control, less caregiver burden, improvement in continuity and coordination of care, fewer admissions, patients dying in their preferred place.

There was fair level of evidence to suggest technological-based interventions had potential in improving outcomes in terms of QOL as well as pain control and depression

Physical well-being
There was sufficient fair to good level of retrievable evidence that suggest;
  i. Palliative care improved physical symptoms, specifically on pain.
  ii. Oral morphine was an effective analgesic for cancer pain, with similar efficacy to other opioids. Both immediate-release and sustained-release formulations of oral morphine can be titrated to analgesic effect.
  iii. Single fraction and multiple fraction radiation treatment regimens demonstrated similar outcomes in pain control and toxicities, but re-treatment was more common for single fraction treatment patients.

There was insufficient evidence retrieved on fatigue, weight loss and palliative pharmacological sedation on QOL or symptom control.

Psychosocial well-being
There was fair to good quality of retrievable evidence that suggest;
  i. Psychosocial interventions improve QOL and emotional wellbeing
  ii. Dignity therapy and therapeutic life review were potentially beneficial for people near the end of life

Spiritual well-being
There was fair level of retrievable evidence that suggest spiritual interventions had a moderate beneficial effect in terms of improving QOL of cancer patients

Paediatric Palliative Care
There was good quality of retrievable evidence that suggest home-based paediatric palliative care improved QOL of patients and their caregivers. However no conclusions can be drawn about efficacy or harm in the use of opioids to treat cancer-related pain in children and adolescents due to low quality of evidence retrieved.

Traditional and Complementary Medicine
There was good quality of retrievable evidence that suggest combined Chinese Herbal Medicine and conventional treatment significantly reduced pain and

constipation. However, more research is warranted on the use of CHM for treating anorexia and fatigue.

Economic evaluation

There was sufficient retrievable evidence that suggest palliative care unit was cost saving. Hospital costs were lower for patients seen by a palliative care consultation team than for patients who not did not receive this care, especially was greater for those with a primary diagnosis of cancer and those with more comorbidities compared. Community-based specialist palliative care associated a reduction of inpatient averaged hospital costs of 9% (7%-10%) to A$1030 (MYR 2,994 per hospitalised decedent per day) across multiple life-limiting conditions. It was associated with reduced acute care admissions, bed days, and costs over the last year of life. Outpatient palliative care significantly reduced total health care costs among patients with terminal or advanced and complex illness. The delivery of early PC does not appear to increase overall medical care expenses for patients with metastatic cancer.

There was also retrievable evidence that suggest home-based palliative care for paediatric patients was cost-saving although results were somewhat mixed in the adults.

Safety

There was fair level of retrievable of evidence that suggest most people will experience tolerable adverse events from using various types of opioids. Prevalence of adverse events related to morphine, fentanyl, oxycodone or codeine ranged from 5% for diarrhoea and insomnia to 25% for constipation and somnolence. No direct evidence that opioids affected patient consciousness, appetite or thirst when used to treat cancer pain.

Organizational

There was retrievable evidence that community-based specialist palliative care teams were effective at reducing acute care use and hospital deaths at the end of life. Competencies identified as critical for the delivery of high-quality PC in critical care settings included; prognostication, conflict mediation, empathic communication as well as patient and family-centred aspects of care. Patient-centred communication intervention resulted in clinically and statistically significant improvements in the primary physician-patient communication end point.

Ethical and cultural considerations

Individuals have three primary goals with respect to making treatment decisions for them during periods of incapacity: involve their family, treat them consistently with their own treatment preferences, and reduce the burden on their family. Culture and religion influence lifestyle and shapes the experiences of illness, pain, and end-of-life care and cannot be generalized to all patients and families.

7.0   REFERENCES

1. World Health Organization. WHO definition of palliative care. Available http//www who.int/cancer/palliative/definition/en/ (cited 18 July 2018).
2. World Health Organization (WHO). Global Atlas of Palliative Care at the End of Life. Worldwide Palliative Care Alliance; 2014. Available from: http://www.who.int/nmh/Global_Atlas_of_Palliative_Care (cited 18 July 2018)
3. World Health Organization. Planning and implementing palliative care services: a guide for programme managers. 2016;91. Available from: http://www.who.int/about/licens-ing/copyright_form/en/index.html
4. World Health Organization (WHO). Global action plan for the prevention and control of noncommunicable diseases 2013-2020. 2013.
5. WHO & UNICEF. 2018. Declaration of Astana. Global Conference Primary Health Care, Astana, Kazakhstan, 25-26 October, 2018. Available from: https://www.who.int/docs/default-source/primary-health/declaration/gcphcdeclaration
6. Sekhar WY, Connor S, McCarthy S, Hamzah E. Palliative Care Needs Assessment Malaysia. 2016; Available from: https://www.hospismalaysia.org/wp-content/uploads/2016/10/Palliative-Care-Needs-Assessment-Malaysia-2016
7. Medical Development Division Ministry of Health Malaysia. Palliative Care Services: Operational Policy. 2010. 70 p.
8. Lim RB., Katiman D. Handbook of Palliative Medicine in Malaysia.
9. Higginson IJ, Evans CJ. What Is the Evidence That Palliative Care Teams Improve Outcomes for Cancer Patients and Their Families? Cancer J. 2010;16(5):423–35.
10. World Health Organization. Cancer control: Knowledge into action: WHO guide for effective programmes: Palliative Care. 2007. Available from: http://apps.who.int/iris/bitstream/10665/44024/1/9241547345_eng
11. World Health Organization, International Association for Hospice and Palliative Care (IAHPC). Essential Medicines in Palliative Care. Executive summary. 2013:73.
12. Martínez M, Arantzamendi M, Belar A et al. 'Dignity therapy', a promising intervention in palliative care: A comprehensive systematic literature review. Palliat Med. 2017;31(6):492–509.
13. Critical Appraisal Skills Programme (CASP) checklist. 2018 [cited 2018 Jul 10]. Available from: https://casp-uk.net/casp-tools-checklists/
14. Health Quality Ontario. Team-based models for end-of-life care: An evidence-based analysis. Ont Health Technol Assess Ser [Internet]. 2014;14(20):1–49. Available from: http://www.hqontario.ca/evidence/publications- and-ohtac-recommendations/ontario-health-technology-assessment-series/eol-team-based-models
15. Wiffen PJ, Wee B, Derry S, Rf B, Ra M. Opioids for cancer pain - an overview of Cochrane reviews (Review). Cochrane Database Syst Rev. 2017;(7).
16. Payne C, Wiffen P, Martin S. Interventions for fatigue and weight loss in adults with advanced progressive illness: A cochrane overview of systematic reviews. Palliat Med. 2012;26(4):385. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L71176194%5Cnhttp://dx.doi.org/10.1177/0269216312446391%5Cnhttp://resolver.ebscohost.com/openurl?sid=EMBASE&issn=02692163&id=doi:10.1177/0269216312446391&atitle=Interventions+for+fat
17. Haun MW, Estel S, Rücker G et al. Early palliative care for adults with

advanced cancer. Cochrane Database Syst Rev. 2017;(6):1–105.

18. Singer AE, Goebel JR, Kim YS et al. Populations and Interventions for Palliative and End-of-Life Care: A Systematic Review. J Palliat Med. 2016;19(9):995–1008. Available from: http://online.liebertpub.com/doi/10.1089/jpm.2015.0367

19. Gomes B, Calanzani N, Curiale V, McCrone P. P, Higginson IJ, Brito M de. Effectiveness and cost-effectiveness of home palliative care services for adults with advanced illness and their caregivers. Cochrane Libr. 2013;(6):93.

20. Beller EM, van Driel ML, Mitchell G. Palliative pharmacological sedation for symptom relief in terminally ill adults. Cochrane Database Syst Rev. 2012;(1). Available from: http://doi.wiley.com/10.1002/14651858.CD010206

21. Parahoo K, McDonough S, McCaughan E et al. Psychosocial interventions for men with prostate cancer. Cochrane database Syst Rev. England; 2013;(12):CD008529.

22. Wang CW, Chow AY, Chan CL. The effects of life review interventions on spiritual well-being, psychological distress, and quality of life in patients with terminal or advanced cancer: A systematic review and meta-analysis of randomized controlled trials. Palliat Med. 2017;1–12. Available from: http://journals.sagepub.com/doi/10.1177/0269216317705101

23. Galway K, Black A, Cantwell M, Cardwell CR, Mills M, Donnelly M. Psychosocial interventions to improve quality of life and emotional wellbeing for recently diagnosed cancer patients. Cochrane Collab. 2012;(11). Available from:
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007064.pub2/abstract %5Cnhttp://onlinelibrary.wiley.com/store/10.1002/14651858.CD007064.pub2/a sset/CD007064.pdf?v=1&t=iljjlcz4&s=8ab822d487f4e3a171061ca31327121c9 c3bbb9d

24. Agboola SO, Ju W, Elfiky A, Kvedar JC, Jethwani K. The effect of technology-based interventions on pain, depression, and quality of life in patients with cancer: A systematic review of randomized controlled trials. J Med Internet Res. 2015;17(3):1–14.

25. Kruizinga R, Hartog ID, Jacobs M et al. The effect of spiritual interventions addressing existential themes using a narrative approach on quality of life of cancer patients: a systematic review and meta-analysis. Psychooncology. 2016;25(3):253–65.

26. Oh PJ, Kim SH. The effects of spiritual interventions in patients with cancer: a meta-analysis. Oncol Nurs Forum. United States; 2014;41(5):E290-301.

27. Chung VCH, Wu X, Hui EP et al. Effectiveness of Chinese herbal medicine for cancer palliative care: overview of systematic reviews with meta-analyses. Sci Rep. England; 2015;5:18111. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med8&NEWS =N&AN=26669761

28. Kassianos AP, Ioannou M, Koutsantoni M, Charalambous H. The impact of specialized palliative care on cancer patients' health-related quality of life: a systematic review and meta-analysis. Support Care Cancer. Supportive Care in Cancer; 2017;26(1):61–79.

29. Gaertner J, Siemens W, Meerpohl JJ et al. Effect of specialist palliative care services on quality of life in adults with advanced incurable illness in hospital, hospice, or community settings: systematic review and meta-analysis. Bmj. 2017;j2925. Available from: http://www.bmj.com/lookup/doi/10.1136/bmj.j2925

30. Kavalieratos D, Corbelli J, Zhang D et al. Association between palliative care and patient and caregiver outcomes: A systematic review and meta-analysis.

JAMA - J Am Med Assoc. 2016;316(20):2104–14.

31. Phongtankuel V, Meador L, Adelman RD et al. Multicomponent Palliative Care Interventions in Advanced Chronic Diseases: A Systematic Review. Am J Hosp Palliat Med. 2018;35(1):173–83.

32. Siouta N, Van Beek K, Van Der Eerden ME et al. Integrated palliative care in Europe: A qualitative systematic literature review of empirically-tested models in cancer and chronic disease. BMC Palliat Care. England: BMC Palliative Care; 2016;15(1):56. Available from: http://dx.doi.org/10.1186/s12904-016-0130-7

33. Vanbutsele G, Pardon K, Van Belle S et al. Effect of early and systematic integration of palliative care in patients with advanced cancer: a randomised controlled trial. Lancet Oncol. 2018;19(3):394–404.

34. Larson JL, Rosen AB, Wilson FA. The Effect of Telehealth Interventions on Quality of Life of Cancer Patients: A Systematic Review and Meta-Analysis. Telemed e-Health. 2017;24(6):tmj.2017.0112. Available from: http://online.liebertpub.com/doi/10.1089/tmj.2017.0112

35. Gomes B, Calanzani N, Curiale V, McCrone P. P, Higginson IJ, Brito M de. Effectiveness and cost-effectiveness of home palliative care services for adults with advanced illness and their caregivers. Cochrane Database Syst Rev. 2013;(6).

36. Wiffen PJ, Wee B, Ra M. Oral morphine for cancer pain (Review). Cochrane Database ofSystematic Rev. 2013;(7):Art. No.: CD003868.

37. Rich SE, Chow R, Raman S et al. Update of the systematic review of palliative radiation therapy fractionation for bone metastases. Radiother Oncol. Elsevier B.V.; 2018;(June 2017). Available from: https://doi.org/10.1016/j.radonc.2018.01.003

38. Parahoo K, Mcdonough S, Mccaughan E et al. Psychosocial interventions for men with prostate cancer. Cochrane Database Syst Rev. 2013;(12):1–99.

39. Prescott AT, Hull JG, Dionne-Odom JN et al. The role of a palliative care intervention in moderating the relationship between depression and survival among individuals with advanced cancer. Heal Psychol. 2017;36(12):1140–6.

40. Chong PH, De Castro Molina JA, Teo K, Tan WS. Paediatric palliative care improves patient outcomes and reduces healthcare costs: Evaluation of a home-based program. BMC Palliat Care. BMC Palliative Care; 2018;17(1):1–8.

41. Wiffen PJ, Derry S, Moore RA. Impact of morphine , fentanyl , oxycodone or codeine on patient consciousness , appetite and thirst when used to treat cancer pain (Review). Cochrane Database Syst Rev. 2014;(5).

42. May P, Normand C, Cassel JB et al. Economics of palliative care for hospitalized adults with serious illness: A meta-analysis. JAMA Intern Med. 2018;178(6):820–9.

43. Isenberg SR, Lu C, McQuade J et al. Economic Evaluation of a Hospital-Based Palliative Care Program. J Oncol Pract. 2017;13(5):e408–20. Available from: http://ascopubs.org/doi/10.1200/JOP.2016.018036

44. Cunningham C, Ollendorf D, Travers K. The effectiveness and value of palliative care in the outpatient setting. JAMA Intern Med. 2017;177(2):264–5.

45. Greer JA, Tramontano AC, McMahon PM et al. Cost Analysis of a Randomized Trial of Early Palliative Care in Patients with Metastatic Nonsmall-Cell Lung Cancer. J Palliat Med. 2016;19(8):842–8. Available from: http://online.liebertpub.com/doi/10.1089/jpm.2015.0476

46. Spilsbury K, Rosenwax L. Community-based specialist palliative care is associated with reduced hospital costs for people with non-cancer conditions during the last year of life. BMC Palliat Care. BMC Palliative Care;

2017;16(1):68. Available from: https://bmcpalliatcare.biomedcentral.com/articles/10.1186/s12904-017-0256-2

47. Youens D, Moorin R. The Impact of Community-Based Palliative Care on Utilization and Cost of Acute Care Hospital Services in the Last Year of Life. J Palliat Med. 2017;20(7):736–44. Available from: http://online.liebertpub.com/doi/10.1089/jpm.2016.0417

48. Brian Cassel J, Kerr KM, McClish DK et al. Effect of a Home-Based Palliative Care Program on Healthcare Use and Costs. J Am Geriatr Soc. 2016;64(11):2288–95.

49. Pham B, Krahn M. End-of-Life Care Interventions: An Economic Analysis. Ont Health Technol Assess Ser. 2014;14(18):1–70.

50. Gardiner C, Ryan T, Gott M. What is the cost of palliative care in the UK? A systematic review. BMJ Support Palliat Care. 2018;1–8.

51. Gans D, Hadler MW, Chen X et al. Cost Analysis and Policy Implications of a Pediatric Palliative Care Program. J Pain Symptom Manage. Elsevier Ltd; 2016;52(3):329–35. Available from: http://dx.doi.org/10.1016/j.jpainsymman.2016.02.020

52. Seow H, Brazil K, Sussman J et al. Impact of community based, specialist palliative care teams on hospitalisations and emergency department visits late in life and hospital deaths: A Pooled analysis. BMJ. 2014;348(June):1–10. Available from: http://dx.doi.org/doi:10.1136/bmj.g3496

53. Schram AW, Hougham GW, Meltzer DO, Ruhnke GW. Palliative Care in Critical Care Settings : A Systematic Review of Communication- Based Competencies Essential for Patient and Family Satisfaction. Am J Hosp Palliat Med. 2016;1–9.

54. Epstein RM, Duberstein PR, Fenton JJ et al. Effect of a Patient-Centered Communication Intervention on Oncologist-Patient Communication, Quality of Life, and Health Care Utilization in Advanced Cancer The VOICE Randomized Clinical Trial. JAMA Oncol. 2016;14620.

55. Kelly B, Rid A, Wendler D. Systematic Review: Individuals' Goals for Surrogate Decision-Making. J Am Geriatr Soc. 2012;60:884–95.

56. Weiner L, Mcconnell DG, Latella L, Ludi E. Cultural and religious considerations in pediatric palliative care. Palliat Support Care. 2013;11(1):47–67.

8.0   APPENDIX

8.1   Appendix 1: LITERATURE SEARCH STRATEGY

Ovid MEDLINE® In-Process & Other Non-indexed Citations and Ovid MEDLINE® 1946 to present

1.	palliative care/
2.	(palliative adj1 (care or therap* or treatment*)).tw.
3.	Palliative Medicine/
4.	((palliative care or palliative) adj medicine).tw.
5.	Hospice.mp. and palliative care/
6.	hospice.mp. and palliative care.tw.
7.	(hospice adj1 care).tw.
8.	(hospice adj1 program*).tw.
9.	life-limiting disease.tw.
10.	terminally ill/
11.	life threatening/
12.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13.	psychosocial intervention.tw.
14.	psychological intervention.tw
15.	social intervention.tw
16.	physical symptom.tw.
17.	pain therap*.tw.
18.	spiritual intervention.tw.
19.	Medicine, Chinese Traditional/ or Complementary Therapies/ or Drugs, Chinese Herbal/ or Plant Extracts/
20.	integrated care.tw.
21.	13 or 14 or 15 or 16 or 17 or 18 or 19
22.	12 and 21
23.	limit 22 to (english language and humans and yr="2000 -Current")

OTHER DATABASES	
EBM Reviews – Cochrane Central Registered of Controlled Trials	
EBM Reviews – Database of Abstracts of Review of Effects	
EBM Reviews – Cochrane database of systematic reviews	Same MeSH, keywords, limits used as per MEDLINE search
EBM Reviews – Health Technology Assessment	
NHS economic evaluation database	
PubMed	
Embase	
INAHTA	

8.2   Appendix 2

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I   Evidence obtained from at least one properly designed randomized controlled trial.

II-I   Evidence obtained from well-designed controlled trials without randomization.

II-2   Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3   Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III   Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

*SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE
            (Harris 2001)*

Evidence Table : **Effectiveness – specialised palliative care**
Question : **Is palliative care intervention effective in improving quality of life of patient with chronic life-limiting illness?**

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comment
1.Gaertner J, Siemens W, Meerpohl JJ et al. Effect of specialist palliative care services on quality of life in adults with advanced incurable illness in hospital, hospice, or community settings: systematic review and meta-analysis. BMJ 2017;j2925.	**Systematic review and meta-analysis** **Objective:** To assess the effect of specialist palliative care on QOL and additional outcomes relevant to patients in those with advanced illness. Secondary outcomes=symptom burden (pain, fatigue, nausea, and dyspnoea),psychosocial variables (distress, depression, anxiety, spiritual wellbeing, social wellbeing, and satisfaction), survival time, place of death, cost of care, and attrition (or completion rate) **Inclusion criteria** Randomised controlled trials with adult inpatients or outpatients treated in hospital, hospice, or community settings with any advanced illness. Minimum requirements for specialist palliative care included the multiprofessional team approach **Quality assessment** Risk of bias was assessed using Cochrane risk of bias tool and evaluated the quality of evidence (GRADE tool) **Primary outcome**=QOL (all tools that covered at least two dimensions of QOL (physical, psychological or social) Pooled SMDs of the analyses of QOL were re-expressed on the global health/QoL scale (item 29 and 30, respectively) of the European Organization for Research and Treatment of Cancer QLQ-C30 (0-100, high values=good quality of life, minimal clinically important difference 8.1)	I	12 articles included 10 randomised controlled trials with 2454 patients (72% ,n=1766) had cancer) Included studies: *Grudzen 2016* *Sidebottom 2015* *Zimmermann 2014* *Wallen, 2012* *Cheung 2010* *Temel 2010 Greer 2014* *Gade 2008* *Rabow, 2004* *Hanks, 2002* *Jordhoy 2001, 2002*	Specialist palliative care = service of health care professional from at least 2 different professions that provides or coordinates comprehensive care for patients The intervention varied across studies. Social workers and chaplains were part of the multiprofessional team in five of the 10 trials (50%); all 10 studies included a nurse and nine studies (90%) included a physician	Standard care		Small effect in favour of specialist palliative care (SMD 0.16, 95% confidence interval 0.01 to 0.31; QLQ-C30 global health/QoL 4.1, 0.3 to 8.2; n=1218, 6 trials). Sensitivity analysis showed an SMD of 0.57 (−0.02 to 1.15; global health/ QoL 14.6, −0.5 to 29.4; n=1385, seven trials). The effect was marginally larger for patients with cancer (0.20, 0.01 to 0.38; global health/QoL 5.1, 0.3 to 9.7; n=828, five trials) and especially for those who received specialist palliative care early (0.33, 0.05 to 0.61, global health/QoL 8.5, 1.3 to 15.6; n=388, two trials) The results for pain and other secondary outcomes were inconclusive. Some methodological problems (such as lack of blinding) reduced the strength of the evidence. **Author' conclusion**: Specialist palliative care was associated with a small effect on QoL and might have most pronounced effects for patients with cancer who received such care early. It could be most effective if it is provided early and if it identifies though screening those patients with unmet needs.	

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2.Kassianos AP, Ioannou M, Koutsantoni M, Charalambous H. The impact of specialized palliative care on cancer patients' health-related quality of life: a systematic review and meta-analysis. Support Care Cancer. Supportive Care in Cancer; 2017;26(1):61–79.	**Systematic review and meta-analysis** **Objective** To critically evaluate the impact of SPC on patients' health-related quality of life (HRQoL) **Methods** The PRISMA reporting statement was followed. A meta-analysis followed using random-effect models separately for RCTs and non-RCTs **Inclusion criteria** Randomized controlled trials (RCTs) and prospective studies using a pre- and post- assessment of HRQoL were included. **Exclusion criteria** Studies that provided supportive care or any other psychosocial intervention or care that was not coordinated or provided by a specialized team Studies that included cancer patients together with other patient groups or where HRQoL was not assessed using standardized and validated questionnaires were also excluded **Quality assessment** Criteria from other studies were used to evaluate the studies' quality **Outcomes measures** Health-related QOL	I	11 studies included (5 RCTs, 6 prospective) Total of 2939 patients with cancer of gastrointestinal tract, lung, breast, female genitals, prostate, male genitals, kidney, vesical, urethra, lymphoma, skin/melanoma, sarcoma, colorectal, head and neck, pancreatic, stomach, liver, bladder, oesophageal, bile duct, and ovarian Mean age patients ranged 52.6 to 68 years Included studies: *Bakitas 2009* *Jordhoy 2001* *Ozcelik 2014* *Temel 2010* *Zimmermann 2014* *Bischoff 2013* *Cohen 2001* *Echteld 2007* *Yamagishi 2014* *Melin-Johansson 2010* *Stomgren 2005*	Specialised palliative care	4 RCT reported as usual care, 1 RCT no information		All studies with the exception of one RCT, showed some evidence of improvement of HRQoL in the intervention compared to the control arm. • lower symptom intensity overall, specifically on pain, fatigue and nausea • improvements in symptoms of depression, mood, anxiety and spiritual well being • Those who received SPC were more likely to die at home and be more satisfied with care • 2 studies also reporting a positive impact on survival The included RCTs were homogeneous to be analyzed with fixed-effects models (Q =8.22, p =0.084, I2 = 51.32%) but there was heterogeneity in non-RCTs (Q = 34.889, p <0.001, I2 = 85.67%). There was a positive moderate impact of SPC in HRQoL (SMD, 0.28; 95% CI, 0.16 to 0.41; p < 0.001) There were non-significant differences on the impact of SPC on HRQoL between RCTs and non-RCTs (p =0.990), types of cancer (p = 0.627), and between inpatients, outpatients, and both (p = 0.172). However, mixed-effects analysis showed that SPC had a positive impact in studies using inpatients (SMD, 0.55; 95% CI, 0.17 to 0.92; p = 0.004) or both (SMD, 0.18; 95% CI, 0.08 to 0.27; p < 0.001) but non-significant effect for outpatients (SMD, 0.20; 95% CI, − 0.03 to 0.44; p =0.89) **Authors conclusion**: The methodological problems and publication bias call for higher-quality studies to be designed, funded, and published. However, there is a clear message that SPC is multi-disciplinary and aims at palliation of symptoms and burden in line with current recommendations.	

Evidence Table : **Effectiveness – team based model of care**
Question **: Is palliative care intervention effective in improving quality of life of patient with chronic life-limiting illness?**

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comment
3.Health Quality Ontario. Team-based models for end-of-life care: An evidence-based analysis. Not Health Techno Assess Seer 2014;14(20):1–49	**Health Technology Assessment** **Objective** to determine whether an optimal team-based model of care exists for service delivery at end of life. **Methods** HTA was conducted to investigate 4 core elements of team-based care delivery- team membership, services provided, setting, and mode of patient contact **Inclusion criteria** Systematic reviews (SRs) with meta-analyses, randomized controlled trials (RCTs), published between January 1, 2000 and October 14, 2013,adults (aged 18 years and over) with advanced disease, study populations comprising at least 90% adults, team-based models of care which include at least 2 different professional services **Exclusion criteria** non-randomized controlled trials, observational studies, case reports, editorials, letters, comments, conference abstracts, children (under 18 years of age) **Quality assessment** The Assessment of Multiple Systematic Reviews (AMSTAR) measurement tool was used. Quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria **Outcomes measures** patient quality of life, patient symptom management, patient satisfaction, informal caregiver satisfaction, health care provider satisfaction, number of emergency department visits, number of hospital admissions, number of admissions to the intensive care unit, hospital length of stay, place of death	I	12 included; 2 SR, 10 RCTs *SRs* Gomes et al 2013 Higginson et al 2003 *RCTs* Cheung et al, 2010 Gide et al, 2008 Hanks et al 2002 Ahronheim et al, 2000 Brumley et al, 2007 Aiken et al, 2006 Mitchell et al 2008 Jordhoy et al 2000 Zimmermann et al 2014 Temel et al 2010 Type of models: evaluated 6 team-based models of care: • hospital, direct contact • home, direct contact • home, indirect contact • comprehensive, indirect contact • comprehensive, direct contact • comprehensive, direct, and early contact	Direct contact =when team members see the patient; indirect contact =when they advise another health care practitioner (e.g., a family doctor) who sees the patient. Comprehensive model is one that provides continuity of service across inpatient and outpatient settings, e.g., in hospital and then at home. A minimum core membership included a physician and nurse, at least one of whom was specialized in end-of-life health care	usual-care group= received multidisciplinary care mostly on an ad hoc basis, uncoordinated, without End of Life care consultations e.g. ICU care, hospital care		Comprehensive Team-Based Model moderate-quality evidence found CTM with direct contact with patient significantly improves patient QOL, symptom management, and patient and informal caregiver satisfaction; -increases the patient's likelihood of dying at home; -decreases the patient's likelihood of dying in a nursing home -has no impact on hospital admissions or hospital length of stay Hospital Team-Based Model -moderate-quality evidence that a hospital team-based model with direct patient contact has no impact on length of hospital stay. -low-quality evidence that this model significantly reduces ICU admissions Home Team-Based Model -low-quality evidence that a home team-based model with direct patient contact: -significantly increases patient satisfaction, and increases the patient's likelihood of dying at home -significantly decreases emergency department visits and hospital admissions **Authors conclusio**n: Moderate-quality evidence shows that a comprehensive, direct-contact, team-based model of care provides the following benefits for end-of-life patients with an estimated survival of up to 9 months: it improves caregiver satisfaction and increases the odds of dying at home while decreasing the odds of dying in a nursing home. Moderate-quality evidence also shows that improvement in patient quality of life, symptom management, and patient satisfaction occur when end-of-life care via this model is provided early (up to 24 months before death). However, using this model to deliver end-of-life care does not impact hospital admissions or hospital length of stay. Team membership includes at minimum a physician and nurse, with at least one having specialist training and/or experience in end-of-life care. Team services include symptom management, psychosocial care, development of patient care plans, end-of-life care planning, and coordination of care.	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments

4.Singer AE, Goebel JR, Kim YS et al. Populations and Interventions for Palliative and End-of-Life Care: A Systematic Review. J Palliat Med 2016;19(9):995–1008	**Systematic review**
	
	Objective
	to identify (1) individuals appropriate for palliative care and (2) elements of health service interventions (personnel involved, use of multidisciplinary teams, and settings of care) effective in achieving better outcomes for patients, caregivers, and the healthcare system
	
	Methods
	Systematic searches of MEDLINE, EMBASE, PsycINFO, Web of Science, and Cochrane Database of Systematic Reviews databases
	
	Inclusion criteria
	• RCTs
	• Adults ≥18 years old with advanced illness, and/or their caregivers
	• Cancer, heart failure and other cardiac conditions, chronic pulmonary disease, dementia and other neuro- logical conditions, end-stage liver disease, or end-stage renal disease, or any advanced illness populations receiving palliative care, hospice, or end-of-life care
	
	Exclusion criteria
	• non-English publications
	• studies with only qualitative data
	• studies of economic outcomes only
	• studies of drugs, devices, or technical care if they were not part of a health service intervention
	• studies of only support groups or psychological interventions unless they addressed an aspect of health service delivery
	
	Quality assessment
	For bias assessed using a Cochrane risk of bias tool modified
	
	Outcomes measures
	Quality of life
		I	124 RCTs included
			
			Majority of studies in cancer (49%, 38 of 77 studies) demonstrated statistically significant patient or caregiver outcomes (e.g., p < 0.05), as did those in congestive heart failure (CHF) (62%, 13 of 21), chronic obstructive pulmonary disease (COPD; 58%, 11 of 19), and dementia (60%, 15 of 25)
				Intervention elements:
				• Palliative care team
				
				  -Inpatient consultation
				  -Outpatient consultation
				• Hospice
				
				• Case management
				
				• Decision support
				
				• Family meetings
				
				• Advance directive completion
				
				-intervention personnel
				-multidisciplinary teams
				-intervention settings
				-supporting technology
							Most interventions included a nurse (70%, 69 of 98), and many were nurse-only (39%, 27 of 69). Social workers were well represented, and home-based approaches were common (56%, 70 of 124).
							
							Home interventions with visits were more effective than those without (64%, 28 of 44; vs. 46%, 12 of 26).
							
							Interventions improved communication and care planning (70%, 12 of 18), psychosocial health (36%, 12 of 33, for depressive symptoms; 41%, 9 of 22, for anxiety), and patient (40%, 8 of 20) and caregiver experiences (63%, 5 of 8).
							
							Many interventions reduced hospital use (65%, 11 of 17), but most other economic outcomes, including costs, were poorly characterized.
							
							Palliative care teams did not reliably lower healthcare costs (20%, 2 of 10)
							
							Authors conclusion:
							Palliative care improves cancer, CHF, COPD, and dementia outcomes.
							
							Effective models include nurses, social workers, and home-based components, and a focus on communication, psychosocial support, and the patient or caregiver experience.
							
							High-quality research on intervention costs and cost outcomes in palliative care is limited.	

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5.Phongtankuel V, Meador L, Adelman RD et al. Multicomponent Palliative Care Interventions in Advanced Chronic Diseases: A Systematic Review. Am J Hosp Palliat Med. 2018;35(1):173–83.	**Systematic review** **Objective**: to (1) describe the delivery of multicomponent palliative care (PC) interventions (2) characterize the disciplines delivering care (3) identify the components being implemented (4) analyze whether the number of disciplines or components being implemented are associated with positive outcomes (e.g. quality of life, pain) **Inclusion criteria**: English- language articles analysing multicomponent palliative care interventions in patients with cancer, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and end-stage renal disease (ESRD) **Exclusion criteria** • Any palliative care intervention that did not specify employing at least 2 of PC components • studies that enrolled patients with a prognosis of 6 months or less or were receiving hospice care **Outcomes Measured**: Delivery of palliative interventions by discipline, components of palliative care implemented, and number of positive outcomes (e.g., pain, quality of life) **Tools used**: Medical Outcomes Study 36 Short Form; European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30); Spitzer Quality of Life Uniscale; the Functional Assessment of Cancer Therapy-General (FACT-G) scale	I	Included 71 articles 64 multicomponent palliative care interventions Most interventions studied were conducted either in the United States or in Europe Most studies were RCTs and observational studies Interventions were conducted in various settings, including outpatient (33%), inpatient (17%), home (16%), and mixed (34%) venues Of the 64 interventions, 24 (38%) incorporated caregivers and/ or families and 24 (38%) explicitly reported communication between the palliative care provider and the primary physician/ team. Mean age of participants in this subgroup of studies was 65.4 years (range: 51-81) 71 articles included; *McCorkle 1989,Ellershaw 1995 Jordhoy, 2000, 2001,Given 2002 Corner, 2003,Jack 2003, Ahlner-Elmqvist 2004, Elsayem,2004, Meyers,2004,Strasser,2004,Northouse,2 005,Stromgren,2005,Rummans,2006,No rthouse,2007,Borneman,2008,Seow,200 8,Bakitas,2009,Maloney, 2012,Follwell 2009,Temel2010,2011,Greer,2011,Pirl,2 012, Meyers 2011, Colombet, 2012 Dyar 2012, Serfaty 2012,Tucarodriguez 012 Wallen 2012, Yennurajalingam 2012 Chasen2013,Daly, 2013 Kao, 2013, Koczywas, 2013 Morita, 2013,Nakau, 2013 Northouse, 2013,Young 2013, Zhang, 2013 Ozcelik, 2014, Paris, 2014, Sun, 2014, Zimmermann, 2014,Bakitas2015 Clark, 2015,Ferrell, 2015 McCorkle, 2015,Rabow, 2015,Rocque 2015 Pattenden, 2012,Schwarz 2012,Brannstrom, 2014 Bekelman, 2014, Bekelman, 2015, Liljeroos, 2015 Sahlen, 2015 Sidebottom, 2015, Horton, 2013 Buckingham, 2015 Weisbord, 2003 ,Chan, 2015 Brumley 2003,Enguidanos 2005,Rabow 2003, 2004 Aiken, 2006, Engelhardt, 2006,Brumley, 2007, Abernethy 2013, Seow 2014*	Multicomponent intervention included 2 or more of the following domains: I.Symptom management ii.psychological support/ counseling iii.spiritual/ existential support iv.advanced care planning v.education of illness or disease vi.care coordination vii.bereavement services			Nurses (n= 64, 88%) were most often involved in delivering care, followed by physicians (n= 43, 67%), social workers (n= 33, 52%), and chaplains (n=19, 30%). The most common palliative care components patients received were symptom management (88%), psychological support / counselling (81%), and disease education (75%), care coordination (50%), advanced care planning (45%), spiritual/existential support (33%), and bereavement services (9%) Total number of components delivered as part of each intervention varied considerably, with 5 (8%) interventions employing 2 components, 30 (47%) employing 3, 11 (17%) employing 4, 11 (17%) employing 5, 4 (6%) employing 6, and 3 (5%) interventions incorporating all 7 components of palliative care The regression of quality of life on number of disciplines is significant (p=0.05), adjusting for number of components. This result is owing solely to the involvement of a physician (the proportion of successful studies is 0.31 when no physician, 0.65 when there is one) and or a physical/occupational therapist (the proportion of successful studies is 0.40 when no physical/occupational therapist, 0.82 when there is one) Statistical analysis did not uncover an association between number of disciplines or components and positive outcomes. **Authors' Conclusions:** Important aspects require additional study such as better inclusion of key groups (e.g., chronic obstructive pulmonary disease, end-stage renal disease, minorities, older adults); incorporating core components of palliative care (e.g., interdisciplinary team, integrating caregivers, providing spiritual support); and developing ways to evaluate the effectiveness of interventions that can be readily replicated and disseminated.	

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6.Vanbutsele G, Pardon K, Van Belle S et al. Effect of early and systematic integration of palliative care in patients with advanced cancer: a randomised controlled trial. Lancet Oncol. 2018;19(3):394–404 Location: Ghent University Hospital (Flanders, Belgium)	**Randomised controlled trial – non-blinded** **Objective** To examine whether early and systematic integration of palliative care alongside standard psychosocial oncological care provides added benefit compared with usual care **Methods** Conducted non-blinded, RCT Eligible patients were 18 years or older, and had an advanced cancer diagnosis (histologically or cytologically confirmed) due to a solid tumour, a European Cooperative Oncology Group performance status of 0–2, an estimated life expectancy of 12 months (assessed by the treating oncologist), were within the first 12 weeks of a new primary tumour or had a diagnosis of progression, and were able to read and respond to questions in Dutch. Patients were randomly assigned (1:1), by block design using a computer-generated sequence, either to early and systematic integration of palliative care into oncological care, or standard oncological care alone in a setting where all patients are offered multidisciplinary oncology care by medical specialists, psychologists, social workers, dieticians, and specialist nurses **Outcomes measures** Primary endpoint: change in global health status/quality of life scale assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC QLQ C30) at 12 weeks. McGill Quality of Life Questionnaire (MQOL), which includes the additional existential wellbeing dimension, was also used	I	468 patients for eligibility - 186 were enrolled and randomly assigned to the early and systematic palliative care group (92 patients) or the standard oncological care group (94)	Early and systematic integration of PC • first consultation with a specialised palliative care nurse within 3 weeks of enrolment • consisted of four major components I. Training sessions by oncologists to inform palliative care nurses and the physician about cancer treatments typically administered early in the disease trajectory, and their associated side-effects ii.Semi-structured monthly palliative care consultations by palliative care nurses allowed for individualised patient care iii.Monthly symptom assessments using Edmonton Symptom Assessment Scale (ESAS) by palliative care nurses iv. Integration of palliative care into oncological care through the participation of the palliative care nurses in the weekly multidisciplinary oncology meetings and their reporting in the electronic patient file	Standard psychosocial oncology care provided by a multidisciplinary team, including oncologists, other medical specialists, psychologists, social workers, dieticians, and specialist nurses	12 weeks	Overall <u>quality of life score</u> at 12 weeks: -by the EORTC QLQ C30, was 54.39 (95% CI 49.23–59.56) in the standard oncological care group versus 61.98 (57.02–66.95) in the early and systematic palliative care group (difference 7.60 [95% CI 0.59–14.60]; p=0.03) -by the MQOL Single Item Scale, 5.94 (95% CI 5.50–6.39) in the standard oncological care group versus 7.05 (6.59–7.50) in the early and systematic palliative care group (difference 1.11 [95% CI 0.49–1.73]; p=0.0006) **Authors conclusion**: The findings of this study show that a model of early and systematic integration of palliative care in oncological care increases the quality of life of patients with advanced cancer. Our findings also show that early and systematic integration of palliative care is more beneficial for patients with advanced cancer than palliative care consultations offered on demand, even when psychosocial support has already been offered. Through integration of care, oncologists and specialised palliative care teams should work together to enhance the quality of life of patients with advanced cancer	

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7.Haun MW, Estel S, Rücker G et al. Early palliative care for adults with advanced cancer (Review). Cochrane Database Syst Rev. 2017;(6):1–105.	**Systematic review and meta-analysis** **Objective** To compare effects of early palliative care interventions versus treatment as usual/ standard cancer care on health-related quality of life, depression, symptom intensity, and survival among adults with a diagnosis of advanced cancer **Inclusion criteria** Randomised controlled trials (RCTs) and cluster-randomised controlled trials on professional palliative care services that provided or co-ordinated comprehensive care for adults at early advanced stages of cancer **Quality assessment** using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions **Outcomes measures** <u>Primary outcomes</u>: health-related quality of life, survival (death hazard ratio), depression, and symptom intensity <u>Secondary outcomes</u>: Caregiver burden, Supportive Care Needs Survey for Partners & Caregivers (SCNS-P&C), BDI, HAM-D, PHQ-9, or CES-D), Healthcare utilisation (e.g. measured as length of hospital stay in days, number of outpatient attendances, direct or indirect medical resource use) as an economic outcome. Harms / adverse events (measured as the binary outcome "Any adverse event: yes/no"	I	7 randomised and cluster-randomised controlled trials that together recruited 1614 participants 4 studies evaluated interventions delivered by specialised palliative care teams, and the remaining studies assessed models of co-ordinated care Included studies *Bakitas 2009* *Bakitas 2015* *Maltoni 2016* *McCorkle 2015* *Tattersall 2014* *Temel 2010* *Zimmermann 2014*	All types of professional palliative care services that provided or coordinated comprehensive care for patients at early advanced stages of cancer	Usual/standard care		Overall, risk of bias at the study level was mostly low, apart from possible selection bias in 3 studies and attrition bias in one study, along with insufficient information on blinding of participants and outcome assessment in 6 studies. <u>HRQOL</u> Compared with usual/standard cancer care alone, early palliative care significantly improved health-related quality of life at a small effect size (SMD 0.27, 95% confidence interval (CI) 0.15 to 0.38; participants analysed at post treatment = 1028; evidence of low certainty). As re-expressed in natural units (absolute change in Functional Assessment of Cancer Therapy-General (FACT-G) score), health-related quality of life scores increased on average by 4.59 (95% CI 2.55 to 6.46) points more among participants given early palliative care than among control participants. <u>Survival</u> 4 studies enrolling a total of 800 participants, did not indicate differences in efficacy (death hazard ratio 0.85, 95% CI 0.56 to 1.28; evidence of very low certainty). Levels of <u>depressive symptoms</u> among those receiving early palliative care did not differ significantly from levels among those receiving usual/standard cancer care (five studies; SMD -0.11, 95% CI -0.26 to 0.03; participants analysed at post treatment = 762; evidence of very low certainty). Results from 7 studies that analysed 1054 participants post treatment suggest a small effect for significantly <u>lower symptom intensity</u> in early palliative care compared with the control condition (SMD -0.23, 95% CI -0.35 to -0.10; evidence of low certainty). The type of model used to provide early palliative care did not affect study results. One RCT reported potential adverse events of early palliative care, such as a higher percentage of participants with severe scores for pain and poor appetite; the remaining 6 studies did not report adverse events in study publications. For these six studies, principal investigators stated upon request that they had not observed any adverse events **Authors conclusion**: 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. Although we found only small effect sizes, these may be clinically relevant at an advanced disease stage with limited prognosis, at which time further decline in quality of life is very common. Effects on mortality and depression are uncertain. Current results needed to be interpreted with caution owing to very low to low certainty of current evidence and between-study differences regarding participant populations, interventions, and methods. In perspective, early palliative care is a newly emerging field, and well-conducted studies are needed to explicitly describe the components of early palliative care and control treatments, after blinding of participants and outcome assessors, and to report on possible adverse events	

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8.Agboola SO, Ju W, Elfiky A, Kvedar JC, Jethwani K. The effect of technology-based interventions on pain, depression, and quality of life in patients with cancer: A systematic review of randomized controlled trials. J Med Internet Res. 2015;17(3):1–14.	**Systematic review and meta-analysis** **Objective** To systematically assess the literature for the effect of supportive telehealth interventions on pain, depression, and quality of life in cancer patients **Methods** Searched PubMed, EMBASE, Google Scholar, CINAHL, and PsycINFO in July 2013 and updated the literature search again in January 2015 **Inclusion criteria** Prospective randomized trials evaluating the effect of telehealth interventions in cancer care with pain, depression, **Quality assessment** Cochrane Collaboration risk of bias tool **Outcomes measures** quality of life pain depression	I	20 RCTs studies included Included studies Kim, 2013, Rustoen, 2013, Kroenke, 2010, Badger, 2013, Borosund, 2014, Duffecy, 2013, Gotay 2007, Lepore, 2014, Livingston 2010, Marcus 2010, Stanton 2013, Freeman 2014, Harrison 2011, Hawkins 2010, Loprinzi, 2011, Nelson 2008, Park 2012 Ryhanen, 2013, Sandgren, 2007 Sherman 2012	Telehealth interventions-telephone based, web based systems, store-and-forward video-recorded sessions Involving professional interventionist (nurses, psychologists, or counsellors) trained to provide counselling, or peer counsellors who are cancer survivors, or utilized automated voice response in conjunction with life-support personnel	Usual care/standard care • treatment of specific cancer • waiting-list control • oral and written education materials • standard internet standard group (ISG) • internet training and access	1 week to 12 months	Studies were largely heterogeneous in the type and duration of the intervention as well as in outcome assessments. Majority of the studies were telephone-based interventions that remotely connected patients with their health care provider or health coach. Most of the studies had low risk of bias but most of the studies had insufficient information about the allocation concealment domain. 2 of 3 studies focused on pain control reported significant effects of the intervention; 4 of 9 studies focus on depression reported significant effects, while only the studies that were focused on quality of life reported significant effects **Authors conclusion**: Telehealth interventions have potential in improving outcomes in cancer care. However, more high-quality large-sized trials are needed to demonstrate evidence of its effectiveness	

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9.Larson JL, Rosen AB, Wilson FA. The Effect of Telehealth Interventions on Quality of Life of Cancer Patients: A Systematic Review and Meta-Analysis. Telemed e-Health 2017;24(6):tmj.2017.011	**Systematic review and meta-analysis** **Objective** To determine the benefits of telehealth-based interventions providing emotional and symptom support in improving quality of life (QOL) among cancer patients **Methods** Conducted systematic review and meta-analysis **Inclusion criteria** Articles included: -must have been published in a peer-reviewed journal -patients must have had any form of cancer and been undergoing active treatment; -adults, 18 years of age or older; -interventions must have used some form of telehealth/ telemedicine, including, but not limited to telephone calls and/ or Web-based interventions; -the focus of each intervention must have been on emotional support or self-management of symptoms through counselling, educational intervention, or telepsychiatry; - used a measurable QOL scale or questionnaire **Exclusion criteria** -written in a language other than English -included paediatric patients; -assessed the efficacy of palliative care -combined in-person and telehealth in the same intervention. **Quality assessment** Not mentioned **Outcomes measures** Quality of life	I	9 studies included Type of studies: 5 of 9 articles used telephone-based interventions 3 studies used Web-based designs or changes in QOL overall 1 utilized video-conferencing 5 articles focused on specific cancers-colorectal, breast, and head and neck cancers, 3 included three or more types of cancer Mean age of the patients ranged from 53 to 67 years of age Included studies Harrison et al. 2011 Shepherd et al. 2006 Ryhänen et al. 2012 Chumbler et al. 2007 Sandgren & McCaul 2003 Hegel et al. 2011 Pfeifer et al. 2015 Berry et al. 2013 Ruland et al. 2013	Telehealth/telemedicine telephone-based interventions, Web-based designs, video-conferencing	Usual care	6 weeks to 1 year	5 of 9 articles used telephone-based interventions 3 studies used Web-based designs or changes in QOL overall 1 utilized video-conferencing Both telehealth (Hedges g = 0.211, p=0.016) and standard of care (Hedges g = 0.217, p < 0.001) cancer treatment delivery methods demonstrated small, but statistically significant improvements in QOL measures. However, there were no statistically significant differences in effectiveness between the telehealth interventions and UC (p =0.76). **Authors conclusion**: Telehealth interventions are as effective at improving QOL scores in patients undergoing cancer treatment as in-person UC. Further studies should be undertaken on different modalities of telehealth to determine its appropriate and effective use in interventions to improve the QOL for cancer patients undergoing treatment	

Evidence Table : **Effectiveness & Economic evaluation – Home palliative care services**
Question : **Is palliative care intervention cost-effective in improving quality of life of patient with chronic life-limiting illness?**

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
10.Gomes B, Calanzani N, Curiale V, McCrone P. P, Higginson IJ, Brito M de. Effectiveness and cost-effectiveness of home palliative care services for adults with advanced illness and their caregivers. Cochrane Database Syst Rev. 2013;(6)	**Systematic review and meta-analysis** **Objective** 1. to quantify the effect of home palliative care services for adult patients with advanced illness and their family caregivers on patients' odds of dying at home; 2. to examine the clinical effectiveness of home palliative care services on other outcomes for patients and their caregivers such as symptom control, quality of life, caregiver distress and satisfaction with care; 3. To compare the resource use and costs associated with these services; 4. To critically appraise and summarize the current evidence on cost-effectiveness. **Methods** 29 relevant systematic reviews, four key textbooks and recent conference abstracts. • carried out meta-analysis where appropriate and calculated numbers needed to treat to benefit (NNTBs) for the primary outcome (death at home) **Inclusion criteria** • Age above 18 years old • randomised controlled trials (RCTs), controlled clinical trials (CCTs), controlled before and after studies (CBAs) and interrupted time series (ITSs) • evaluating the impact of home palliative care services on outcomes for adults with advanced illness or their family caregivers, or both **Exclusion criteria** • Interventions that did not directly deliver care to patients or care- givers were excluded • Services delivered in skilled nursing facilities, day care centres, residential homes or prisons were excluded • interventions delivering only one component of palliative care (not holistic nature of palliative care) **Outcomes measures** Death at home, time the patient spent at home satisfaction with care Symptoms control Quality of life caregiver pre- and post-bereavement outcomes Economic impact	I	23 studies (16 RCTs, 6 of high quality), including 37,561participants and 4042 family caregivers, largely with advanced cancer but also congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), HIV/AIDS and multiple sclerosis (MS), among other conditions. <u>23 Studies on effectiveness;</u> Ahlner-Elmqvist 2008, Aiken 2006, Axelsson 1998, Bakitas 2009, Brumley 2007, Buckingham 1978, Grande 1999, Greer 1986, Gómez-Batiste 2010, Harding 2004, Higginson 2009, Hudson 2005, Hughes 1992, Jordhøy 2000, McCorkle 1989, McKegney 1981, McMillan 2007, McWhinney 1994, Rabow 2004, Tramarin 1992, Walsh 2007, Ward 1987, Zimmer 1985 <u>6 Studies on economic evaluation;</u> Brumley 2007, Higginson 2009, Zimmer 1985, Hughes 1992, Tramarin 1992, Greer 1986	Home based palliative care i) specialist palliative/hospice care was defined as health and social care provided by: a) one or more doctors who have undergone higher specialist training in palliative medicine, and b) one or more nurses who have undergone higher specialist training, and c) one or more professionals attached to the team from a profession allied to medicine who have had further training in palliative care. Also professionals from differing clinical disciplines working full- time or most of the time in palliative/hospice care, who have not undergone any higher specialist training	usual care, which could include community care (primary or specialist care at home and in nursing homes), hospital care (inpatient and outpatient) and in some instances palliative or hospice care (or both)		4 studies found significantly better outcomes with the intervention (increased probability of death at home and participant's ability to stay at home as long as wanted, reduced probability of death in hospital, decreased symptom burden, pain and caregiver burden, higher satisfaction with care and better quality of death). Meta-analysis showed increased odds of dying at home (odds ratio (OR) 2.21, 95% CI 1.31 to 3.71; Z = 2.98, P value = 0.003; Chi2 = 20.57, degrees of freedom (df) = 6, P value = 0.002; I^2 = 71%; NNTB 5, 95% CI 3 to 14 (seven trials with 1222 participants, three of high quality)). In addition, evidence of small but statistically significant beneficial effects of home palliative care services compared to usual care on reducing symptom burden for patients (three trials, two of high quality, and one CBA with 2107 participants) and of no effect on caregiver grief (three RCTs, two of high quality, and one CBA with 2113 caregivers). Evidence on cost-effectiveness (six studies) is inconclusive. 6 studies (five RCTs and one CBA including 2047 patients and 1678 caregivers, all considered high quality economic evaluations) compared the impact on the total care costs of receiving home palliative care as opposed to usual care, alongside an evaluation of clinical effectiveness. Together, the RCTs analysed data related to 590 patients (samples ranged from 33 to 297 patients), adding to 1754 patients in Greer 1986. All studies measured institutional and non-institutional costs, 3 included medication costs and 1 calculated the costs associated with informal care. Studies reported lower costs in the intervention groups with differences ranging from 18% to 35% except Greer 1986 where the costs under the hospital-based intervention were 2% lower than conventional care as opposed to 32% lower under the community-based intervention. Notwithstanding, differences were statistically significant only in Brumley 2007. **Authors conclusion**: The results provide clear and reliable evidence that home palliative care increases the chance of dying at home and reduces symptom burden in particular for patients with cancer, without impacting on caregiver grief. This justifies providing home palliative care for patients who wish to die at home. More work is needed to study cost-effectiveness especially for people with non-malignant conditions, assessing place of death and appropriate outcomes that are sensitive to change and valid in these populations, and to compare different models of home palliative care, in powered studies.	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comment
11.Wiffen PJ, Wee B, Derry S, Rf B, Ra M. Opioids for cancer pain - an overview of Cochrane reviews. 2017;(7) Cochrane review	**Systematic review** **Objective** To provide an overview of the analgesic efficacy of opioids in cancer pain, and to report on adverse events associated with their use **Methods** Conducted systematic reviews examining any opioid for cancer pain published to 4 May 2017 in the Cochrane Database of Systematic Reviews in the Cochrane Library **Inclusion criteria** all Cochrane Reviews of randomised, controlled trials (RCTs) of opioid drugs for the treatment of cancer pain in adults **Quality assessment** Used Assessment of Multiple Systematic Review (AMSTAR), GRADE for overall quality of evidence **Outcomes measures** 1. Proportion of participants reporting no worse than mild pain on treatment by 14 days after start of treatment. 2. Patient Global Impression of Change (PGIC) of much or very much improved. 3. Withdrawals due to adverse events	I	9 Cochrane studies included (152 included studies and 13,524 adults participants) All Cochrane reviews are of good quality: • Bao 2016: Hydromorphone - outcome not determined or poorly reported in studies; very low quality. • Nicholson 2017: Methadone - limited data poorly reported in studies; very low quality • Schmidt-Hansen 2015a: Oxycodone - scores given were average pain, but most participants appeared to have achieved no worse than mild pain; very low quality. • Schmidt-Hansen 2015b: Buprenorphine - outcome not assessed; very low quality • Straube 2014: Codeine - outcome not determined or poorly reported in studies; very low quality • Wiffen 2015: Tapentadol - outcome not determined or poorly reported in studies • Wiffen 2017c: Tramadol - outcome not determined or poorly reported in studies; very low quality	opioid drugs: buprenorphine, codeine, fentanyl hydrocodone, hydromorphone, methadone, morphine, oxycodone, tramadol, tapentadol Various routes of administration of opioids were considered; oral with most opioids, transdermal administration with fentanyl, and buprenorphine No subcutaneous opioid administration	Compared with either a different formulation of the same opioid, or a different opioid; or placebo control		Most participants had moderate or severe pain associated with a range of different types of cancer Pain outcomes reported were varied and inconsistent. -Studies of older opioids, such as codeine, morphine, and methadone, had low average study sizes while those involving newer drugs tended to have larger study sizes. -Reviews on buprenorphine, codeine with or without paracetamol, hydromorphone, methadone, tramadol with or without paracetamol, tapentadol, and oxycodone did not have information about the primary outcome of mild or no pain at 14 days, although that on oxycodone indicated that average pain scores were within that range. -Only two reviews reported on more than 200 events (Hadley 2013; Wiffen 2016). Both showed that when doses were titrated to effect, 96% of participants achieved no worse than mild pain. -Hadley 2013: Tansdermal fentanyl - 461/479 (96%); -Wiffen 2016: Oral morphine - 362/377 (96%) 5 reviews included PGIC as an outcome (Hadley 2013; Schmidt-Hansen 2015b; Straube 2014; Wiffen 2015; Wiffen 2017c). None was able to determine this outcome from any of the included studies Adverse event withdrawal was reported by 5 reviews, at rates of between 6% (oral morphine). and 19% (oral oxycodone). Participants with at least 1 adverse event were reported by 3 reviews, at rates of between 11% and 77% **Authors conclusion:** The amount and quality of evidence around the use of opioids for treating cancer pain is low -evidence indicates that around 95% of people with moderate or severe pain should be able to titrate to no or only mild pain within 14 days -Oral morphine remains the gold standard for treating moderate to severe cancer pain - first line treatment in guidelines and textbooks -Oxycodone (major opioid in the USA) offers similar levels of pain relief and overall adverse events to other strong opioids including morphine -Fentanyl as a transdermal patch is widely used in higher income countries and may cause less constipation than oral opioids. -Codeine has no proven role from clinical trial data in treating cancer pain -Most people will experience adverse events, and help may be needed to manage the more common undesirable adverse effects such as constipation and nausea. -Perhaps between 1 in 10 and 2 in 10 people treated with opioids will find these adverse events intolerable	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comment
12.Rich SE, Chow R, Raman S et al. Update of the systematic review of palliative radiation therapy fractionation for bone metastases. Radiother Oncol 2018	**Systematic review** **Objective** To update the previous meta-analyses of randomized trials comparing single fraction to multiple fractions of radiation therapy in patients with uncomplicated bone metastases **Methods** 10 new randomized trials were identified since 2010, five with adequate and appropriate data for inclusion, resulting in a total of 29 trials that were analyzed. Search terms were similar to prior meta-analyses Forest plots based on each study's odds ratios were computed using a random effects model and the Mantel–Haenszel statistic **Inclusion criteria** All published reports, with both full and abstract publications, from randomized trials comparing single fraction and multiple fraction schedules for the treatment of uncomplicated painful bone metastases with radiation therapy Only trials using conventional external beam radiation therapy for palliation of uncomplicated bone metastases **Exclusion criteria** Studies of stereo-tactic radiation therapy, studies related to the treatment of oligometastases, studies of retreatment of bone metastases, or studies of complicated bone metastases **Quality assessment** Not mentioned **Outcomes measures** Primary outcomes complete response and overall response rates as reported and defined by the identified trials. Secondary outcomes Re-treatment rates, pathological fracture rates, and acute toxicities	I	In total, 26 randomized trials about bone metastases were included in the calculation of overall response rates Only 5 included in meta-analysis Majority of patients had prostate or breast cancer in most of the trials studied Included studies Price et al Cole et al Kagel et al Gaze et al Nielson et al Foro et al Koswig & Budach Bone Party Trial Working Party Kirkbride et al Ozsaran et al Altundag et al Sarkar et al Badzio et al Van der Linden et al Hartsell et al Roos et al El-Shenshawy et al Hamouda et al Safwat et al Foro Arnalot et al Amouzegar-Hashemi et al Majumder et al Malik et al El Hawwari et al Gutierrez et al Anter et al	Single fraction radiotherapy	Multiple fraction		26 randomized trials about bone metastases were included in the calculation of overall response rates. In intention-to-treat analysis, 3059 patients were included in the single fraction arm and 3040 patients in the multiple fraction arm Overall response rate was similar in patients for single fraction treatments (61%; 1867/3059) and those for multiple fraction treatments (62%; 1890/3040). For each study, odds ratios ranged from 0.84 to 1.08 with a pooled odds ratio of 0.98 (95% confidence interval 0.95–1.01) 21 trials provided information regarding complete response, with 2802 patients in the single fraction arm and 2783 patients in the multiple fraction arm, 23% (645/2802) and 24% (660/2783) of patients in these arms had a complete response. OR varied 0.52–1.86 and the pooled odds ratio was 0.97 (95% confidence interval 0.89–1.06). Re-treatment was significantly more frequent in the single fraction treatment arm, with 20% receiving additional treatment to the same site versus 8% in the multiple fraction treatment arm (p < 0.01). No significant difference was seen in the risk of pathological fracture at the treatment site, rate of spinal cord compression at the index site, or in the rate of acute toxicity **Authors conclusion**: Single fraction and multiple fraction radiation treatment regimens continue to demonstrate similar outcomes in pain control and toxicities, but re-treatment is more common for single fraction treatment patients. Outcomes including overall response, complete response, and pathological fracture rates were similar for single fraction and multiple fraction radiation therapy for palliation of uncomplicated bone metastases, consistent with the prior meta-analyses Unlike the previous meta-analyses, a small but statistically significant difference in overall response rates, favouring multiple fraction radiotherapy (75% vs 72%, p = 0.01)	

Evidence Table : **Effectiveness –physical well-being-palliative pharmacological sedation**
Question : **Is palliative care intervention effective in improving physical well-being of patient with chronic life-limiting illness?**

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
13.Beller EM, van Driel ML, Mitchell G. Palliative pharmacological sedation for symptom relief in terminally ill adults. Cochrane Database Syst Rev 2012;(1). (Updated published in Issue 1, 2017)	**Systematic review** **Objective** To assess the evidence for the benefit of palliative pharmacological sedation on quality of life, survival, and specific refractory symptoms in terminally ill adults during their last few days of life **Methods** Searched the Cochrane Central Register of Controlled Trials, MEDLINE (1946 to November 2014), and EMBASE (1974 to December 2014), using search terms representing the sedative drug names and classes, disease stage, and study designs Meta-analyses were not done due to insufficient data for pooling on any outcome **Inclusion criteria** Randomised controlled trials (RCTs), quasi-RCTs, non-RCTs, and observational studies (e.g. before-and-after, interrupted- time-series) with quantitative outcomes **Exclusion criteria** studies with only qualitative outcomes or that had no comparison (i.e. no control group or no within-group comparison) (e.g. single arm case series). **Quality assessment** Cochrane 'Risk of bias' assessment tool **Outcomes measures** -Quality of life- measured by a proxy (e.g. doctor, nurse, carer), but in certain circumstances may have been measured by the person during periods of adequate consciousness -Control of specific symptom - Adverse effects of treatment	I	14 included studies, involving 4167 adults, of whom 1137 received palliative sedation More than 95% of people had cancer Settings: hospices, palliative care units, hospital oncology wards, and home-based palliative care Included studies: Alonso-Babarro 2010; Bulli 2007; Caraceni 2012; Chiu 2001; Fainsinger 1998; Kohara 2005; Maltoni 2009; Maltoni 2012b; Muller-Busch 2003; Radha Krishna 2012; Rietjens 2008; Stone 1997; Sykes 2003; Vitetta 2005	Any medication with a sedative effect (e.g. benzodiazepines, barbiturates, anaesthesia, opioids, antipsychotics, antihistamines, or other hypnotics) where the intention was sedation for symptom relief All 14 studies used midazolam, to achieve palliative sedation. Other drugs were haloperidol (eight studies) and chlorpromazine (5 studies). A small proportion of people received only opioids (morphine, fentanyl, and methadone), or propofol, other benzodiazepines (lorazepam, diazepam, clonazepam, flunitrazepam, and levomepromazine/ methotrimeprazine), antihistamines (promethazine and chlorphenamine), phenobarbital, scopolamine hydrobromide, or ketamine hydrochloride	No sedation		No studies were randomised or quasi-randomised. All were consecutive case series, with only three having prospective data collection. Risk of bias was high, due to lack of randomisation. No studies measured quality of life or participant well-being, which was the primary outcome of the review 5 studies measured <u>symptom control</u>, using four different methods, so pooling was not possible. -despite sedation, delirium and dyspnoea were still troublesome symptoms in these people in the last few days of life -Control of other symptoms appeared to be similar in sedated and non-sedated people. -Only 1 study measured unintended adverse effects of sedative drugs and found no major events; however, 4 of 70 participants appeared to have drug-induced delirium. - no respiratory suppression -13 of the 14 studies measured <u>survival time</u> from admission or referral to death, and all demonstrated no statistically significant difference between sedated and non-sedated groups **Authors' conclusion:** Insufficient evidence about the efficacy of palliative sedation in terms of a person's quality of life or symptom control -There was evidence that palliative sedation did not hasten death, which has been a concern of physicians and families in prescribing this treatment -However, this evidence comes from low quality studies, so should be interpreted with caution. -Further studies that specifically measure the efficacy and quality of life in sedated people, compared with non-sedated people, and quantify adverse effects are required.	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments

14.Payne C, Wiffen P, Martin S. Interventions for fatigue and weight loss in adults with advanced progressive illness: A Cochrane overview of systematic reviews. Palliat Med 2012;26(4):385.
 	
Cochrane reviews
	Systematic review
	
	Objective
	To conduct an overview of the evidence available on the efficacy of interventions used in the management of fatigue and/or unintentional weight loss in adults with advanced progressive illness
	
	Methods
	Searched the Cochrane Database of Systematic Reviews (CDSR) for all systematic reviews evaluating any interventions for the management of fatigue and/or unintentional weight loss in adults with advanced progressive illness (The Cochrane Library 2010, Issue 8)
	
	Adults 18 years or older with an advanced progressive illness known to have clinically significant fatigue and/or weight loss in the latter stages of illness.
	
	Inclusion criteria
	All Cochrane reviews that assessed the effects of an intervention on fatigue and/or unintentional weight loss in adults with advanced progressive illness
	
	Quality assessment
	AMSTAR (Assessment of Multiple Systematic Reviews) to assess the methodological quality of each systematic review
	
	Outcomes measures
	Primary outcomes:
	1.Clinically significant improvements in fatigue and/or unintentional weight loss.
	2.Improvements in quality of life of people who have fatigue and/or unintentional weight loss.
	3.Withdrawals due to adverse events
		I	27 systematic reviews (302 studies with 31,833 participants) in included
			
			Conditions include: multiple sclerosis, Parkinson's disease and dementia, irreversible organ failure, cancer with distant metastasis and acquired immune deficiency syndrome (AIDS).
			
			Included studies:
			Berenstein et al 2005, Bradley et al 2008, Conway et al 2008, Cramp et al 2008, Cruickshank et al 2008, Dal Bello-Haas et al 2008, Dewey et al 2007, Effing et al 2007, Farinotti et al 2007, Ferreira et al 2005, Goedendorp et al 2009, Cavenagh et al 2008, Johns et al 2005, Lacasse 2006, Langmore et al 2006, Mahlungulu et al 2007, Minton et al 2008, Nugent et al 2010, O'Brien et al 2004, O'Brien et al 2010, Pucci et al 2007, Rietberg et al 2004, Smyth & Walters 2007, Solà et al 2004, Steultjens et al 2003, Tejani et al 2010
				Any intervention primarily aimed at the management of fatigue and unintentional weight loss in advanced progressive illness was included. Interventions could have included pharmacological interventions, exercise, behavioural management, use of assistive devices, lifestyle management, nutritional support, complementary or alternative therapy and counselling.			None of the included systematic reviews reported quantitative data on the efficacy of interventions to manage fatigue or weight loss specific to people with advanced progressive illness.
							All of the included reviews apart from one were deemed of high methodological quality.
							
							<u>Management of fatigue</u>
							Amyotrophic lateral sclerosis/motor neuron disease (ALS/MND) - 1 systematic review (2 studies and 52 participants); studies too small
							
							Cancer - 5 systematic reviews (116 studies with 17,342 participants);
							-pharmacological interventions: eicosapentaenoic acid (EPA) and any drug therapy for the management of cancer-related fatigue
							  - 1 SR (51 studies, 10,296 participants) reported a small but significant improvement in fatigue over placebo with the psychostimulant drug methylphenidate
							  - No benefit over placebo was seen for fatigue with antidepressant drug paroxetine, nor with progestational steroids.
							-non-pharmacological interventions:
							  -exercise: 1 SR (28 studies, 2083 participants) supported the use of exercise
							   -psychosocial interventions: insufficient evidence
							
							Chronic obstructive pulmonary disease (COPD) -
							3 systematic reviews (59 studies and 4048 participants); the interventions: self-management education programmes, nutritional support and pulmonary rehabilitation.
							  - 1 Meta-analysis showed a statistically and clinically significant improvement in fatigue scores compared with conventional community care.
							  - 1 RCT (135 participants) showed a statistically significant improvement in fatigue at 12 months follow-up with a GP practice-based self-management education programme compared to usual care
							
							Cystic fibrosis - 1 systematic review (nine studies and 833 participants); physical training- None of the included studies independently assessed fatigue outcomes
							
							HIV/AIDS - 2 systematic reviews (21 studies and 748 participants); the interventions were progressive resistive exercise and aerobic exercise
							-1 included study (60 participants) found significant decreases in fatigue in exercisers compared to non- exercisers but the participants were not in the advanced stages of illness
							
							Multiple sclerosis (MS) - 5 systematic reviews (23 studies and 1502 participants);
							-pharmacological interventions:
							  -amantadine: 1 SR found small inconsistent improvements in fatigue
							  -carnitine: No conclusions could be drawn	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments

							-non-pharmacological interventions:
							- diet: insufficient evidence
							- exercise: No evidence found
							-occupational therapy: 2 lower-quality studies showed a small significant improvement in fatigue using energy conservation strategies but this observation was not corroborated by the higher-quality RCT
							
							Mixed conditions in advanced stages of illness – no evidence
							
							Management of weight loss
							ALS/MND – no evidence
							
							Cancer - 3 systematic reviews (66 studies and 5601 participants);
							-pharmacological interventions:
							  -megestrol acetate: cancer-specific studies (27 studies, 4148 participants) showed slight statistically significant weight gain for people with cancer vs placebo in 6 studies conducted over at least 6 weeks with 856 participants [risk ratio (RR) 1.86, 95% CI 1.31 to 2.63]
							  - eicosapentaenoic acid (EPA):insufficient evidence
							-non pharmacological interventions:
							  -In 1 included study of 96 people with non-small cell lung cancer receiving chemotherapy, nutritional intervention was effective in increasing caloric intake but had a limited effect on weight
							
							COPD - 1 systematic review (59 studies and 4048 participants);
							  -nutritional support: no statistically significant differences in weight between those receiving supplements and controls receiving a placebo, other active therapy or usual care
							
							Cystic fibrosis - 2 systematic reviews (three studies and 131 participants); None of the included studies examined the use of oral calorie supplements
							
							HIV/AIDS - 4 systematic reviews (42 studies and 2071 participants);
							-pharmacological intervention
							  -anabolic steroids: there was a statistically significant small increase in both lean body mass and body weight compared to placebo interventions
							-non-pharmacological interventions:
							  -nutritional interventions: Whilst macronutrient supplementation had a statistically significant impact on calorie intake as compared to no nutritional supplementation or placebo therapy, this did not result in a statistically significant body weight increase
							  -progressive resistive exercise: Although the included studies were small (24 to 61 participants) meta-analysis showed a statistically significant increase in body weight compared to non-exercising controls and also when the resistive exercise was combined with aerobic exercise interventions
							  -aerobic exercise: Meta-analyses demonstrated no difference in change in mean body weight for those undertaking aerobic exercise versus a non-exercising	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
							control group but advanced stage patients not included **MS - no evidence** **Mixed conditions in advanced stages of illness pharmacological interventions**: -megestrol acetate: 1 SR (34 studies 4826 participants) showed slight statistically significant weight gain specifically for people with cancer versus placebo -non-pharmacological interventions: nutrition- no evidence **Authors' conclusion**: Lack of robust evidence for interventions to manage fatigue and/or unintentional weight loss in the advanced stage of progressive illnesses such as advanced cancer, heart failure, lung failure, cystic fibrosis, multiple sclerosis, motor neuron disease, Parkinson's disease, dementia and AIDS. The evidence contained within this overview provides some insight into interventions which may prove of benefit within this population such as exercise, some pharmacological treatments and support for self-management. More research is required to ascertain the best interventions to manage fatigue and/or weight loss in advanced illness. There is a need for standardised reporting of these symptoms and agreement amongst researchers of the minimum duration of studies and minimum percentage change in symptom experience that proves the benefits of an intervention.	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comment
15.Wang CW, Chow AY, Chan CL. The effects of life review interventions on spiritual well-being, psychological distress, and quality of life in patients with terminal or advanced cancer: A systematic review and meta-analysis of randomized controlled trials. Palliat Med. 2017;1-12	**Systematic review and meta-analysis** **Objective** To evaluate the effects of therapeutic life review on spiritual well-being, psychological distress, and quality of life in patients with terminal or advanced cancer **Methods** Conducted systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses methodology Five databases were searched from their respective inception through February 2017 for relevant randomized controlled trials. The effects of therapeutic life review were pooled across the trials. Standardized mean differences were calculated for the pooled effects. Heterogeneity was assessed using the I2 test. **Quality assessment** Study quality was assessed using the Cochrane criteria. **Outcomes measures** spiritual well-being, psychological distress, and quality of life Spiritual well-being was assessed with the Functional Assessment of Chronic Illness Therapy– Spiritual (FACIT-Sp) scale. Psychological distress was assessed with the Hospital Anxiety and Depression Scale (HADS) QOL was evaluated with different measures, including a single-item QOL scale, a two- item QOL scale, EuroQol five dimensions questionnaire (EQ-5D), the McGill Quality of Life Questionnaire (MQOL) and Quality-of-Life Concerns in the End-of- Life questionnaire (QOLC-E)	I	8 randomized controlled trials included -published between 2010 and 2014 met - conducted in Canada, Hong Kong, Japan, Mainland China, Portugal, United Kingdom, and United States. Total of 955 participants, including 427 in the intervention groups and 528 in the control groups, respectively Included studies Ando et al 2010 Hall et al 2011 Henry et al 2010 Chochinov et al 2011 Mok et al 2012 Xiao et al 2013 Juliao et al 2014 Breitbart et al 2012	Life review interventions	no psychological intervention or a placebo intervention	3 months after intervention	The pooled results suggested a desirable effect of therapeutic life review on; (when compared to usual care only) • the meaning of life domain of spiritual well-being (standardized mean difference = 0.33; 95% confidence interval, 0.12 to 0.53) • general distress (standardized mean difference = −0.32; 95% confidence interval, −0.55 to −0.09) • Overall quality of life (standardized mean difference = 0.35; 95% confidence interval, 0.15 to 0.56). • Of the three outcomes examined, only the pooled effect on overall quality of life remained statistically significant at follow-ups up to 3 months after the intervention (standardized mean difference = 0.82; 95% confidence interval, 0.47 to 1.18) **Authors conclusion**: Therapeutic life review is potentially beneficial for people near the end of life. However, the results should be interpreted with caution due to the limited number of randomized controlled trials and associated methodological weaknesses. Further rigorously designed randomized controlled trials are warranted	

Evidence Table : **Effectiveness – Psychological well-being-– Dignity therapy**
Question : **Is palliative care intervention effective in improving psychological well-being of patient with chronic life-limiting illness?**

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comment
16.Martínez M, Arantzamendi M, Belar A et al. 'Dignity therapy', a promising intervention in palliative care: A comprehensive systematic literature review. Palliat Med. 2017;31(6):492–509.	**Systematic review** **Objective** To analyse the outcomes of dignity therapy in patients with advanced life-threatening diseases **Methods** Conducted systematic review and evaluated quality using Critical Appraisal Skills Programme. The years searched were 2002 (year of dignity therapy development) to January 2016. **Inclusion criteria** Studies on dignity therapy on patients with advanced life-threatening diseases were included, regardless of design **Exclusion criteria** Editorials, commentaries and publications on research protocols were excluded. **Quality assessment** Using Critical Appraisal Skills Programme (CASP) **Outcomes measures** reducing psychological, existential, and spiritual distress	I	Of 121 studies, 28 were included. Quality of studies was high. Studies from: United Kingdom the United States Canada, Australia, Denmark, Portugal, Sweden, Japan and Spain Included studies: Passik et al. Chochinov et al. McClement et al. Houman et al. Chochinov et al. Hall et al.16 Montross et al. Akechi et al. Chochinov et al. Hall et al. Goddard et al. Hall et al. Hall et al. Hall et al. Johns et al. Juliao et al. Montross et al Bentley et al. Bentley et al Houmann et al. Javaloyes et al. Juliao et al. Vergo et al. Aoun et al. Johnston et al. Juliao et al. Lindquist et al. Rudilla et al.	Dignity therapy = psychotherapy to relieve psychological and existential distress in patients at the end of life	standard palliative care client-centred care (CCC)= a type of psychotherapeutic support approach that focuses on non-generativity themes, that is, on here-and-now issues		Results were grouped into effectiveness, satisfaction, suitability and feasibility, and adaptability to different diseases and cultures. • 2 of 5 RCT applied dignity therapy to patients with high levels of baseline psychological distress. • One showed statistically significant decrease on patients' anxiety and depression scores over time. • The other showed statistical decrease on anxiety scores pre–post dignity therapy, not on depression. • Nonrandomized studies suggested statistically significant improvements in existential and psychosocial measurements. • Patients, relatives and professionals perceived it improved end-of-life experience **Authors conclusion**: Evidence suggests that dignity therapy is beneficial. One randomized controlled trial with patients with high levels of psychological distress shows DT efficacy in anxiety and depression scores. Other design studies report beneficial outcomes in terms of end-of-life experience. Further research should understand how dignity therapy functions to establish a means for measuring its impact and assessing whether high level of distress patients can benefit most from this therapy	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comment
17.Parahoo K, Mcdonough S, Mccaughan E et al. Psychosocial interventions for men with prostate cancer. Cochrane Database Syst Rev. 2013;(12):1–99.	**Systematic review and meta-analysis** **Objective** To evaluate the effectiveness of psychosocial interventions for men with prostate cancer in improving quality of life (QoL), self-efficacy and knowledge and in reducing distress, uncertainty and depression **Methods** Searched trials using a range of electronic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and PsycINFO to October 2013, together with hand searching of journals and reference lists Means and standard deviations (SDs) were extracted, and, when appropriate, standard errors (SEs) were converted into SDs for meta-analysis by using the standardised mean difference (SMD) and 95% confidence intervals (CIs) **Inclusion criteria** Randomised controlled trials of psychosocial interventions for men at any stage of prostate cancer. We included psychosocial interventions that explicitly used one or a combination of the following approaches: cognitive behavioural, psychoeducational, supportive and counselling. Interventions had to be delivered or facilitated by trained or lay personnel **Quality assessment** Risk of bias tool recommended in the Cochrane Handbook for Systematic Reviews of Interventions, Using GRADE **Outcomes measures** Primary outcomes were: • quality of life; GHQoL, SF36 • self-efficacy= belief in one's	I	19 studies = total of 3204 men with prostate cancer were included They were randomly assigned to psychosocial intervention or control groups All but 3 of these studies were conducted in the United States Included studies: Ames 2011; Bailey 2004; Campbell 2007; Manne 2011; Zhang 2006 Berglund 2007 Chambers 2013 Davison 1997 Campbell 2007 Giesler 2005 Manne 2011 Mishel 2002 Mishel 2009; Northouse 2007 Thornton 2004 Berglund 2007; Fawzy 1995 Raingruber 2011 Carmack Taylor 2006 Parker 2009 Lepore 2003	Psychosocial interventions= One or a combination of the following approaches: psychoeducational therapy, cognitive behavioural therapy (group or individual), group supportive therapy and individual supportive therapy, including counselling as well as those interventions designed to provide information, physical exercise, relaxation, or art and music therapies. Psychosocial interventions can be delivered face-to-face, online, by telephone or through a combination of these approaches -delivered or facilitated by trained or lay personnel	Usual care	Up to 12 months post intervention	Men in the psychosocial intervention group had a small, statistically significant improvement in the physical component of general health-related quality of life (GHQoL) at end of intervention (1414 participants, SMD 0.12, 95% CI 0.01 to 0.22) based on low- quality evidence. A small improvement in favour of psychosocial interventions (SMD 0.24, 95% CI 0.02 to 0.47) was also seen in the physical component of GHQoL at end of intervention for group-based interventions. No clear evidence of benefit was found for GHQoL scores at end of intervention with individual-based interventions compared with controls. Also, no clear evidence suggested that psychosocial interventions were beneficial in improving the physical component of GHQoL at four to six and at eight to 12 months post-intervention. In addition, no clear evidence showed benefit associated with psychosocial interventions for the mental component of GHQoL at end of intervention (1416 participants, SMD -0.04, 95% CI -0.15 to 0.06) based on moderate-quality evidence. Results for the mental component of GHQoL at four to six and at eight to 12 months post-intervention were compatible with benefit and harm. At end of intervention, cancer-related QoL showed a small improvement following psychosocial interventions (SMD 0.21, 95% CI 0.04 to 0.39), but at eight and 12 months, the effect was compatible with benefit and harm. For prostate cancer- specific and symptom-related QoL, the differences between groups were not significant. No clear evidence indicated that psychosocial interventions were beneficial in improving self-efficacy at end of intervention (337 participants, SMD 0.16, 95% CI -0.05 to 0.38) based on very low-quality evidence in three studies that assessed individual-based interventions. The results for self-efficacy at six to eight and at 12months post-intervention were compatible with benefit and harm. Men in the psychosocial intervention group had a moderate increase in prostate cancer knowledge at end of intervention (506 participants, SMD 0.51, 95% CI 0.32 to 0.71) based on very low-quality evidence in two studies; this increase was also observed in the subgroups of group-based and individual-based interventions. A small increase in knowledge with psychosocial interventions was noted at three months post-intervention (SMD 0.31, 95% CI 0.04 to 0.58). The results for uncertainty (916 participants, SMD -0.05, 95% CI -0.35 to 0.26) and distress (916 participants, SMD 0.02, 95% CI -0.11 to 0.15) at end of intervention were compatible with both benefit and harm based on very low-quality evidence. No clear evidence suggests that psychosocial interventions were beneficial in reducing uncertainty and distress between groups at six to eight and at 12 months post-intervention. No clear evidence of benefit is associated with psychosocial	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comment
	ability to deal with problems related to cancer • knowledge						interventions for depression at end of intervention (434 participants, SMD -0.18, 95% CI -0.51 to 0.15) based on very	
	• uncertainty= is the inability to determine the meaning of illness-related events • distress • depression						Low quality evidence. Individual-based interventions significantly reduced depression when compared with usual care groups. The results for depression at six and at 12 months post-intervention were compatible with benefit and harm. The overall risk of bias in the included studies was unclear or high, primarily as the result of performance bias. No data regarding stage of disease or treatment with androgen deprivation therapy (ADT) were extractable for subgroup analysis. Only one study addressed adverse effects. High attrition could indicate that some participants may not have been comfortable with the interventions. **Authors conclusion**: Psychosocial interventions may have small, short-term beneficial effects on certain domains of well- being, as measured by the physical component of GHQoL and cancer-related QoL when compared with usual care. Prostate cancer knowledge was also increased. However, this review failed to demonstrate a statistically significant effect on other domains such as symptom-related QoL, self-efficacy, uncertainty, distress or depression. Moreover, when beneficial effects were observed, it remained uncertain whether the magnitude of effect was large enough to be considered clinically important. The quality of evidence for most outcomes was rated as very low according to GRADE, reflecting study limitations, loss to follow-up, study heterogeneity and small sample sizes. Although some findings of this review are encouraging, they do not provide sufficiently strong evidence to permit meaningful conclusions about the effects of these interventions in men with prostate cancer.	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comment
18.Galway K, Black A, Cantwell M, Cardwell CR, Mills M, Donnelly M. Psychosocial interventions to improve quality of life and emotional wellbeing for recently diagnosed cancer patients. Cochrane Collab 2012;(11).	**Systematic review and meta-analysis** **Objective** To assess the effects of psychosocial interventions to improve quality of life (QoL) and general psychological distress in the 12-month phase following an initial cancer diagnosis **Methods** Searched Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2010, Issue 4), MEDLINE, EMBASE, and PsycINFO up to January 2011. -searched registers of clinical trials, abstracts of scientific meetings and reference lists of included studies. Electronic searches were carried out across all primary sources of peer-reviewed publications using detailed criteria. No language restrictions were imposed. **Inclusion criteria** Randomised controlled trials (RCTs) and quasi-RCTs of psychosocial interventions with recently diagnosed adult cancer patients. Only trials with adults (18+ years) who had been formally diagnosed with any type or stage of cancer within the past 12 months **Exclusion criteria** Trials involving a combination of pharmacological therapy and interpersonal dialogue, physical therapy, that is massage; alterative therapy, that is acupuncture; educational media, that is leaflets, brochures, CDs or DVDs, or other media were excluded, as were trials involving couples, family members or group formats **Quality assessment** Yes- Cochrane tool **Outcomes measures** Quality of life, general psychological distress (including anxiety and depression)	I	30 studies included Majority of the studies focused on patients with a single site malignancy Included studies: QOL Chan 2005 Edgar 2001 Johansson 2008 Parker 2009 Stanton 2005 Trask 2003 Dow Meneses 2007 Holtedahl 2005 Sandgren 2003 Ross 2005 Lev 2000 Scura 2004 Jacobsen 2002 Scholten 2001 Linn 1981 Mood well-being Fawzy 1995 McQuellon 1998 Edgar 2001 Peterson 2002 Kanzaki 2002 Sandgren 2003 Nezu 2003 Allard 2007 Downe-Wamboldt 2001 McArdle 1996 Moynihan 1998 Puig 2006	psychosocial interventions involving interpersonal dialogue between a 'trained helper' and individual newly diagnosed cancer patients were	free of any intervention-must be receiving standard care only		• No significant effects were observed for QoL at 6-month follow up (in 9 studies, SMD 0.11; 95% CI -0.00 to 0.22); • However, a small improvement in QoL was observed when QoL was measured using cancer-specific measures (in 6 studies, SMD 0.16; 95% CI 0.02 to 0.30). • General psychological distress as assessed by 'mood measures' improved also (in 8 studies, SMD - 0.81; 95% CI -1.44 to - 0.18), but no significant effect was observed when measures of depression or anxiety were used to assess distress (in 6 studies, depression SMD 0.12; 95% CI -0.07 to 0.31; in 4 studies, anxiety SMD 0.05; 95% CI - 0.13 to 0.22). • Psychoeducational and nurse-delivered interventions that were administered face to face and by telephone with breast cancer patients produced small positive significant effects on QoL (in 2 studies, SMD 0.23; 95% CI 0.04 to 0.43) **Authors conclusion**: Significant variation that was observed across participants, mode of delivery, discipline of 'trained helper' and intervention content makes it difficult to arrive at a firm conclusion regarding the effectiveness of psychosocial interventions for cancer patients. It can be tentatively concluded that nurse-delivered interventions comprising information combined with supportive attention may have a beneficial impact on mood in an undifferentiated population of newly diagnosed cancer patients	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
19.Prescott AT, Hull JG, Dionne-Odom JN et al. The role of a palliative care intervention in moderating the relationship between depression and survival among individuals with advanced cancer. Heal Psychol. 2017;36(12):1140–6	**Randomised controlled trial** **Objective** To determine the effects of the palliative care interventions and depression on survival - examine the association between participants' baseline depression scores and subsequent survival time - examine the moderating effect of receiving the palliative care intervention on this association **Methods** Combined data set from the two RCTs ENABLE ((Educate, Nurture, Advise, Before Life Ends) studies (Bakitas et al., 2009, 2015) was used: -Bakita 2009-enrollment between November 2003 and May 2007, participants were randomly assigned upon enrolment to either (a) an intervention condition or (b) a usual cancer care control condition. -Bakita 2015-enrollment between October 2009 and March 2013; a wait-list control design was employed wherein all participants received the intervention but were randomly assigned to receive it either (a) early (upon enrolment) or (b) after a delay of 12 weeks. Cox proportional-hazards regression analyses were used to model the effects of intervention status and baseline depression on survival, with and without adjustment for baseline covariates. -involved survival over time among a control group that never received the intervention (usual care), an experimental group that received the intervention upon enrolment (early intervention), and an experimental group that received the intervention 12 weeks after enrolment (delayed intervention) **Outcomes measures** Survival, patient-reported depression, quality of life, symptom intensity, and resource use.	I	529 patients: 161 received usual care (Bakita 2009 only) 265 received the early intervention (161 from Bakita 2009, 104 from Bakita 2015) 103 received the delayed intervention (Bakita 2015 only)	ENABLE (Educate, Nurture, Advise, Before Life Ends) Intervention-psychoeducational approach After an initial in-person palliative care consult, advanced practice nurses specializing in palliative care facilitated semi-structured psychoeducational telephone coaching sessions with patients using an author-developed informational guidebook called Charting Your Course, followed by monthly check-in calls until the patient died or the study ended. Topics discussed during sessions included problem-solving, coping, self-care, symptom management, building a support system, communication skills, decision-making, advance care planning, and life review	Usual care		The Cox analysis confirmed an effect of depression (Wald = 12.377, HR = 1.038, CI: 1.017–1.060, p < 0.001) such that higher depression at baseline was associated with shorter survival. In addition, there was a significant interaction between depression and the intervention (Wald = 4.451, HR = 0.973, CI: 0.949–0.998, p = 0.035), such that depression was more strongly associated with shorter survival among participants receiving usual cancer care than among those receiving the intervention Analysis was repeated including all baseline covariates (the variable other cancer was omitted to avoid model co-linearity). In this full model, depression remained associated with shorter survival (Wald = 10.869, HR = 1.042, CI: 1.017–1.067, p = 0.001) and the depression by intervention interaction again remained significant (Wald = 5.636, HR = 0.963, CI: 0.933–0.993, p = 0.018) despite inclusion of the 19 covariates. Of these, six were associated with longer survival (married, college graduate, gastrointestinal cancer, lung cancer, haematological cancer, and DNR) and one (days in hospital) was associated with shorter survival **Authors conclusion**: The intervention had a greater impact on survival for individuals with higher baseline depression, and this moderation effect remained significant independent of demographics, cancer site, and illness severity This demonstrates the power of early palliative care to moderate the relationship between depression and survival among individuals newly diagnosed with advanced cancer. Although depression was associated with higher mortality risk in the sample overall, this relationship was diminished among individuals who received the ENABLE palliative care intervention. In contrast, depressed individuals who received only usual cancer care demonstrated significantly higher mortality risk than other patients. Despite decades of investigation, researchers have yet to agree on the mechanisms explaining the relationship between depression and mortality. From a clinical perspective, this suggests programmes should prioritize such patients when offering early palliative care services, because these individuals are most likely to benefit from these types of interventions	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
20. Kruizinga R, Hartog ID, Jacobs M et al. The effect of spiritual interventions addressing existential themes using a narrative approach on quality of life of cancer patients: a systematic review and meta-analysis. Psycho-Oncology. 2016;25(3):253–65.	**Systematic review and meta-analysis** **Objective** To examine whether spiritual interventions that address existential needs using a narrative approach improve quality of life of cancer patients **Methods** Conducted systematic review and meta-analysis **Inclusion criteria** All clinical trials were included that compared standard care with a spiritual intervention that addressed existential themes using a narrative approach Study population of the intervention should include >50% cancer patients, with all types of cancer, and aged 18 years and older. -a control group of either no intervention or a placebo intervention. **Quality assessment** Study quality was evaluated by the Cochrane Risk of Bias Tool Note: Blinding of patients and personnel cannot be carried out (due to face-to-face intervention) in narrative interventions. Outcome assessors could not be blinded for the intervention, as patients were the assessors and they knew to which group they were assigned **Outcomes measures** -mean difference in QoL between the control group and intervention group 0–2 weeks after the intervention. -Secondary outcome: mean difference in QoL 3–6 months after the intervention	I	14 clinical trials included (published between 2005 and 2013) 2050 patients met the inclusion criteria 2 trials (1878 patients) were included in the meta-analysis Patients included were mostly advanced cancer patients without specific cancer diagnosis mentioned, breast cancer, cancer patients with at least 1 month diagnosed, cancer patients with depressive disorder and advanced ovarian cancer patients Types of interventions ranged from only spiritual interventions to multidisciplinary interventions with spiritual components Included studies: Breitbart 2012 Chochinov, 2011 Daly 2013 Hall 2011 Henry 2010 Jafari 2013 Kristeller, 2005 Loyd-Williams 2013 Mok 2012 Piderman, 2013 Rummans. 2006 Steinhauser, 2008 Vega 2010 Xiao 2013	spiritual intervention that addressed existential themes using a narrative approach -performed by various trained people, mostly psychologists/psychiatrists and oncology professionals or general healthcare professionals or by spiritual healers or chaplain	Not described		Overall risk of bias was high. When combined, all studies showed a moderate effect d= 0.50 (95% CI = 0.20–0.79), 0–2 weeks after the intervention on overall quality of life in favour of the spiritual interventions. Heterogeneity was very high (I^2 =84%.) Overall effect size of the five studies that assessed quality of life 3–6 months after intervention was d=0.11 (95% CI:-0.08 to 0.35), a small and insignificant effect (p=0.21). Heterogeneity was low (I^2 =0%) Meta-analysis with the interventions grouped into three subgroups as follows: (1) life reviewing interventions; (2) multidisciplinary interventions; and (3) meaning-making interventions. All studies showed a trend towards a positive outcome on QoL of cancer patients in favour of the intervention. The strongest effect was seen in subgroup 3: meaning-making interventions (d=0.63; 95% CI: 0.01–1.26, p=0.05) -Subgroup analysis including only the western studies showed a small effect of 0.17 (95% CI= 0.05–0.29) -Including only studies that met the allocation concealment criteria showed an insignificant effect of 0.14 (95% CI=-0.05 to 0.33) **Authors conclusion**: Directly after the intervention, spiritual interventions had a moderate beneficial effect in terms of improving quality of life of cancer patients compared with that of a control group. No evidence was found that the interventions maintained this effect up to 3–6 months after the intervention. Further research is needed to understand how spiritual interventions could contribute to a long-term effect of increasing or maintaining quality of life	

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Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comment
21.Oh PJ, Kim SH. The effects of spiritual interventions in patients with cancer: a meta-analysis. Oncol Nurs Forum. United States; 2014;41(5):E290-301.	**Systematic review and meta-analysis** **Objective** To evaluate the effects of a spiritual intervention in patients with cancer **Methods** Conducted a meta-analysis of 15 studies involving 14 controlled trials (7 randomized and 7 nonrandomized) with 889 patients with cancer. Spiritual interventions were compared with a usual care control group or other psychosocial interventions. **Inclusion criteria** RCTs, non-RCT **Exclusion criteria** Studies using pharmacologic interventions were excluded **Quality assessment** RCTs assessed using a Risk of Bias (RoB), by the Cochrane Bias Method Group RoB Assessment tool for Non-Randomized Studies (RoBANS) was used for non-RCTs **Outcomes measures** Primary: spiritual and psychological outcomes, including spiritual well-being, meaning of life, anxiety, and depression -Spiritual well-being measured by Paloutzian and Ellison's (1982) conceptualization of spiritual well-being (n = 3), the Functional Assessment of Chronic Illness Therapy–Spiritual Well-Being (FACIT-SWB) scale (n = 2), FACIT-Spiritual (FACIT-Sp) subscale (n = 2), and the World Health Organization Quality of Life (WHOQOL) spiritual subscale (n = 1). Meaning of life was evaluated in six studies using the FACIT-Sp meaning subscale (n = 1), the Quality of Life Concerns in the End of Life (QOLC-E) scale (n = 1), the Purpose in Life (PIL) scale (n = 1), the Life Orientation Test (LOT) scale (n = 1), Crumbaugh's scale	I	15 studies included (7 randomized and 7 nonrandomized) 889 participants - adults aged 18 years or older who had been diagnosed with cancer of any type (solid or hematologic), at any tumour stage, with any kind of treatment mode, and at any time since diagnosis Included studies: Breitbart et al., 2012 (USA) Cole et al., 2012 (USA) Mok et al., 2012 (Hong Kong) Breitbart et al., 2010 (USA) Henry et al., 2010 (Canada), Djuric et al., 2009 (USA) Kristeller et al., 2005 (USA) Korean studies; Koo, 2008, Kim et al., 2006 Chung, 2005 Kim & Song, 2004 Yoon, 2004a, Yoon, 2004b Yoon, 2001 Kim, 1988	Spiritual intervention= any approach Involving two components, religious (i.e., achieving harmony with God) and existential aspects (i.e., finding meaning and purpose in one's life), based on Paloutzian and Ellison's (1982) conceptualization of spirituality. Interventions could be provided in any of multiple formats, including individual, group, telephone, or Internet-based modalities	Usual care or other psychosocial intervention		Of the 15 studies, 10 applied religious interventions, including spiritual nursing care (n = 7), spiritual counselling (n = 1), oncologist-assisted spiritual intervention (n = 1), and spiritually focused meditation (n = 1). All conducted in Korea Five studies used existential intervention, specifically meaning-centered psychotherapy (n = 2), a meaning-of-life intervention (n = 1), a meaning-making intervention (n = 1), and a logo therapy-based resilience promotion program (n = 1) Nurses were the most frequent intervention providers (n = 10), followed by clinical psychologists (n = 4), dietitians (n = 1), and oncologists (n = 1) Weighted average effect size across studies was −0.48 (p = 0.006, I^2= 65%) for spiritual well-being, −0.58 (p = 0.02, I^2= 70%) for meaning of life, −0.87 (p = 0.02, I^2 = 87%) for anxiety, and −0.62 (p = 0.001, I^2 = 73%) for depression When studies were grouped by study design, significant large effects on spiritual well-being (d = −0.78, 95% CI [−1.3, −0.27], I^2 = 59%), anxiety (d = −1.23, 95% CI [−1.76, −0.7], I^2= 24%), and depression (d = −1.36, 95% CI [−1.84, −0.88], I^2= 45%) were found in non-RCT studies. In the subgroup analysis by intervention type, existential intervention yielded significant moderate effects on meaning of life (d = −0.59, 95% CI [−0.87, −0.31], I^2= 0%) and significant small effect on anxiety (d = −0.35, 95% CI [−0.67, −0.03], I^2 = 0%). In contrast, studies that applied religious intervention demonstrated a significant moderate-to-large effect on spiritual well-being (d = −0.54, 95% CI [−1, −0.08], I^2=71%) and depression (d = −0.79, 95% CI [−1.33, −0.25], I^2= 79%). However, this subgroup is substantially heterogeneous. **Authors conclusion**: Spiritual interventions had significant but moderate effects on spiritual well-being, meaning of life, and depression. However, the evidence remains weak because of the mixed study design and substantial heterogeneity The current study indicates that facilitating spiritual aware-ness and needs may be a worthwhile intervention for patients with cancer	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comment
	(n = 1), and the existential subscale from the McGill Quality of Life (MQOL) questionnaire (n = 1) Secondary outcome: psychological distress, including anxiety and depression. -Depression was measured using the Hospital Anxiety and Depression Scale (HADS) (n = 3), Zung's Depression Inventory (n = 2), the Center for Epidemiological Studies–Depression (CES-D) scale (n = 2), Symptom Checklist–90 revised (SCL-90R) (n = 1), and Brief Symptom Inventory Depression (BSID) subscale (n = 1). -To measure anxiety, HADS (n = 3), SCL-90R (n = 1), and the State-Trait Anxiety Inventory (STAI) (n = 2) were used							

Evidence Table : **Effectiveness & Economic impact – Paediatric Palliative Care**

Question : **Is palliative care intervention effective in improving quality of life of patient with chronic life-limiting illness?**

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
22.Chong PH, De Castro Molina JA, Teo K, Tan WS. Paediatric palliative care improves patient outcomes and reduces healthcare costs: Evaluation of a home-based program. BMC Palliat Care. 2018;17(1):1–8. Singapore	**Mixed retrospective & prospective cohort, cost analysis** **Objective** 1.To compare patient-related outcomes and healthcare expenditures between those who received home-based paediatric palliative care (PPC) and standard care 2. Quality of life and caregiver burden for patients receiving home-based paediatric palliative care were tracked over the first year of enrolment to evaluate the service's longitudinal impact **Methods** A structured impact and cost evaluation of Singapore-based HCA Hospice Care's Star PALS (Paediatric Advance Life Support) programme was conducted Patients: Age less than 19 years of age at the time of diagnosis, received home-based palliative care, diagnosed with a life-shortening condition 2 phases: • Retrospective design to answer objective 1. The cohort consisted of 2 groups of deceased patients: those enrolled in paeds PC and those who were not enrolled in the programme (control group) and had died in hospital. Cost from healthcare system perspective • Single-group prospective design for patients who had received PPC at home was employed to address objective 2. **Outcomes measures** Patient-related outcomes and healthcare expenditures For the single-group prospective cohort study, Health-Related Quality of Life (HRQL) of patients enrolled in the PPC group was assessed at 0, 3, 6, and 12 months using the Health Utilities Index (HUI). -HUI consists of two complementary health status classification systems – HUI2 and HUI3, assessing 6 and 8 health-related attributes respectively Caregiver burden was assessed prospectively at 0, 3, 6, and 12 months. using Zarit Burden Interview (ZBI) – a face-to-face, 22-item instrument	II-2	Total of 71 patients 67 in control group Mean age at death: 12 yrs (PPC grp), 6 yrs (control grp) Male 63.4%, female 36.6% in PPC Male 61.2%,female 38.8% in control grp Causes of death: Other causes(54.1%) Cancers (45.1%) Healthcare costs= cost of healthcare resources utilized, including hospitalization, ED visits and outpatient visits. Total medical bill before any deduction for government subsidies and insurance claims, used to estimate healthcare resources consumed	home-based paediatric palliative care Star PALS= Paediatric Advance Life Support programme	Standard care	3 years	<u>Patient outcomes & healthcare utilization</u> Compared to the control group (n = 67), patients receiving home-based paediatric palliative care (n =71) spent more time at home than in hospital in the last year of life by 52 days (OR = 52.30, 95% CI: 25.44–79.17) -at least two fewer hospital admissions (OR = 2.46, 95% CI: 0.43–4.48); -5 times more likely to have an advance care plan formulated (OR = 5.51, 95% CI: 1.55–19.67). <u>Economic impact</u> Cost of care for control group at the end of life was SGD $253,168 per year, with 32% (SGD$80,958) incurred within the final month of life. Cost of care per year was significantly lower (SGD$74,683) in the PPC group (p <0.05) At 12 months prior to death, medical costs for PPC group were 70% (SGD$ 175 K) lower than the control group. Cost savings increased to 87% (SGD$ 72 K) at one month prior to death <u>Prospective evaluation on patient quality of life and caregiver burden</u> Both patients' quality of life (in terms of pain and emotion), and caregiver burden showed improvement within the first year of enrolment into the programme. <u>HRQoL</u> -improved emotion and reduced pain odds of being pain-free at 3 months (OR = 2.58, 95% CI: 1.12–5.95) were significantly higher than at baseline (p < 0.05) -unchanged or more severe level of sensation, mobility, cognition and self-care (based on HUI2), as well as vision, speech, ambulation, dexterity and cognition (based on HUI3), on all periods of follow-ups **Authors conclusion**: Home-based paediatric palliative care brings improved resource utilization and cost-savings for both patients and healthcare providers. QoL of patients and their caregivers have improved	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
23.Widger K, Seow H, Rapoport A. Children's End-of-Life Health Care Use and Cost. Pediatrics. 2017;139(4): e20162956 Ontario, Canada	**Population-based retrospective cohort** **Objective** To examine demographics, location, cause of death, and health care use and costs over the last year of life for children aged 1 month to 19 years who died in Ontario, Canada **Methods** Conducted population-based retrospective cohort study using administrative data to examine demographics, diagnosis, location of death and health care use and costs incurred in the last year of life Cohort: children aged ≤ 19 years who died during 3 year period from 2010-2013 Infants aged <30 days of age were excluded (majority didn't have health card number) Cause of death: 4 broad categories based on International Classification of of death, which includes ICD-10 (1) perinatal/congenital causes (eg related to pregnancy, perinatal periods, congenital malformations) (2) chronic causes (eg. Infectious diseases, cancer, circulatory, and nervous systems) (3) external causes (eg accidents, assault, drowning, and complications of medical care) (4) Other causes (eg sudden infant death syndrome) Health care use and cost were assessed over the last year of life (1) Continuing care (complex continuing care, home care and rehab) (2) acute care complex continuing care (inpatient with/without ICU, ED) (3) outpatient care (ie, outpatient clinics, physician services, non-physician services) *hospice care not included since data admission & discharges not included in admin data). Other costs typically associated with hospice care reflected in home care costs. Payer (ministry of Health) costing perspective	II-2	1620 childen aged 1 month-19 years More boys than girls Largest proportion of deaths (37.6%) occurred in 15-19 year old group Majority diagnosed with chronic disease (41.6%)				Of 1620 children, 41.6% died of a chronic disease with wide variation across age groups. Majority of children (76%) died in an institution including 36% in ICU and 31% in ED Children died of perinatal/ congenital diseases, external cause and those with chronic illnesses tend to die more often in ICU Regardless of cause of death, children received most care in acute care settings over last 30 days (mean 6.7 days) and 90 days (mean 14.6 days). Complex continuing care and ED has the next highest mean number of days with little use of home care Mean Health care cost over the last year of life was $78,332 (Canadian) with a median of $18,450, reflecting the impact of high-cost decedents. 75% of these costs were incurred in acute care sector Highest median total costs were for children in perinatal/congenital disease ($103,472) followed by chronic disease ($63,101). Mean cost for children with perinatal/congenital illnesses nearly doubled between 12 and 5 months before death, but then increased another 2.5 times over the last 4 months of life Across all disease groups, highest mean hospital costs were among those with at least 1 ICU visit Only 33.4% of children received home care in the last year of life **Author's conclusion** Children in Ontario receive the majority of their end-of-life care in acute care settings at a high cost to the health care system Initiatives to optimize care should focus on early discussion of the goals of care and assessment of whether the care provided fit with these goals	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
24.Gans D, Hadler MW, Chen X et al. Cost Analysis and Policy Implications of a Pediatric Palliative Care Program. J Pain Symptom Manage 2016;52(3):329–35 California, US	**Pre-post intervention study** **Objective** To assess a paediatric palliative care programme model, Partners for Children (PFC), California - the change from before PFC enrolment to the enrolled period in 1) health care costs per enrolee per month (PEPM) 2) costs by service type and diagnosis category 3) health care utilization (days of inpatient care and length of hospital stay). **Methods** A pre-post analysis compared enrolees' health care costs and utilization up to 24 months before enrolment with their costs during participation in the pilot, from January 2010 through December 2012. Analyses were conducted using paid Medicaid claims and program enrolment data **Inclusion criteria**: • Children and their families either self-referred to PFC or were referred by a physician, or a hospice or home health agency, or a nurse liaison. • To be enrolled in PFC, children and young adults had to be 20 years of age or younger; live in one of the 11 participating counties; and have full-scope, no share-of-cost Medicaid, and an eligible condition. • Eligible children also had to meet the necessary level of care-physician had to declare on the referral form that a child was at risk of having at least 30 inpatient days during the subsequent 12 months as a result of his/her qualifying condition if the child did not enroll in PFC **Outcomes measures** Cost Service utilization	II-2	151 children enrolled in the PFC pilot - 132 enrolled in the program for at least 60 days and were included in the cost analyses Enrolees were more likely to be male (57%) and Latino (60%) Majority aged 0-10 years old (64%), 10-20 (36%) Most frequent primary diagnosis was a neurologic condition (30%), followed by cancers (20%) and pulmonary and neuromuscular conditions (11% each)	Partners for Children (PFC) provides the following PC services: 1) comprehensive care coordination 2)expressive therapies, including art, music, play, and massage for the child 3) family education, including instruction on providing care and operating medical equipment 4) respite care in and out of the home to provide needed rest for the primary caregivers 5)family and bereavement counselling 6) pain and symptom management 7) 24/7 on-call nursing support services through participating hospice and home health agencies		24 months	Costs Mean PEPM health care costs of children in PFC decreased significantly from $15,643 before their participation in the program to $12,312 while enrolled, a pre-post difference of $3331 Most of the savings were realized through a reduction in inpatient costs of $4897 PEPM, which was slightly modified by increases in outpatient and pharmacy services Enrolees on the higher end of the cost spectrum exhibited larger savings in the post-enrolment period than those on the lower end of the cost spectrum, with the median costs (not shown here) higher in the pre-enrolment period than post-enrolment, but with 75% already showing a significant reduction in cost Reductions in inpatient costs were consistent across nearly all of the disease categories studied Extrapolated across the three program years, the savings of $3331 PEPM equated to $5.2 million in 2010, $10.5 million in 2011, and $15.7 million in 2012, based on increasing enrolment in the program over the pilot period Utilization PFC enrolees experienced a nearly 50% reduction in the average number of inpatient days per month, from 4.2 to 2.3 statistically significant difference Average number of hospitalizations reduced during the program period, from 0.26 PEPM before enrolment to 0.20 PEPM during the program, although not statistically significant Average length of stay per hospitalization dropped significantly from an average of 16.7 days before enrolment to 6.5 days while in the program. The 30-day readmission rate (hospital admission within 30 days of the previous discharge) reduced from 45% of admissions to 37% of admissions, although not statistically significant **Authors conclusion**: Through the provision of home-based therapeutic services, 24/7 access to medical advice, and enhanced, personally tailored care coordination, PFC demonstrated an effective way to reduce costs for children with life-limiting conditions by moving from costly inpatient care to more coordinated and less expensive outpatient care. PFC's home-based care strategy is a cost-effective model for paediatric palliative care elsewhere	

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Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
25.Wiffen PJ, Cooper TE, Anderson A-K et al. Opioids for cancer-related pain in children and adolescents (Review). Cochrane Database Syst Rev 2017;(7).	**Systematic review** **Objective** To assess the analgesic efficacy, and adverse events, of opioids used to treat cancer-related pain in children and adolescents aged between birth and 17 years, in any setting **Methods** Searched the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online, MEDLINE via Ovid and Embase via Ovid from inception to 22 February 2017 **Inclusion criteria** Randomised controlled trials (RCTs), with or without blinding, of any dose, and any route, treating cancer-related pain in children and adolescents, comparing opioids with placebo or an active comparator **Exclusion criteria** excluded studies of perioperative pain, short-term infection pain, short-term injury or trauma pain, acute pain, functional abdominal pain, burn pain, and musculoskeletal pains, headache and migraine, sickle cell disease acute crisis pain, mucositis, or any other chronic non-cancer related pain **Quality assessment** GRADE approach to assess the quality of the body of the evidence **Outcomes measures** pain intensity and pain relief using validated rating scale	II-1	No studies included Retrieved all 5 full text reports but excluded in study: -2 studies were randomised controlled trials (RCTs) conducted only in adult populations (Argoff 2015; Marinangeli 2004), -3 studies were not RCTs (Collins 1999; Finkel 2007; Geeta 2009)	opioids	placebo or an active comparator		No studies were identified that were eligible for inclusion in this review (very low quality evidence) Several studies tested opioids on adults with cancer-related pain, but none in participants aged from birth to 17 years. **Authors' conclusion:** No conclusions can be drawn about efficacy or harm in the use of opioids to treat cancer-related pain in children and adolescents. As a result, there is no RCT evidence to support or refute the use of opioids to treat cancer-related pain in children and adolescents. This means that at present, treatment was based on clinical experience and advice from respected authorities. There is need for research for the treatment of cancer-related pain in children and adolescents	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
26.Chung VCH, Wu X, Lu P et al. Chinese Herbal Medicine for Symptom Management in Cancer Palliative Care. Medicine 2016;95(7):e2793.	**Systematic review and meta-analysis** **Objective** To conduct a systematic review with meta-analysis to summarize results from CHM randomized controlled trials (RCTs) focusing on symptoms that are undertreated in conventional cancer palliative care **Methods** 5 international and 3 Chinese databases were searched. RCTs evaluating CHM, either in combination with conventional treatments or used alone, in managing cancer-related symptoms were considered eligible. Effectiveness was quantified by using weighted mean difference (WMD) using random effect model meta-analysis **Inclusion criteria** 1.RCTs comparing effect of CHM, either in combination with other treatments or used alone, in managing cancer or cancer treatment-related symptoms. There is no restriction of the type of cancer diagnosis. 2. The RCT has to report the effectiveness of CHM on at least 1 of the following outcomes measured with validated instruments: fatigue, paresthesias and dysesthesias, chronic pain, anorexia, insomnia, limbs oedema, and constipation. For measurement of pain, 3 validated scales (Visual Analogue Scales, Numerical Rating Scales, and Verbal Rating Scales) recommended by the Research Network of the European Association of Palliative Care23 should be used. 3. The RCT included at least 1 CHM indexed in the 2010 China Pharmacopeia Chinese herbal medicine index. 4. Control group included conventional treatment, chemotherapy, radiotherapy, placebo, or no treatment. 5. RCT reported detailed information on the regimens prescribed in both treatment and control groups. Follow- up duration should also be clearly reported where applicable. **Quality assessment** Cochrane risk of bias tool **Outcomes measures** cancer-related symptoms – pain, constipation,fatigue, anorexia	I	14 RCTs were published between 2006 and 2013, and all were conducted in mainland China. Majority of the included RCTs did not have any restrictions on the site of tumours Included studies Ju, 2006 Zhao, 2006 Zhang, 2009 Gao, 2010 Sun, 2010 Gui, 2010 Lin, 2011 Li, 2011 Wu,2011 Wang,2012 Huang, 2012 Zhao,2013 Jiang,2013	CHM, either in combination CHM indexed in the 2010 China Pharmacopeia Chinese herbal medicine index. Any forms of CHM, with single herbs, herbal formulations, and Chinese proprietary medicines	conventional cancer palliative care		Fourteen RCTs were included. Compared with conventional intervention alone, meta-analysis showed that combined CHM and conventional treatment significantly reduced pain (3 studies, pooled WMD: -0.90, 95% CI: -1.69 to -0.11). 6 trials comparing CHM with conventional medications demonstrated similar effect in reducing constipation. One RCT showed significant positive effect of CHM plus chemotherapy for managing fatigue, but not in the remaining 3 RCTs. The additional use of CHM to chemotherapy does not improve anorexia when compared to chemotherapy alone, but the result was concluded from 2 small trials only. Adverse events were infrequent and mild. CHM may be considered as an add-on to conventional care in the management of pain in cancer patients. CHM could also be considered as an alternative to conventional care for reducing constipation. Evidence on the use of CHM for treating anorexia and fatigue in cancer patients is uncertain, warranting further research **Authors conclusion**: CHM may be considered as an add-on to conventional care in the management of pain in cancer patients. CHM could also be considered as an alternative to conventional care for reducing constipation Evidence on the use of CHM for treating anorexia and fatigue in cancer patients is uncertain, warranting further research	

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27.Wiffen PJ, Derry S, Moore RA. Impact of morphine, fentanyl, oxycodone or codeine on patient consciousness, appetite and thirst when used to treat cancer pain Cochrane Database Syst Rev. 2014;(5) (updated published in Issue 10, 2017)	**Systematic review** **Objective** To determine the impact of opioid treatment on patient consciousness, appetite and thirst in randomised controlled trials of morphine, fentanyl, oxycodone or codeine for treating cancer pain **Methods** Systematically reviewed adverse event data reported in studies included in current Cochrane reviews of opioids for cancer pain: specifically morphine, fentanyl, oxycodone, and codeine **Inclusion criteria** included randomised studies using multiple doses of four opioid drugs (morphine, fentanyl, oxycodone, and codeine) in cancer pain -taken from 4 existing or ongoing Cochrane reviews. Participants were adults aged 18 and over **Outcomes measures** Primary outcomes -numbers of participants experiencing adverse events of reduced consciousness, appetite, and thirst Secondary outcomes -possible surrogate measures of the primary outcomes: delirium, dizziness, hallucinations, mood change and somnolence relating to patient consciousness, and nausea, vomiting, constipation, diarrhoea, dyspepsia, dysphagia, anorexia, asthenia, dehydration, or dry mouth relating to appetite or thirst.	I	77 studies with 5619 randomised participants included Individual treatment groups had fewer than 50 participants in 60 studies Participants were relatively young, with mean age in the studies typically between 50 and 70 years.	morphine, fentanyl, oxycodone, and codeine			Multiple major problems with adverse event reporting were found, including failing to report adverse events in all participants who received medication, all adverse events experienced, how adverse events were collected, and not defining adverse event terminology or whether a reporting system was used Direct measures of patient consciousness, patient appetite, or thirst were not apparent adverse event incidence rates - opioids: 25% for constipation, 23% for somnolence, 21% for nausea, 17% for dry mouth, and 13% for vomiting, anorexia, and dizziness, 5% and below for asthenia, diarrhoea, insomnia, mood change, hallucinations and dehydration Authors conclusion: No direct evidence that opioids affected patient consciousness, appetite or thirst when used to treat cancer pain. However, somnolence, dry mouth, and anorexia were common adverse events in people with cancer pain treated with morphine, fentanyl, oxycodone, or codeine.	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comment
28.Wiffen PJ, Wee B, Derry S, Rf B, Ra M. Opioids for cancer pain - an overview of Cochrane reviews. 2017;(7) Cochrane review	**Systematic review** **Objective** To provide an overview of the analgesic efficacy of opioids in cancer pain, and to report on adverse events associated with their use **Methods** Conducted systematic reviews examining any opioid for cancer pain published to 4 May 2017 in the Cochrane Database of Systematic Reviews in the Cochrane Library **Inclusion criteria** all Cochrane Reviews of randomised, controlled trials (RCTs) of opioid drugs for the treatment of cancer pain in adults **Quality assessment** Used Assessment of Multiple Systematic Review (AMSTAR), GRADE for overall quality of evidence **Outcomes measures** 1. Proportion of participants reporting no worse than mild pain on treatment by 14 days after start of treatment. 2. Patient Global Impression of Change (PGIC) of much or very much improved. 3. Withdrawals due to adverse events	II-1	9 Cochrane studies included (152 included studies and 13,524 adults participants) All Cochrane reviews are of good quality: • Bao 2016: Hydromorphone - outcome not determined or poorly reported in studies; very low quality. • Nicholson 2017: Methadone - limited data poorly reported in studies; very low quality • Schmidt-Hansen 2015a: Oxycodone - scores given were average pain, but most participants appeared to have achieved no worse than mild pain; very low quality. • Schmidt-Hansen 2015b: Buprenorphine - outcome not assessed; very low quality • Straube 2014: Codeine - outcome not determined or poorly reported in studies; very low quality • Wiffen 2015: Tapentadol - outcome not determined or poorly reported in studies • Wiffen 2017c: Tramadol - outcome not determined or poorly reported in studies; very low quality	opioid drugs: buprenorphine, codeine, fentanyl hydrocodone, hydromorphone, methadone, morphine, oxycodone, tramadol, tapentadol Various routes of administration of opioids were considered; oral with most opioids, transdermal administration with fentanyl, and buprenorphine No subcutaneous opioid administration	Compared with either a different formulation of the same opioid, or a different opioid; or placebo control		Adverse event withdrawal was reported by 5 reviews, at rates of between 6% (oral morphine). and 19% (oral oxycodone). Participants with at least 1 adverse event were reported by 3 reviews, at rates of between 11% and 77% **Authors conclusion**: The amount and quality of evidence around the use of opioids for treating cancer pain is low -Most people will experience adverse events, and help may be needed to manage the more common undesirable adverse effects such as constipation and nausea. -Perhaps between 1 in 10 and 2 in 10 people treated with opioids will find these adverse events intolerable	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
29.May P, Normand C, Cassel JB et al. Economics of palliative care for hospitalized adults with serious illness: A meta-analysis. JAMA Intern Med. 2018;178(6):820–9 Study done in US	**Systematic review and meta-analysis** **Objective** To estimate the association of palliative care consultation (PCC) with direct hospital costs for adults with serious illness **Methods** Eight eligible studies were identified, all cohort studies, of which 6 chosen for inclusion. The study estimated the association of PCC within 3 days of admission with direct hospital costs for each sample and for subsamples defined by primary diagnoses and number of comorbidities at admission. Confounders controlled with an instrumental variable when available and otherwise propensity score weighting. i. Elixhauser index, an additive count of the presence of 31 serious conditions to act as a measure of illness burden, ii. van Walraven index a weighted count designed specifically to predict in-hospital mortality. Sensitivity analysis with hospital decedents removed was also performed Treatment effect estimates were pooled in the meta-analysis. **Inclusion criteria** Economic evaluations of interdisciplinary PCC for hospitalized adults with at least 1 of 7 illnesses (cancer; heart, liver, or kidney failure; chronic obstructive pulmonary disease; AIDS/HIV; or selected neurodegenerative conditions) in the hospital inpatient setting vs usual care only, controlling for a minimum list of confounders **Exclusion criteria** Patients who were admitted for trauma or received an organ transplant **Quality assessment** described in Supplement **Outcomes measures** Total direct hospital costs taken from the accounting database of each hospital site and are traceable to specific staffing, equipment, pharmaceuticals, and procedures during an inpatient stay		6 cohort studies (5 retrospective and 1 prospective) studies included Total adult patients: 133,118 patients (range, 1020-82 273) Mean age range: 50 – 71 years old Studies included: Morrison et al 2008 Morrison et al 2011 Penrod et al, 2010 May et al, 2015 McCarthy et al, 2015 May et al, 2017	Palliative care within 3 days of admission to a hospital	Usual care-without palliative care	Earliest study collected data from May 2001 to December 2004 Most recent from February 2010 to October 2015	93.2% were discharged alive (range, 89.0%-98.4%) 40.8% had a primary diagnosis of cancer (range, 15.7%-100.0%) 3.6% received a PCC (range, 2.2%-22.3%) Mean Elixhauser index scores ranged from 2.2 to 3.5 among the studies When patients were pooled irrespective of diagnosis, there was a statistically significant reduction in costs (−$3237; 95% CI, −$3581 to −$2893; P <0.001) In the stratified analyses, there was a reduction in costs for the cancer (−$4251; 95% CI, −$4664 to −$3837; P < 0.001) and non-cancer (−$2105; 95% CI, −$2698 to −$1511; P < 0.001) subsamples. The reduction in cost was greater in those with 4 or more comorbidities than for those with 2 or fewer **Authors conclusion**: The estimated association of early hospital PCC with hospital costs may vary according to baseline clinical factors. Estimates may be larger for primary diagnosis of cancer and more co-morbidities compared with primary diagnosis of non-cancer and fewer co-morbidities. Increasing palliative care capacity to meet national guidelines may reduce costs for hospitalized adults with serious and complex illnesses.	

Evidence Table : **Economic evaluation – Comprehensive palliative care**
Question : **Is palliative care intervention cost-effective in improving quality of life of patient with chronic life-limiting illness?**

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
30.Gardiner C, Ryan T, Gott M. What is the cost of palliative care in the UK? A systematic review. BMJ Support Palliat Care. 2018;1–8 Palliative care in UK only	**Systematic review** **Objective** to review evidence on the costs of palliative care in the UK and to explore different approaches used for capturing cost and activity data **Methods** Four electronic databases (CINAHL, Cochrane, PsycINFO; Medline) were searched from 1997 to October 2017. The search was limited to the last 20 years **Inclusion criteria** • Papers relating to adults (≥18 years) • costs of a palliative care approach (defined as a comprehensive package of care incorporating specialist and/or generalist elements). • full economic costs of palliative care, or costs in more than one setting or from the viewpoint of more than one provider. • Studies providing data from the UK or countries within the UK. **Exclusion criteria** Papers published before 1997 or papers where all the cost data were collected pre-1997 Using **health provider perspective**, social care & informal care **Quality assessment** Study quality was evaluated using the 'Weight of Evidence Framework **Outcomes measures** Per patient cost inflated to 2017 prices		10 studies included (5 cross-sectional/ cohort, 4 modelling studies, 1 secondary analysis of trial data) Year published: 1999-2018 Type of disease: Cancer, advanced disease and refractory breathlessness, any non-curative, heart failure, advanced melanoma, any palliative care 4 studies only estimated the cost of palliative care from an NHS perspective 4 studies included social care costs in addition to NHS costs. 2 studies capture comprehensive costs including informal care Round et al 2015, Hatzindreu et al 2018 ,Hollingworth et al 2016, Dzingina et al 2017, Coyle et al 1999, Guest et al 2006, McBride et al 2011,Georghiou and Bardsley 2014, Bardsley et al 2010, Johnston et al 2012	Comprehensive package of palliative care incorporating specialist and / or generalist elements. Specialist palliative care is provided by professionals who have undergone recognised specialist palliative care training and generalist palliative care is palliative care provided as part of standard clinical practice by any healthcare professional that is not part of a specialist palliative care team.			Studies in this review displayed significant variation in their estimates of the cost of end-of-life care and ranged from £4140 for 1 week of life to £38 377 for the last year of life. 2 studies found informal care to represent a significant percentage of the total cost of care (33% and 72%, respectively) **Authors conclusion**: The data are limited, and the heterogeneity is such that it is not possible to provide an aggregate cost of palliative care in the UK. It is notable that the costs of hospice care and informal care are often neglected in economic studies.	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
31.Isenberg SR, Lu C, McQuade J et al. Economic Evaluation of a Hospital-Based Palliative Care Program. J Oncol Pract [Internet]. 2017;13(5):e408–20 Palliative care unit in John Hopkins Medicine	**Cost-effectiveness Analysis** **Objective** To establish costs of an inpatient palliative care unit (PCU) and conduct a threshold analysis to estimate the maximum possible costs for the PCU to be considered cost effective **Methods** Used administrative data PCU between March 2013 and March 2014 Calculated total costs of the PCU and the cost per patient encounter (PE). PEs = each distinct stay of a patient in the unit 3 categories of costs: • palliative direct (i.e., patients transferred from ED and clinics) • palliative transfers (i.e., patients transferred to the PCU from other departments, pre-PCU) • professional fees for physician services 3 types of costs considered; • variable costs alone = sum of the variable direct and indirect costs, and the professional fees for the physician or advance practice nurse staffing the unit • contribution margin (i.e., revenue minus variable costs)= losses incurred after accounting for the difference between the net revenue generated from insurance companies and out- of-pocket/patient co-payments, and the total variable costs of the program, including professional fees • PCU cost savings compared to usual care (from existing literature) - used a threshold analysis to assess the maximum costs for the PCU to be considered cost effective, incorporating willingness to pay ($180,000) Fixed costs are excluded from the calculation of costs **Perspective:** provider (hospital) **Time Horizon: 13 months** **Discounting:** not done-short length of time before death **Outcomes measures** QALY		153 patient encounters The unit received patients from the Emergency Department and clinics, as well as transfers from other departments (e.g., Intensive Care Units, Oncology). Patients were discharged to homecare, home hospice, or subacute institutional care (e.g., nursing home) PCU shared the floor with a high-amenities unit that had higher costs and was serviced by non-palliative nursing staff There were limited PC staff to both provide care in the PCU and PC consultations When not used for the PCU, beds generated revenue from surgical and medical patients.	Palliative care in its first year of operation Active management (e.g., transfusions, epidural pain therapy, radiation therapy, physical therapy) and specialized support (e.g., chaplaincy and social work)	Standard care	13 months of data	The data showed that that there were 153 patient encounters (PEs), a contribution margin of $318,413 ($407 per PE per day), and variable costs of $1,050,031 ($1,343 per PE per day). PCU saved the hospital (Cost- minimization analysis result) $353,645 overall ($452 per PE per day), a 25% cost reduction, compared to pre-PCU On the basis of the literature, the program was estimated to generate 3.11 quality-adjusted life years (QALYs) from patients (0.05 QALY) and caregivers (3.06 QALYs). The threshold analysis determined that the PCU could cost up to $559,800 more than standard care (i.e., the PCU could spend an additional $716 per PE per day) and still be considered cost effective **Authors conclusion**: According to variable costs, the PCU was not cost effective; however, when considering savings of the PCU compared with usual care, the PCU was cost saving. The contribution margin showed that the PCU was cost saving. This study supports efforts to expand PCUs, which enhance care for patients and their caregivers and can generate hospital savings. Future research should prospectively explore the cost utility of PCUs.	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
32.Cunningham C, Ollendorf D, Travers K. The effectiveness and value of palliative care in the outpatient setting. JAMA Intern Med. 2017;177(2):264–5.	**Systematic review** **Objective** To synthesize evidence describing the relative effectiveness of outpatient palliative care relative to usual care, its drivers, and associated costs **Methods** Focused on higher-quality comparative studies of outpatient palliative care interventions delivered in the United States or Canada, incorporating elements directed at both physical and psychosocial patient care, including a multidisciplinary care team, palliative care specialist, patient and family education, advanced care planning, and monthly in-person office visits **Quality assessment** Done but method not described **Outcomes measures** 7 studies reported QOL outcomes. Four of these studies were conducted in cancer populations using various forms of the Functional Assessment of Cancer Therapy (FACT) or Functional Assessment of Chronic Illness Therapy (FACIT) instruments		13 fair- or good-quality studies, comparing a palliative care intervention to usual or standard treatment for advanced or serious disease 8 RCTs 10 described specialist- vs generalist-led interventions 4 evaluated early interventions 5 evaluated outpatient palliative care's effect on patients with cancer only	Palliative care Outpatient - incorporating elements directed at both physical and psychosocial patient care, including a multidisciplinary care team, palliative care specialist, patient and family education, advanced care planning, and monthly in-person office visits	Standard or usual care		All documented statistically significant **QOL** improvements over 3 to 13 months of follow-up with mean differences exceeding the minimum clinically important change measurable QOL in the remaining 3 studies improved similarly in both intervention and control groups. The quantity and direction of evidence was similar in studies of the impact of palliative care on anxiety and depression Nine studies evaluated at least 1 measure of **resource utilization**, either location of death or use of acute health care services. 1 RCT reported a 2-fold increase in the likelihood of death at home in the palliative care group(odds ratio, 2.20vs usual care; 95%CI, 1.3- 3.7; P < 0.001)5; another recorded a more than 50% reduction in the risk of dying in hospital (relative risk, 0.46; 95%CI, 0.40-0.52). In contrast, evidence was mixed regarding the effects of palliative care on the use of emergency department and hospital care; only approximately one-half of available studies reported significantly reduced resource utilization among the palliative care group One RCT of early palliative care in patients with cancer documented a 3-month improvement in **survival** (11.6 vs 8.9months for usual care; P = 0.02); another cancer RCT described a 30% reduction in the risk of death during the first year of follow-up (hazard ratio, 0.67; 95% CI, 0.50-0.91; P = 0.01). Outpatient palliative care significantly reduced total **health care costs** among patients with terminal or advanced and complex illness.5,7,8 One RCT reported a significantly lower adjusted mean cost of care associated with outpatient care compared with usual care ($12 670 vs $20 222; P =0.03) among Kaiser Permanente patients; an earlier study in the same setting reported similar results ($7990 vs $14570) P <0.001). Significant reductions in cost of 18 months of care after outpatient palliative care enrolment compared with pre enrolment costs were also reported in a retrospective study set in the mid-Atlantic region ($16 467 vs $23 386; P < 0.001). It is worth noting that costs saved by the health care system may be transferred to unpaid family or other informal caregivers. Despite this concern, our budget impact analysis suggests that even if only 10% of patients with advanced illness enrolled in palliative care programs in the last year of life, reductions in direct medical costs would exceed $4 billion in the United States. **Authors conclusion**: Outpatient palliative care improves outcomes relative to usual care in patients with serious illness, although the strength of evidence is moderate. Barriers to outpatient palliative care access be minimized by increasing availability of alternative delivery options; and that further research be supported to evaluate current models of outpatient palliative care and generate evidence comparing these models	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
33.Greer JA, Tramontano AC, McMahon PM et al. Cost Analysis of a Randomized Trial of Early Palliative Care in Patients with Metastatic Nonsmall-Cell Lung Cancer. J Palliat Med [Internet]. 2016;19(8):842–8.	**Cost analysis** **Objective** To determine the impact of early involvement of palliative care (PC) in the outpatient setting on the cost of care **Methods** Data for this secondary analysis came from a trial of 151 patients with metastatic non-small-cell lung cancer (NSCLC) who were randomized to early PC integrated with standard oncology care (SC) or SC alone. Costs were calculated based on the visit type, including inpatient care, outpatient care, chemotherapy administration, or hospice care Costs for hospital and outpatient care, including intravenous chemotherapy were abstracted from the hospital accounting system. Oral chemotherapy costs were estimated based on actual drug costs. Medicare reimbursement rate was used to estimate hospice costs. Between-group differences in costs of care were determined throughout the entire study period and during the last 30 days before death using the bootstrap-t method **Outcomes measures** ICER		Cost data from RCT of 151 patients with newly diagnosed metastatic non-small-cell lung cancer (NSCLC) At the time of analysis, 138 participants (91%) had died, for whom we analysed the medical care utilization and cost data. Of these, 70 were in the standard care group and 68 were in the early PC group.	Early palliative care integrated with standard oncology care	Standard palliative care alone	median time of follow-up for the participants in the sample who had died was 8.1months	The analytic sample includes the 138/151 patients who died by July 15, 2013. Early PC was associated with a lower mean total cost per day of $117 (p = 0.13) compared to SC. In the final 30 days of life, patients in the early PC group incurred higher hospice care costs (mean difference = $1,053; p = 0.07), while expenses for chemotherapy were less (mean difference = $757; p = 0.03). Costs for emergency department visits and hospitalizations did not differ significantly between groups over the course of the study or at the end of life Using hospital costs, rather than insurance reimbursements, as a measure of resource use, we found that randomization to early PC was associated with a cost-effectiveness ratio of $41,938/life year saved, compared to standard care. **Authors conclusion**: The delivery of early PC does not appear to increase overall medical care expenses for patients with metastatic NSCLC. Larger, sufficiently powered cost studies of early PC are needed.	

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Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
34.Spilsbury K, Rosenwax L. Community-based specialist palliative care is associated with reduced hospital costs for people with non-cancer conditions during the last year of life. BMC Palliat Care BMC Palliative Care; 2017;16(1):68 Western Australia	**Retrospective cohort** **Objective** to determine if community-based palliative care provided to people dying from non-cancer conditions was associated with reduced hospital costs in the last year of life and how this compared with people dying from cancer **Methods** A retrospective population-based cohort study of all decedents in Western Australia who died January 2009 to December 2010 from a life-limiting condition considered amenable to palliative care. Hospital costs were assigned to each day of the last year of life for each decedent with a zero cost applied to days not in hospital. Day-specific hospital costs averaged over all decedents (cohort averaged) and decedents in hospital only (inpatient averaged) were estimated. Two-part models and generalised linear models were used **Cohort selection** Death records, hospital records and community-based care records of all decedents spanning the last 2 years of life was obtained. 12, 817 people who died during the 2 year study period in WA and who had mention on Part I of their death certificate of one or more of the ten disease conditions considered amenable for palliative care. When a decedent had more than one of the ten conditions of interest on Part 1 of their death certificate, then the most antecedent condition was assigned as the principal condition **Exposure variable:** community-based specialist palliative care **Outcomes measures:** day-specific hospital costs. Each day of the last year of life for every decedent was assigned a day number ranging from 1 (365 days before death) to 365 (day of death). A hospital cost was applied to each day of the last year of life for every decedent with days not spent in hospital considered to have incurred zero costs. From these day-specific hospital costs, two cost-based outcome measures were defined	II-2	12,817 individuals included in the study. After excluding 34 decedents with incomplete demographic information and 19 decedents with Huntington's disease or HIV/AIDS due to small numbers, there remained 12,764 decedents in this study cohort	Community-based specialist palliative care -provided by Silver Chain WA which supplied over 90% of referred community-based specialist palliative care in WA -multidisciplinary team of palliative care clinicians and nurses, allied health professionals and volunteers provide home nursing care, counselling, respite options, practical support and links to other services with the aim of enabling people with a life limiting illness to remain at home			The cohort comprised 12,764 decedents who, combined, spent 451,236 (9.7%) days of the last year of life in hospital. Overall, periods of time receiving community-based specialist palliative care were associated with a 27% decrease from A$112 (A$110-A$114) per decedent per day to $A82 (A$78-A$85) per decedent per day of CA hospital costs. Community-based specialist palliative care was also associated a reduction of inpatient averaged hospital costs of 9% (7%-10%) to A$1030 per hospitalised decedent per day. Hospital cost reductions were observed for decedents with organ failures, chronic obstructive pulmonary disease, Alzheimer's disease, Parkinson's disease and cancer but not for motor neurone disease. Cost reductions associated with community-based specialist palliative care were evident 4 months before death for decedents with cancer and by one to 2 months before death for decedents dying from other conditions. **Authors conclusion**: Community-based specialist palliative care was associated with hospital cost reductions across multiple life-limiting conditions	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
35.Youens D, Moorin R. The Impact of Community-Based Palliative Care on Utilization and Cost of Acute Care Hospital Services in the Last Year of Life. J Palliat Med 2017;20(7):736–44 Study conducted in Australia	**Retrospective cohort** **Objective** To examined the impact of accessing community - based palliative care on hospital use in the last 12 months of life among cancer decedents **Methods** Study used linked individual administrative records from cancer registry, hospital, emergency department (ED), mortality, and PCS databases Exposure was determined as ever versus never exposed, with people categorized based on having had a PCS record at any point in time before death Place of death was determined as either in hospital or not In hospital based on coding of this variable on the HMDS. Episodes of inpatient hospitalization, which were constructed while taking into account inter-hospital transfers, were categorized as emergency (i.e., unplanned) versus nonemergency ascertained by using admission status recorded in the HMDS. Length of stay (LOS), constructed by using the number of days between the first and the last calendar day of each episode of care, was used to calculate the total bed days spent in hospital and average LOS in each look-back period. ED presentations were assigned to look-back periods based on the date of presentation **Outcomes measures** Total costs Length of stay Unplanned hospitalisation ED presentations Place of death	II-2	39,247 people died due to cancer in Western Australia and were eligible for inclusion in this study Majority of decedents; men, aged older than 75 years, had a partner, were born in either Australia or New Zealand, were diagnosed within one year of death, were diagnosed with a single cancer, and had comorbidity	Community based PC provided by single not-for-profit provider, Silver Chain Palliative care teams comprising nurses, doctors, care aides, counsellors, chaplains, social workers, and volunteers		last 12 months of life among cancer decedents Time before death was categorized to several look-back periods as follows: 12 months, 6 months, 3 months, 1 month, and 1 week before the date of death	Place of death differed substantially between people who did and did not access the service. Those who accessed the service had triple (3.2, 95% confidence interval 3.0–3.4) the odds of dying out of hospital compared with decedents who did not access the service Over the last 12 months of life, accessing the service was associated with a significant reduction in the rate of unplanned hospitalizations across all look-back periods. Reductions were largest within the last month (incidence rate ratio [IRR] 0.70 and IRR 0.51) and last week (IRR 0.58 and IRR 0.35) of life for all and unplanned hospitalizations, respectively. Access to the service was also associated with reduced rates of ED presentations, with the magnitude of the effect greatest over the final month (IRR 0.50) and week of life (IRR 0.25). Over the last 12months of life, accessing the service was associated with a significant reduction in the average number of days spent in hospital and the average LOS regardless of the type of hospitalization or look-back period. Accessing the service was associated with LOS that was significantly lower than the average for the AR-DRG over the final three months of life. This association was reversed at shorter look-backs, with no significant difference over the last month of life and significantly higher LOS in the final week. In comparison, the average cost for both all acute care services and unplanned hospitalizations was significantly lower for decedents who accessed the service regardless of look-back **Authors conclusion**: Access to community-based palliative care was associated with improved outcomes at the end of life, specifically lower rates of hospital and ED use, and an increased likelihood of death occurring out of hospital The provision of high-quality palliative care in the community alleviates the burden on acute care hospitals and, thus, may partially offset public funding of this model	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
36.Cassel JB, Kerr KM, McClish DK et al. Effect of a Home-Based Palliative Care Program on Healthcare Use and Costs. J Am Geriatr Soc. 2016;64(11):2288–95.	**Retrospective study** **Objective** To evaluate the non-clinical outcomes of a proactive palliative care program funded and operated by a health system for Medicare Advantage plan beneficiaries (Transition®) **Methods** Conducted observational, retrospective study using propensity-based matching. Transitions® program is self-funded by Sharp HealthCare and not reimbursed by third-party payers. Costs were analysed from the perspective of the health system (Sharp Health- Care) - includes hospitalizations, out-patient care, home health, transportation services, diagnostic services, durable medical equipment, injectable drugs, chemotherapy agents, and professional services. It does not include hospice care, because beneficiaries revert to the traditional Medicare hospice benefit when they elect hospice. **Outcomes measures** hospital costs, other healthcare costs, readmission rates, hospital admissions and bed days, intensive care unit use in final 30 days of life, and death within 30 days of an admission		Individuals who received the intervention between 2007 and 2014 (n = 368) were matched with 1,075 comparison individuals within each of 4 disease groups: cancer, chronic obstructive pulmonary disease, heart failure, and dementia. All were known to be dead at the time of the retrospective study, were Medicare Advantage beneficiaries, and had 2 years of usage data before death. Median age at death for each disease group was older than 80	Home- and clinic-based palliative care (PC) services provided by a multidisciplinary team Transitions® is a concurrent care home-based program designed for individuals with advanced chronic illness who would benefit from support provided by a trained specialty PC team comprising doctors, nurses, spiritual care providers, and social workers. The Transitions program has 4 components: in-home medical consultation, ongoing evidence-based prognostication of further survival, care-giver support, and advance healthcare planning	(propensity-based matching)		For each disease, hospital costs and total costs per month were lower for Transitions® participants (all p ≤ 0.002). For three of the four disease groups, there was not a significant difference in non-hospital costs (p = 0.32 for cancer, p = 0.08 for COPD, p = 0.09 for HF). For each disease, the percentage of participants hospitalized, number of hospital days, admisssion in the final 30 days of life, using the intensive care unit in the final 30 days of life were lower for Transitions® than for controls (all p ≤ 0.001). Mean 30-day readmission rate was also lower for Transitions® participants with COPD, HF and dementia (p<0.01), but not those with cancer (p = 0.08). Transitions® participants' costs increased only slightly in the final months of life (from USD1,550 4 months before death to USD3,711 in final month), whereas comparison participants' costs increased dramatically (from USD2,631 four months before death to USD17,006 in final month). Adding the USD642 in costs per month for Transitions services to the Transitions® group, the net savings per participant per month were USD4,258 for cancer, USD4,017 for COPD, USD3,447 for HF, and USD2,690 for dementia. The return on investment (net cost reduction divided by programme costs) thus ranged from 4.2 for dementia to 6.6 for cancer. **Authors conclusion**: Intervention participants in all four disease groups had less hospital use and lower hospital costs non- intervention participants, which drove lower overall healthcare costs. In the final 6 months of life, healthcare costs for the intervention groups stayed largely the same from month to month, whereas costs for comparison participants increased dramatically.	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
37.Pham B, Krahn M. End-of-Life Care Interventions: An Economic Analysis. Ont Health Technol Assess Ser. 2014;14(18):1–70.	**Cost-effectiveness analysis** **Objective** To evaluate the cost-effectiveness of end-of-life (EoL) care interventions included in the EoL care mega- analysis **Methods** The authors conducted the primary economic analysis and budget impact analysis for an Ontario cohort of decedents and their families and included interventions pertaining to team-based models of care, patient care planning discussions, educational interventions for patients and caregivers, and supportive interventions for informal caregivers. **Perspective** The analysis was conducted from the perspective of the Ontario Ministry of Health and Long-Term Care. Costs were expressed in 2013 Canadian dollars **Time horizon**= last year of life. Costs were in 2013 Canadian dollars. **Discounting**: No discounting was used for health outcomes and costs. The authors used the cohort's last year of life to define a 1-year time horizon A Markov model was developed; model inputs were obtained from a cohort of Ontario decedents assembled from Institute for Clinical Evaluative Sciences databases and published literature **Outcomes measures** days at home, percentage dying at home, and quality- adjusted life-days		6 relevant studies met the inclusion criteria (1 systematic review and 5 cost-effectiveness studies) studies included • palliative team care – in-home • palliative team care – inpatient • palliative team care – comprehensive palliative team care (in which a single team is in charge of care coordination across all settings) • patient care planning discussions –identifying LTC residents with EoL goals and preferences for early palliative care – ethics consultation for intensive care unit (ICU) patients with treatment conflicts among providers, patients and family that could lead to incompatible courses of action –improving family conferences for relatives of patients dying in the ICU -educational interventions for patients and caregivers –multicomponent psycho-educational interventions for patients and families supportive interventions for informal caregivers	Strategies: -team-based models for EoL care -patient care planning discussions -educational interventions for patients and caregivers -supportive interventions for informal caregivers	Current patterns of EoL care; decedents were identified with a palliative prognosis if they received at least 1 palliative care service		In-home palliative team care was cost-effective; it increased the chance of dying at home by 10%, increased the average number of days at home (6 days) and quality-adjusted life-days (0.5 days), and it reduced costs by approximately $4,400 per patient. Expanding in-home palliative team care to those currently not receiving such services (approximately 45,000 per year, at an annual cost of $76–108 million) is likely to improve quality of life, reduce the use of acute care resources, and save $191–$385 million in health care costs. Results for the other interventions were uncertain **Authors conclusion**: In-home palliative team care was cost-effective, but firm conclusions about the cost-effectiveness of other interventions were not possible.	

Evidence Table **:** **Organizational – Resource utilisation**

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
38.Seow H, Brazil K, Sussman J et al. Impact of community based, specialist palliative care teams on hospitalisations and emergency department visits late in life and hospital deaths: A Pooled analysis. BMJ 2014;348(June):1–10	**Pooled analysis of retrospective cohort** **Objective** To determine the pooled effect of exposure to one of 11 specialist palliative care teams providing services in patients' homes **Methods** Conducted pooled analysis of a retrospective cohort study. Estimated the relative risk of using acute care in the last two weeks of life and dying in hospital in each of the 11 teams separately and also the overall pooled effect (weighted). Methods appropriate for matched samples were used in all cases (for example, McNemar's test for binary outcomes) Sensitivity analysis conducted to examine separately the pooled results for the two approaches (historical and geographical) used to identify a control group **Inclusion criteria** included formal palliative care specialist teams that met the following criteria: (a) provided interdisciplinary, home based, palliative care; (b) were the only such team in their respective region; (c) had little or no change in staffing between 2009 until 2012; (d) had broad admission criteria not limited to one disease (such as cancer); (e) admitted more than 50 patients a year; (f) were available to patients 24/7; and (g) had the same core members of their team as the past randomised trials **Exclusion criteria** Alive after 2011, were <18 years old, or had an invalid or missing provincial health insurance number **Outcomes measures** Patients (a) being in hospital in the last two weeks of life; (b) having an emergency department visit in the last two weeks of life; or (c) dying in hospital	II-2	3109 patients who received care from specialist palliative care teams in 2009-11 (exposed) matched by propensity score to 3109 patients who received usual care (unexposed)	Palliative care teams studied served different geographies and varied in team composition and size but had the same core team members and role: a core group of palliative care physicians, nurses, and family physicians who provide integrated palliative care to patients in their homes. The teams' role was to manage symptoms, provide education and care, coordinate services, and be available without interruption regardless of time or day.			In both exposed and unexposed groups, about 80% had cancer and 78% received end of life homecare services for the same average duration. Across all palliative care teams, 970 (31.2%) of the exposed group were in hospital and 896 (28.9%) had an emergency department visit in the last two weeks of life respectively, compared with 1219 (39.3%) and 1070 (34.5%) of the unexposed group (P<0.001). The pooled relative risks of being in hospital and having an emergency department visit in late life comparing exposed versus unexposed were 0.68 (95% confidence interval 0.61 to 0.76) and 0.77 (0.69 to 0.86) respectively. Fewer exposed than unexposed patients died in hospital (503 (16.2%) v 887 (28.6%), P<0.001), and the pooled relative risk of dying in hospital was 0.46 (0.40 to 0.52) **Authors conclusion**: Community based specialist palliative care teams, despite variation in team composition and geographies, were effective at reducing acute care use and hospital deaths at the end of life.	

Evidence Table : Organisational issues – Communication-based competencies

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
39.Schram AW, Hougham GW, Meltzer DO, Ruhnke GW. Palliative Care in Critical Care Settings: A Systematic Review of Communication- Based Competencies Essential for Patient and Family Satisfaction. Am J Hosp Palliat Med. 2016;1–9 USA	**Systematic review** **Objective** To evaluate the physician competency domains outside technical aspects of clinical care most important for patient- and family-centered outcomes in the ICU at the end of life (EOL) **Methods** Review of qualitative and quantitative empirical studies of the impact of physician competencies on patient- and family-reported outcomes conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines for systematic reviews. The data sources used were PubMed, MEDLINE, Web of Science, and Google Scholar **Inclusion criteria** Articles selected for inclusion were original research (not reviews or commentaries) that identified physician competencies thought to impact patient and/or family satisfaction **Exclusion criteria** case reports and all publications in other than English, studies that did not include measures of satisfaction were excluded **Quality assessment** Not mentioned	I	15 studies (5 qualitative and 10 quantitative) meeting inclusion and exclusion criteria were identified.				The competencies identified as critical for the delivery of high-quality PC in critical care settings are: i. Prognostication—The ability to effectively communicate prognostic information to patients and family members ii.conflict mediation —The ability to detect and mediate disagreement between family members and clinicians iii.empathic communication —The ability to provide support to patients and family members during conversation using both specific statements and nonverbal cues iv.family-centered aspects of care —The ability to respect families and respond to their needs and wishes to facilitate shared decision-making, particularly when the patient cannot communicate **Authors conclusion**: Prognostication, conflict mediation, empathic communication, and family-centered aspects of care are the most important identified competencies for patient- and family-centered PC in critical care settings. Incorporation of education on these competencies is likely to improve patient and family satisfaction with EOL care.	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
40.Epstein RM, Duberstein PR, Fenton JJ et al. Effect of a Patient-Centred Communication Intervention on Oncologist-Patient Communication, Quality of Life, and Health Care Utilization in Advanced Cancer The VOICE Randomized Clinical Trial. JAMA Oncol. 2016;E1-9 USA	**Cluster randomized controlled trial** **Objective** To determine whether a combined intervention involving oncologists, patients with advanced cancer, and caregivers would promote patient-centred communication, and to estimate intervention effects on shared understanding, patient-physician relationships, QOL, and aggressive treatments in the last 30 days of life **Methods** Multisite cluster RCT at community- and hospital-based cancer clinics in Western New York and Northern California- 4 community-based cancer clinics, 3 academic medical centres and 3 community hospitals **The Values and Options in Cancer Care (VOICE) study** combined 2 interventions, a brief individualized oncologist skill-based training, and individualized patient and caregiver coaching incorporating a question prompt lists (QPL) Oncologists randomized to the intervention arm: individualized communication training using standardized patient-instructors (SPIs) Patients (with caregivers) participated in an individualized communication coaching session with follow-up telephone calls. After a pre-randomization phase designed to assess baseline communication patterns of participating oncologists, participants enrolled (from August 2012 through June 2014) and followed up until October 2015 **Outcome measures** Primary outcome patient-centred communication in these domains: engaging patients to participate in the consultation, responding to patients' emotions, informing patients about prognosis and treatment choices, and framing information in a balanced manner Secondary outcomes Shared understanding, patient-physician relationships, QOL, and health care utilization in the last 30 days of life	I	38 medical oncologists -mean age 44.6 years; -11 (29%) female 265 community-dwelling adult patients with advanced non-hematologic cancer participated -mean age, 64.4 years, -146 [55.0%] female, 235 [89%] white -enrolled August 2012 to June 2014 -followed for 3 years -194 patients had participating caregivers Median survival was 16months: 19months in the intervention group and 14 months in the control (hazard ratio, 0.84; 95%CI, 0.61-1.15)	Oncologists received individualized communication training using standardized patient instructors -2-session in-office physician training (1.75hours) using a brief video A single 1-hour patient and caregiver coaching session incorporating a question prompt list to help patients bring their most important concerns to their oncologist's attention at an upcoming office visit, plus up to 3 follow-up phone calls Both interventions focused on engaging patients in consultations, responding to emotions, informing patients about prognosis and treatment choices, and balanced framing of information	Control participants received no training	3 years	Data from 38 oncologists (19 randomized to intervention) and 265 patients (130 interventions) were analyzed. In fully adjusted models, the intervention resulted in clinically and statistically significant improvements in the primary physician-patient communication end point (adjusted intervention effect, 0.34; 95% CI, 0.06-0.62; P =0.02). Of the individual communication component measures, only the engaging measure (APPC) was statistically significant. Differences in other secondary outcomes were not statistically significant. Overall, QOL and health care utilization differences between intervention and control were not statistically significant **Authors conclusion**: A combined intervention that included oncologist communication training and coaching for patients with advanced cancer was effective in improving patient-centred communication but did not affect secondary outcomes	

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
41.Kelly B, Rid A, Wendler D. Systematic Review: Individuals' Goals for Surrogate Decision-Making. J Am Geriatr Soc 2012 60: 884–95	**Systematic review** **Objective** To determine to what extent current practice promotes the goals of individuals who did not designate a surrogate while competent with respect to decision- making during periods of decisional incapacity **Methods** Conducted systematic literature search for studies published in English and listed in PubMed, Scopus, Embase, CINAHL, or PsycINFO. Quantitative surveys and qualitative interview studies assessing individuals' goals. The quantitative articles used a range of instruments. Most of the qualitative articles used semi- structured interviews **Inclusion criteria** Studies were eligible if they provided quantitative or qualitative empirical data on how adults want treatment decisions to be made for them during periods of incapacity **Quality assessment** Assessed using specific criteria adapted from an article	I	14 qualitative articles: 26 quantitative articles, providing data on the views of 22,828 individuals, met the inclusion criteria The articles surveyed individuals in the United States, Canada, France, Japan, Sweden, Australia, and Singapore Most of the respondents were elderly or seriously ill 20 articles reported the views of elderly individuals, typically aged 65 and older 9 reported the views of terminally or seriously ill patients. 10 articles focused on the views of particular patient or ethnic groups. Only 6 articles surveyed a larger cross-section of a given population				The majority wanted close family members to act as their surrogate. The most common reason for preferring family members was the belief that they know which treatments the patient would want. Individuals also wanted to reduce the burden on their families. 17 articles provided quantitative data regarding whether respondents had any discussion with someone else regarding end-of-life decision-making; none quantified the frequency, length, or depth of discussion. Of these 17 articles, 11 found end-of-life discussion rates of lower than 50%. An additional 5 articles found rates lower than 70%. Only 1 reported discussion rates higher than 70%. There was significant variation in the extent to which respondents wanted their surrogates to have leeway when making treatment decisions. One quantitative article reported that 58% of respondents wanted their surrogates to have none or a little leeway, whereas 42% wanted their surrogates to have a lot or complete leeway. Another quantitative article found that 63% of respondents wanted their surrogates to follow their advance directives strictly or as much as possible, whereas 33% wanted their surrogates to use their advance directives as a reference only, and 3% did not care if their wishes were followed. The qualitative articles, which found that some respondents "granted permission to proxies to freely interpret their written preferences," whereas others insisted that their surrogates "follow their instructions precisely," supported these findings **Authors conclusion**: Individuals have 3 primary goals with respect to making treatment decisions for them during periods of incapacity: involve their family, treat them consistently with their own treatment preferences, and reduce the burden on their family Unfortunately, prior systematic reviews have found that family members often are not able to determine which treatment patients want, and family members frequently experience substantial distress when acting as surrogates. These findings suggest that current practice frequently fails to promote individuals' primary goals for treatment decision-making. Future research should evaluate ways to better promote individuals' goals. In the meantime, clinicians should be aware of these findings and should encourage patients to document their own goals, including their treatment preferences and their preferences regarding how they want decisions to be made for them during periods of decisional incapacity	

Evidence Table : **Cultural and religious considerations in paediatric palliative care**

Bibliographic citation	Study Type/Methods	LE	Number of Studies/ Patients & Studies/ Patients Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
42.Weiner L, Mcconnell DG, Latella L, Ludi E. Cultural and religious considerations in pediatric palliative care. Palliat Support Care.2013;11(1):47–67	**Systematic review** **Objective** To explore and address the influence of religion in paediatric palliative care, with emphasis on how culture informs lifestyle and shapes the universal experiences of illness, pain, and death **Methods** Comprehensive literature searches were completed through an online search of nine databases for articles published between 1980 and 2011: PsychINFO, MEDLINE®, Journal of Citation Reports-Science Edition, Embase, Scopus, CINAHL®, Social Sciences Citation Index (SSCI), EBSCO, and Ovid. Key terms included: culture, transcultural, spiritual, international, ethnic, customs or religion AND end-of-life, palliative care, death, dying, cancer, or hospice, and children, paediatrics, or paediatric oncology **Quality assessment** Not mentioned	I	37 studies included Studies done among cultures included: Chinese, Japanese, Korean, South Asian (India, Bangladesh, Nepal, Pakistan, Maldives, Sri Lanka), Latino, Filipino, Vietnamese, African-American, Native American, Caribbean-American, Russian-American				7 distinct themes emerged that have implications for pediatric palliative care: role of culture in decision- making Appreciation of cultural norms and customs is critical as it pertains to family decision makers and those who learn about the diagnosis or prognosis. Child-rearing practices in different cultures may also play a role in decision making faith and the involvement of clergy Parents of children receiving palliative care have noted that faith is central to their efforts to provide guidance, make sense of their situation, grant permission around end-of-life decision making, and to better cope. However, the involvement of pastoral workers in paediatric palliative care is not universal communication (spoken and unspoken language Breakdowns in communication can lead to improper diagnosis, inadequate pain management, underutilization of prescription medications, and difficulty in obtaining informed consent - emphasizes the need for trained medical interpreters to be used to mediate communication between family and healthcare professionals communicating to children about death (truth telling) Management of their child's pain and suffering is a critical issue for all parents. The perception and experience of physical pain and the meaning pain has to one's existence varies by culture. Choice of treatment at the end of life may also reflect cultural differences that are incongruous or supplemental with the medical treatment provided in the hospital or as recommended by hospice providers. Chinese, Korean, Vietnamese, and Native Americans have been reported to view asking for assistance with pain as a sign of disrespect. the meaning of pain and suffering, the meaning of death and dying A common existential or spiritual issue often grappled is the search for the meaning of pain, illness, suffering, and death - not static across cultures. Vietnamese families describe illness as a conflict between the body and nature, other Asian individuals of Buddhist, Confucian, or Hindu faiths may attribute illness and suffering to bad karma or sin in previous life and view suffering as a mechanism for atoning for sins committed in a former life. Muslims believe that illness can result from bad actions, in this or past lives, and that illness washes away a person's sins location of end-of-life care Limited literature is available on cultural differences pertaining to whether one's final days are best spent at home or in a medical facility. Some culture believe that death in the home is a sign of bad luck, whereas others fear that if an individual dies while in the hospital, his or her soul will be lost. When death occurs, cultural differences in expressions of grief may be observed **Authors conclusion**: This provides insight into the influence of religion and how culture informs lifestyle and shapes the experiences of illness, pain, and end-of- life care. Cultural traditions are dynamic, never static, and cannot be generalized to all families. Guidelines to aid in approaches to palliative care are provided, and providers are encouraged to define these important differences for each family under their care.	