

APPENDIX A. SEARCH STRATEGIES

PubMed search date (KQ 1, KQ 2): November 21, 2016

Set	Terms	Results
#1	"Neoplasms"[Mesh] OR neoplasms[tiab] OR neoplasm[tiab] OR cancer[tiab] OR cancers[tiab] OR malignancy[tiab] OR malignant[tiab] OR carcinoma[tiab] OR carcinomas[tiab] OR blastoma[tiab]	3312258
#2	"Hospice and Palliative Care Nursing"[Mesh] OR "Palliative Medicine"[Mesh] OR "Palliative Care"[Mesh] OR "Terminal Care"[Mesh:NoExp] OR "Hospice Care"[Mesh] OR "Hospices"[Mesh] OR palliative[tiab] OR palliation[tiab] OR hospice[tiab] OR "end of life care"[tiab]	100731
#3	"Ambulatory Care"[Mesh] OR "Ambulatory Care Facilities"[Mesh] OR "Primary Health Care"[Mesh] OR "Home Care Services"[Mesh] OR "Residential Facilities"[Mesh] OR "Physicians, Primary Care"[Mesh] OR "Physicians, Family"[Mesh] OR "Outpatients"[Mesh] OR "Emergency Medical Services"[Mesh] OR ambulatory[tiab] OR primary care[tiab] OR outpatient[tiab] OR outpatients[tiab] OR clinic[tiab] OR clinics[tiab] OR home[tiab] OR community[tiab] OR "emergency department"[tiab] OR "out patient"[tiab] OR "out patients"[tiab]	1200038
#4	("early palliative care"[tiab] OR "early palliative intervention*"[tiab])	166
#5	(#2 AND #3) OR #4	16509
#6	((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR "Comparative Study"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR Nonrandom[tiab] OR non-random[tiab] OR nonrandomized[tiab] OR non-randomized[tiab] OR nonrandomized[tiab] OR non-randomised[tiab] OR quasi-experiment*[tiab] OR quasiexperiment*[tiab] OR quasirandom*[tiab] OR quasi-random*[tiab] OR quasi-control*[tiab] OR quasicontrol*[tiab] OR (controlled[tiab] AND (trial[tiab] OR study[tiab]))) NOT (animals[mh] NOT humans[mh]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]))	3043573
#7	#1 AND #5 AND #6	1364

PubMed search date (KQ 3): January 19, 2017

Set	Terms	Results
#1	Search ("Hospice and Palliative Care Nursing"[Mesh] OR "Palliative Medicine"[Mesh] OR "Palliative Care"[Mesh] OR "palliative care"[tiab])	53475
#2	Search ("Hospice Care"[Mesh] OR "Hospices"[Mesh] OR hospice[tiab] OR "end of life care"[tiab])	19112
#3	Search (#1 OR #2)	65099
#4	Search (barrier[tiab] OR barriers[tiab] OR implement[tiab] OR implementation[tiab])	408456
#6	Search "Health Plan Implementation"[Mesh]	4610
#7	Search (#4 OR #6)	410440
#8	Search (veteran OR veterans)	114612
#9	Search (#3 AND #7)	3068
#10	Search (#9 AND #8)	75

APPENDIX B. STUDY ELIGIBILITY CRITERIA

PICOTS Study Element	Inclusion Criteria	Exclusion Criteria
Population	<p>Adults ≥ 18 years of age with symptomatic or advanced malignancy defined as one of the following:</p> <ul style="list-style-type: none"> • Malignancy causing symptoms such as fatigue, pain, or breathlessness, or unmet needs related to the malignancy • Malignancy without curative treatment options • Advanced stage (eg, stage III or IV malignancy), including statements of “late stage” or “advanced cancer” 	<ul style="list-style-type: none"> • Patients with cancer not associated with systemic symptoms (eg, non-melanoma skin cancer) • Patients with non-cancer advanced illness • Studies enrolling mixed samples unless the majority are enrolled because of a symptomatic or advanced malignancy
Intervention	<p>Integrated palliative care meeting the following definition:</p> <ul style="list-style-type: none"> • An individual or multidisciplinary team of clinicians working together with a patient’s oncology physician(s) and having a focus on relief of symptoms and stress of serious illness. Goal is to improve quality of life for the patient and family. • One or more of the palliative care clinicians must have specialized training in palliative care, and the intervention must be multidimensional (<i>ie</i>, targeting at least the physical and psychosocial domains of quality of life). <p>Integration may be broad, ranging from basic collaboration at a distance (eg, information exchanged to address specific patient treatment issues) to colocated care, to fully integrated care.</p> <p>Studies that evaluate barriers to implementing an integrated palliative care program in a research or clinical context are included</p>	<ul style="list-style-type: none"> • Standalone palliative care interventions (eg, palliative chemotherapy, palliative radiotherapy) • Palliative care services delivered by clinicians without specialized training • Palliative care services (<i>ie</i>, hospice) delivered exclusively in the home (no outpatient clinic-based assessment) for the terminal stages of illness • Palliative care consultation without longitudinal services • Palliative care restricted to care for a single symptom (eg, opioids for dyspnea) • Palliative care intervention that targets only the caregiver
Comparators	<p>KQ 1, KQ 2: Usual oncology care</p> <p>KQ 3: No comparator required for studies conducted in VA settings. For studies conducted outside of VA settings, the study must have an eligible comparator as specified for KQ 1 and KQ 2.</p>	No eligible comparator

PICOTS Study Element	Inclusion Criteria	Exclusion Criteria
Outcomes	<p>KQ 1, KQ 2:</p> <ul style="list-style-type: none"> • Care recipient primary outcomes: <ul style="list-style-type: none"> ○ Functional status or healthcare quality of life, defined as overall QOL (<i>ie</i>, global QOL) and then further defined as functional status, including physical functioning (<i>eg</i>, activities of daily living), general psychological functioning (<i>eg</i>, psychological well-being) and social functioning (<i>eg</i>, social well-being) ○ Disease-related symptoms, overall symptom burden (if overall symptom burden was not reported, then include symptom assessment of fatigue, pain, or sleep) ○ Care experience • Care recipient secondary outcomes: <ul style="list-style-type: none"> ○ Survival ○ Site of death ○ Healthcare utilization such as emergency department, inpatient, intensive care unit days, total costs ○ Adverse effects • Caregiver outcomes: <ul style="list-style-type: none"> ○ Care experience ○ Caregiver burden (<i>eg</i>, Caregiver Strain Index), depression (<i>eg</i>, PHQ-9) <p>The foregoing outcomes must be assessed using a standard instrument.</p> <p>KQ 3: Barriers to implementation, including workforce, stigma, financial, logistical (<i>eg</i>, space, communication and coordination between clinicians)</p>	<p>Studies that do not plan to report any included outcomes; but studies that plan to report an included outcome but give only cursory results (<i>eg</i>, p not significant) were included</p>
Timing	<p>KQ 1, KQ 2: Studies reporting outcomes at ≥ 28 days (approximately 1 month) following initiation of integrated palliative care intervention</p> <p>KQ 3: No follow-up requirement; may be cross-sectional</p>	<p>KQ 1, KQ 2: Studies reporting outcomes at < 28 days</p>

PICOTS Study Element	Inclusion Criteria	Exclusion Criteria
Setting	<p>All KQs: Outpatient palliative care integrated with outpatient oncology services. Palliative care may be colocated or located in a separate outpatient setting. Services may be delivered in the emergency department, patient's home, by telephone, or by video.</p> <p>KQ 3: VA settings for any studies that address implementation barriers but were not eligible for KQ 1 or KQ 2</p>	<p>Institutional settings (eg, skilled nursing facility) or interventions delivered primarily to hospitalized patients</p>
Study design	<p>KQ 1, KQ 2:</p> <ul style="list-style-type: none"> • Randomized controlled trials • Cluster-randomized trials • Nonrandomized cluster trials • Controlled before-and-after studies with at least 2 intervention sites and 2 control sites <p>KQ 3: Quantitative studies (eg, surveys) and qualitative studies (eg, focus groups, key informant interviews, qualitative case studies) that address barriers to implementation related to studies eligible for KQ 1 or KQ 2 and studies addressing barriers in VA settings</p> <p>Study country limited to North America, Australia, New Zealand, and Western, Northern, and Southern Europe</p>	<ul style="list-style-type: none"> • Case reports, case-series, cross-sectional studies, and all studies without a comparator • Sample size <20 (ie, small pilot studies that are lower quality, prone to publication bias, and not powered to detect effects on clinically important outcomes)
Publication type	<ul style="list-style-type: none"> • English-language only • Peer-reviewed articles • Published from 1995 forward 	<ul style="list-style-type: none"> • Non-English articles • Abstracts only • Letters to the editor • Editorials • Dissertations

APPENDIX C. EXCLUDED STUDIES

All studies listed below were reviewed in their full-text version and excluded for the reasons cited. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles. The reference list for these excluded studies follows the table.

Exclusion reason	Not English or primary study	Not population of interest	Not eligible study design	Not eligible setting	Not eligible intervention	Not eligible outcomes	Not OECD country	N<20
Study								
Abernethy, 2013 ¹					X			
Acorn, 2008 ²					X			
Addington-Hall, 1992 ³	X							
Arnold, 2010 ⁴	X							
Bakitas, 2009 ⁵	X							
Barrett, 2009 ⁶			X					
Barth, 2013 ⁷			X					
Beernaert, 2014 ⁸				X				
Begue, 2012 ⁹			X					
Blackhall, 2016 ¹⁰			X					
Booth, 2010 ¹¹	X							
Borneman, 2008 ¹²			X					
Breitbart, 2012 ¹³					X			
Brumley, 2003 ¹⁴		X						
Brumley, 2007 ¹⁵		X						
Bucher, 2001 ¹⁶			X					
Cameron, 2004 ¹⁷			X					
Chambers, 2008 ¹⁸	X							
Chochinov, 2011 ¹⁹			X					
Critchley, 1999 ²⁰			X					
Daly, 2013 ²¹			X					
Davis, 2012 ²²	X							

Exclusion reason	Not English or primary study	Not population of interest	Not eligible study design	Not eligible setting	Not eligible intervention	Not eligible outcomes	Not OECD country	N<20
Study								
DeSanto-Madeya, 2009 ²³				X				
Dionne-Odom, 2016 ²⁴		X						
Dionne-Odom, 2016 ²⁵					X			
Dionne-Odom, 2016 ²⁶			X					
do Carmo, 2015 ²⁷					X			
Douglas, 2014 ²⁸					X			
Duursma, 2011 ²⁹	X							
Dyar, 2012 ³⁰								X
Edwards, 2014 ³¹					X			
El-Jawahri, 2010 ³²					X			
El-Jawahri, 2016 ³³		X						
Engelhardt, 2006 ³⁴		X						
Eschbach, 2014 ³⁵	X							
Farquhar, 2014 ³⁶					X			
Ferrell, 2015 ³⁷			X					
Fischer, 2015 ³⁸		X						
Follwell, 2009 ³⁹			X					
Fontani, 2011 ⁴⁰		X						
Geiger, 2011 ⁴¹			X					
Given, 2002 ⁴²					X			
Gomes, 2013 ⁴³			X					
Gomez-Batiste, 2010 ⁴⁴					X			
Goodwin, 2003 ⁴⁵					X			
Gray, 1987 ⁴⁶	X							
Greer, 1986 ⁴⁷	X							
Greer, 2012 ⁴⁸	X							
Grudzen, 2014 ⁴⁹				X				

Exclusion reason	Not English or primary study	Not population of interest	Not eligible study design	Not eligible setting	Not eligible intervention	Not eligible outcomes	Not OECD country	N<20
Study								
Grudzen, 2016 ⁵⁰				X				
Hainsworth, 2002 ⁵¹			X					
Hanks, 2002 ⁵²				X				
Hannon, 2013 ⁵³	X							
Hannon, 2014 ⁵⁴	X							
Hannon, 2015 ⁵⁵	X							
Hannon, 2016 ⁵⁶						X		
Hermann, 2012 ⁵⁷					X			
Higginson, 2010 ⁵⁸			X					
Higginson, 2010 ⁵⁹		X						
Higginson, 2014 ⁶⁰					X			
Hinton, 1998 ⁶¹			X					
Hollen, 2000 ⁶²		X						
Holm, 2016 ⁶³		X						
Holm, 2016 ⁶⁴					X			
Hughes, 1992 ⁶⁵	X							
Jack, 2003 ⁶⁶				X				
Jelinek, 2014 ⁶⁷				X				
Johnsen, 2014 ⁶⁸						X		
Johnson, 2011 ⁶⁹			X					
Jones, 2013 ⁷⁰				X				
Jordhøy, 2000 ⁷¹					X			
Jordhoy, 2001 ⁷²					X			
Jung, 2013 ⁷³			X					
Kandarian, 2014 ⁷⁴						X		
Kane, 1984 ⁷⁵	X							
Keating, 2010 ⁷⁶			X					

Exclusion reason	Not English or primary study	Not population of interest	Not eligible study design	Not eligible setting	Not eligible intervention	Not eligible outcomes	Not OECD country	N<20
Study								
Kissane, 2016 ⁷⁷					X			
Kotzsch, 2015 ⁷⁸			X					
Lau, 2012 ⁷⁹	X							
Lazenby, 2010 ⁸⁰	X							
Lidstone, 2003 ⁸¹			X					
Lowe, 2009 ⁸²			X					
Lowery, 2013 ⁸³			X					
Lukas, 2013 ⁸⁴		X						
Maeda, 2016 ⁸⁵			X					
McCorkle, 1998 ⁸⁶					X			
McDonald, 2015 ⁸⁷	X							
McDonald, 2015 ⁸⁸	X							
McDonald, 2016 ⁸⁹						X		
McLoughlin, 2015 ⁹⁰	X							
McMillan, 2002 ⁹¹			X					
McMillan, 2011 ⁹²		X						
Mills, 2009 ⁹³					X			
Moore, 2002 ⁹⁴					X			
Morita, 2009 ⁹⁵		X						
Nabal, 2013 ⁹⁶			X					
Nakajima, 2016 ⁹⁷			X					
Nipp, 2016 ⁹⁸			X					
Nordly, 2014 ⁹⁹						X		
Northouse, 2005 ¹⁰⁰					X			
Northouse, 2007 ¹⁰¹					X			
Northouse, 2013 ¹⁰²					X			
Obel, 2014 ¹⁰³			X					

Exclusion reason	Not English or primary study	Not population of interest	Not eligible study design	Not eligible setting	Not eligible intervention	Not eligible outcomes	Not OECD country	N<20
Study								
Obermeyer, 2016 ¹⁰⁴			X					
Odejide, 2014 ¹⁰⁵				X				
Oliver, 2012 ¹⁰⁶	X							
Ornstein, 2017 ¹⁰⁷					X			
Otsuka, 2013 ¹⁰⁸			X					
Ozcelik, 2014 ¹⁰⁹				X				
Pachman, 2011 ¹¹⁰			X					
Parikh, 2013 ¹¹¹	X							
Phillips, 2008 ¹¹²		X						
Rabow, 2003 ¹¹³			X					
Rabow, 2003 ¹¹⁴		X						
Rabow, 2004 ¹¹⁵		X						
Raftery, 1996 ¹¹⁶					X			
Ragnarson-Tennvall, 1999 ¹¹⁷			X					
Raphaël, 2005 ¹¹⁸			X					
Reville, 2009 ¹¹⁹	X							
Schenker, 2015 ¹²⁰			X					
Sekelja, 2010 ¹²¹		X						
Seow, 2014 ¹²²			X					
Silveira, 2011 ¹²³	X							
Smeenk, 1998 ¹²⁴					X			
Smeenk, 1998 ¹²⁵				X				
Sochor, 2014 ¹²⁶	X							
Steel, 2016 ¹²⁷					X			
Steinhauser, 2008 ¹²⁸			X					
Stern, 2012 ¹²⁹		X						
Strasser, 2016 ¹³⁰					X			

Exclusion reason	Not English or primary study	Not population of interest	Not eligible study design	Not eligible setting	Not eligible intervention	Not eligible outcomes	Not OECD country	N<20
Study								
Sun, 2015 ¹³¹			X					
Tattersall, 2014 ¹³²					X			
Temel, 2007 ¹³³			X					
The SUPPORT Principal Investigators, 1995 ¹³⁴		X						
Thomas, 2016 ¹³⁵	X							
Tuca-Rodriguez, 2012 ¹³⁶			X					
Uitdehaag, 2014 ¹³⁷					X			
Vinciguerra, 1986 ¹³⁸	X							
Vinciguerra, 1986 ¹³⁹	X							
Vuksanovic, 2016 ¹⁴⁰					X			
Wang, 2011 ¹⁴¹		X						
Warren, 2011 ¹⁴²			X					
Wentlandt, 2012 ¹⁴³					X			
Wilkie, 2016 ¹⁴⁴					X			
Yennu, 2014 ¹⁴⁵	X							
Yoong, 2012 ¹⁴⁶								X
Yoong, 2013 ¹⁴⁷								X
Young, 2013 ¹⁴⁸		X						
Zimmermann, 2010 ¹⁴⁹			X					
Zimmermann, 2012 ¹⁵⁰	X							

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APPENDIX D. INTERVENTION ELEMENTS AND DEFINITIONS

Below are the definitions for the 8 clinical elements of palliative care interventions. The table that follows shows which elements were present in each included study. For full study citations, please refer to the report's main reference list.

- **Structural** and processes of care: interdisciplinary team engagement (engagement with patients or families, coordinated assessment and continuity of care across healthcare settings)
- **Physical** aspects of care: what is being done to decrease symptoms (assessment and pharmacological, interventional, behavioral and/or complementary treatments)
- **Psychological** or psychiatric aspects of care: what is being done to address mental health issues (assessment and treatment of psychological and/or psychiatric concerns for patient or caregiver)
- **Social** aspects of care: interdisciplinary engagement and collaboration with patients and families (identify, support or capitalize on their strengths; facilitate patient-family understanding of illness; perform social assessment including caregiving or adaptive equipment needs, or need/access to community resources)
- **Spiritual**, religious, and existential aspects of care: support of spiritual belief system, if present (practices or rituals for comfort/relief; this ideally involves a trained chaplain on the palliative care team)
- **Cultural** aspects of care: identification of and respect for cultural differences (tailored communication to literacy level and language spoken; accommodation of cultural practices and traditions)
- **End of life** care of patient: guidance through the dying process (information on what to expect at end of life, suggestions of coping strategies; *eg*, the stages of grief: denial through acceptance)
- **Ethical and legal** aspects of care: goals of care (discussions about impact of treatment decisions, determination of patient's decision-making capacity, advance care planning completion; *eg*, Do Not Resuscitate [DNR])

Study Impact Rating	Structural	Physical	Psychological	Social	Spiritual	Cultural	End of Life	Ethical/Legal
Bakitas, 2009 ¹² Moderate	No	Physical symptom management; eg, self-care	Psychological symptom management; eg, problem-solving	Attention to communication and coordination of resources	No	No	Advance care planning	Decision-making about advance care planning
Bakitas, 2015 ⁴¹ Low	No	Physical symptom management; eg, self-care	Psychological symptom management; eg, problem-solving	Attention to communication and coordination of resources	Framing advanced illness challenges as personal growth opportunities	No	Life review as applies to advance care planning	Decision-making about advance care planning
Clark, 2013 ⁴³ Low	No	Physical therapy exercises and management of health behavior, substance use, symptoms	Psychological symptom and mood management	Social needs & communication strategies	Exploration of meaning, purpose, grief, and loss	No	No	Writing advance directives
Maltoni, 2016 ³⁹ Low	Yes, but no details	Yes, but no details	Yes, but no details	No	Yes, but no details	No	No	No
McCorkle, 2015 ⁴⁰ None	Coordinated inter-disciplinary team that collaborates with other providers to teach patients and families	Physical symptom management: executing care procedures and addressing adverse events	Counseling to clarify illness experience and enhance QOL	Enhancing self-efficacy for decision-making and problem-solving about family and caregivers	No	No	No	Goals for advance care discussed

Study Impact Rating	Structural	Physical	Psychological	Social	Spiritual	Cultural	End of Life	Ethical/Legal
Rummans, 2006 ⁴⁴ Low	No	Physical therapy exercises and discussion of healthy lifestyle	Cognitive behavioral therapy for mood; stress management and irrational thinking	Sources and use of support, communication, interpersonal relationships and coping	Explore grief, guilt, hope, purpose, meaning, rituals, beliefs, death	No	Explore end of life, death, and afterlife; other "spiritual aspects"	No
Temel, 2010 ¹⁴ Moderate	Yes, but no details	Yes, but no details	Yes, but no details	Yes, but no details	Yes, but no details	No	Yes, but no details	Yes, but no details
Temel, 2017 ⁴⁵ Low	Regular palliative care appointments; oncologist could schedule extra palliative care visits; inpatient palliative care team followed if admitted	Helping to understand prognosis, treatment options; then making treatment goals, communicate care preferences	Addressed coping, depression, and anxiety	Addressed coping with family, familial understanding of illness, and family caregiver referral	Addressed spiritual coping, rituals, and belief systems	No	Discussed end-of-life care preferences and life review	Discussed advance care planning
Zimmermann, 2014 ⁴² Low	Multi-disciplinary assessment	Assessment of symptoms; urgent care if necessary	Assessed psychological distress	Assessed social support	No	No	No	No

APPENDIX E. AUTHOR SURVEY OF INCLUDED PALLIATIVE CARE INTERVENTION ELEMENTS

Please provide your name. For each question, please answer to describe the intervention arm in the cited study.

Q1. Are palliative care provider(s) and oncology provider(s) physically or virtually located in the same space?

Yes, colocated in the same clinical space

Yes, virtually colocated by video link or similar

No

Unsure

Q2. Is written or electronic information exchanged routinely between palliative and oncology clinicians? (eg, alert in medical record, faxed documents)

Yes

No

Unsure

Q3. Is communication between oncology and palliative care interactive? (ie, “two way”)

Yes

No, exchange of information is without interactive communication

Unsure

Q4. Do providers from palliative care and oncology communicate on a “standard and routine practice” basis to address specific patient treatment issues? Communication may be in-person, by email exchange, team meeting, or phone call conversation.

Yes

No

Unsure

Q5. Do the palliative care and oncology care health providers have equal roles in decision making? Are they both involved in the approach to individual patient care?

Yes

No

Unsure

Q6. Were providers involved in care in a standard way across ALL patients? (*eg*, do all staff use the same tools and resources, and then ensure that all patients with the same score or outcome receives the same options for treatment?)

Yes

No

Unsure

Q7. Is there one joint treatment plan for cancer patients that is shared by palliative care and oncology care providers?

Yes

No

Unsure

APPENDIX F. DEFINITIONS AND DATA USED FOR IMPACT RATING DETERMINATIONS

The table that follows contains details related to how the impact rating was determined for each study comparing integrated palliative and oncology care interventions to a comparator or control. Table cells show what was measured, the timepoint of measurement, and an indication of the effect size. All comparisons are in the direction of intervention versus control. For full study citations, please refer to the report's main reference list.

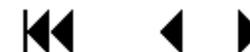
Definitions of the impact ratings:

- **High**—Pattern of positive effects across all patient-centered outcomes; may also have positive effects on end-of-life care and/or utilization. Magnitude of effects include at least 1 primary outcome with summary or median SMD/effect size of 0.8 or greater; mean difference that substantially exceeds the minimum clinically important difference; or risk ratio (RR) or hazard ratio (HR) ≥ 2 or odds ratio (OR) ≥ 3 .
- **Moderate**—Pattern of mostly positive effects across patient-centered outcomes; may also have positive effects on end-of-life care and/or utilization. Magnitude of effects include at least 1 primary outcome with summary or median SMD/effect size of ≥ 0.5 ; mean difference that meets or exceeds the minimum clinically important difference; or RR or HR ≥ 1.5 or OR ≥ 2 .
- **Low**—Inconsistent pattern of statistically positive and negative effects across patient-centered outcomes; may also have inconsistent effects on end-of-life care and/or utilization. Magnitude of effects include at least 1 primary outcome with summary or median SMD/effect size of ≥ 0.25 ; mean difference that is statistically significant but does not meet the minimum clinically important difference; or RR or HR ≥ 1.25 or OR ≥ 1.5 .
- **No impact**—Pattern of statistically nonsignificant effects or inconsistent pattern of statistically positive and negative effects but all patient centered outcomes are statistically nonsignificant.

Study	QOL	Symptom Burden	Mortality	Site of Death	End-of-Life Treatment	HC Utilization	Final Impact Rating
Bakitas, 2009 ¹²	At 13 months FACT-PC mean difference: 4.6 (SE 2.0), p=0.02	At 13 months CES-D mean difference: -1.8 (SE 0.81), p=0.02 ESAS mean difference: -27.8 (SE 15), p=0.06	Survival at longest follow-up: 49/16 vs 42/161, p=0.14 Median survival time: 14 months vs 8.5 months, p=NR	NR	NR	At 13 months Hospital days (range 0 to 25), p=0.14 ICU days (range 0 to 2), p>0.99 ER visits (range 0 to 4), p=0.53	Moderate
Bakitas, 2015 ⁴¹	At 3 months TOI Cohen's d: 0.11, p=0.24 At 12 months Cohen's d: 0.11, p=0.24;	At 3 months QUAL-E Cohen's d: -0.21, CES-D Cohen's d: 0.04, At 12 months QUAL-E Cohen's d: -0.31, CES-D Cohen's d: 0.1, Significance over all timepoints (3,6,9,12)- QUAL-E, p=0.09 CES-D, p=0.33	1 year survival rate: 66/104 vs 49/103, p=0.038 Average length of survival: 18.3 vs 11.8 months	Died at home: 27/50 vs 28/59, p=0.60	In decedents, chemotherapy during last 2 weeks of life measured at end of study RR=1.57 (95% CI 0.37 to 6.7)	In decedents, hospital days at end of study: RR=0.73 (95% CI 0.41 to 1.27), p=0.26 ICU days at end of study: RR=0.68 (95% CI 0.23 to 2.02), p=0.49 ED visits at end of study: RR=0.73 (95% CI 0.45 to 1.19), p=0.21	Low
Clark, 2013 ⁴³	At 4 weeks FACT-G mean difference: 5.5 (no SD), p=0.02 At 27 weeks mean difference: 0.1, p=0.88	Exact timepoints unknown POMS: p=NS FACT Spiritual Well-being Scale: p=NS	NR	NR	NR	NR	Low



Study	QOL	Symptom Burden	Mortality	Site of Death	End-of-Life Treatment	HC Utilization	Final Impact Rating
Maltoni, 2016 ³⁹	At 12±3 weeks TOI mean difference: 6.3 (95% CI 0.75 to 11.95)	Overall HCS mean difference: 3.78 (95% CI 0.86 to 6.71), p=0.008 At 12±3 weeks HADS-A: p=0.06 HADS-D: p=0.28, NS	Survival probability at study end: 22.4% vs 12.3%, NS	At home vs hospice: p=0.138, NS At nursing home: p=0.702, NS	Chemotherapy last 30 days: p=0.192, NS Admission 30 days before death: p=0.539, NS ER visits 30 days before death: p=0.729, NS	Primary care visits at 12±3 weeks and at study end: p=0.0001 Hospitalizations, timeframe unclear: p=0.417, NS ER visits to study end: p=0.891, NS	Low
McCorkle, 2015 ⁴⁰	At 3 months FACT-G: p=0.371	At 3 months SDS: p=0.610 for time*group HADS-A: p=0.1173 PHQ-9: p=0.927 for time*group	NR	NR	NR	NR	None
Rummans, 2006 ⁴⁴	At 4 weeks Spitzer Uniscale mean difference: 8.7 (no SD), p=0.047, % of people improved by 8 points, p=0.025 At 27 weeks mean difference: 0, p>.99, improved by 8 points NR	At 4 weeks SDS: p=NS POMS: p=NS FACIT-SP mean difference: 9, p=0.003	NR	NR	NR	NR	Low
Temel, 2010 ¹⁴	At 12 weeks TOI mean difference: 6.0 (95% CI 1.5 to 10.4), Cohen's d 0.52, p=0.009	At 12 weeks overall LCS mean difference: 1.7 (95% CI 0.1 to 3.2), p=0.04 Specific diagnosis, % meeting threshold-	Overall median survival: 11.6 months (95% CI 6.4 to 16.9) vs 8.9 (95% CI 6.3 to 11.4), p=0.02	At 18 mo follow-up Place of death (home vs other): 40/61 vs 36/66, p=0.28	Aggressive care: 16/49 vs 30/56, p=0.05 Hospitalization (30 days before death): 18/49 vs	Hospitalizations from enrollment to death: 36/49 vs 43/56, p=NR ED days during entire study: 26/49 vs 32/56, p=NR	Moderate



Study	QOL	Symptom Burden	Mortality	Site of Death	End-of-Life Treatment	HC Utilization	Final Impact Rating
	FACT-L: mean difference 6.5 (95% CI 0.5 to 12.4), Cohen's d 0.42, p=0.03	PHQ-9: p=0.04 HADS-D: p=0.0 HADS-A: p=0.66, NS			30/56, p=NR; Chemotherapy (last 60 days of life): 32/61 vs 47/67, p=0.05 ED (30 days before death): 11/49 vs 17/56, p=NR	Cost savings mean difference: \$117 (\$74)	
Temel, 2017 ⁴⁵	<u>At 12 weeks</u> FACT-G mean difference: 2.40 (95% CI -0.38 to 5.18), p=0.09 <u>At 24 weeks</u> mean difference: 5.36 (95% CI 2.04 to 8.69), p=0.02	<u>At 12 weeks</u> PHQ-9 mean difference: -0.78 (95% CI -1.76 to 0.21), p=0.12 <u>At 24 weeks</u> Mean difference: -1.17 (95% CI -2.33 to -0.01), p=0.048	NR	NR	NR	NR	Low
Zimmermann, 2014 ⁴²	<u>At 3 months</u> FACIT-SP mean difference: 3.56 (95% CI, -0.27 to 7.40), p=0.07 <u>At 4 months</u> mean difference: 6.44 (95% CI, 2.13 to 10.76), p=0.006	<u>At 3 months</u> ESAS mean difference: -1.70 (95% CI, -5.26 to 1.87), p=NS <u>At 4 months</u> mean difference: -4.41 (95% CI, -8.76 to -0.06), p=0.05	Raw data for number of deaths: 44/228 vs 26/233, p=NR	NR	NR	NR	Low

Abbreviations: CES-D=Center for Epidemiologic Studies Depression Scale; CI=confidence interval; ED=emergency department; ER=emergency room; ESAS=Edmonton Symptom Assessment Scale; FACIT-SP=Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being; FACT-G=Functional Assessment of Cancer Therapy-General; FACT-L=Functional Assessment of Cancer Therapy-Lung; HADS=Hospital Anxiety and Depression Scale; HCS=Hepatobiliary Cancer Subscale; LCS=Lung cancer subscale; NR=not reported; PHQ=Patient Health Questionnaire; POMS=Profile of Mood States; QUAL-E=Quality of life at end of life symptom impact subscale; SDS=Symptom Distress Scale; TOI=Trials Outcome Index



APPENDIX G. PEER REVIEW COMMENTS

Question Text	Comment	Response
Are the objectives, scope, and methods for this review clearly described?	Yes	Acknowledged, thank you.
	Yes	Acknowledged, thank you.
Q2		
Is there any indication of bias in our synthesis of the evidence?	No	Acknowledged, thank you.
	No	Acknowledged, thank you.
Q3		
Are there any <u>published</u> or <u>unpublished</u> studies that we may have overlooked?	No	Acknowledged, thank you.
	No	Acknowledged, thank you.
Q4		
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.	<p>VA ESP Integrated Outpatient Palliative Care in Oncology Scott Shreve's comments</p> <p>General: 1) Very impressed with the quality and depth of the analyses to include objectively assessing the strength of evidence and contacting authors for info related to integration, wow!</p> <p>2) Interesting that decreased mortality comes out as a key finding whereas this was not found in a large recent meta-analysis (Kavalieratos et al, JAMA)</p>	<p>Thank you!</p> <p>We agree this a very interesting finding of the report. Our report was focused on integrated delivery for patients with malignancy compared to the JAMA report which included a broader range of patients and interventions.</p>

Question Text	Comment	Response
	<p>3) Identified barriers have strong face validity (cost, space and perception pall care is for end stage)</p> <p>4) Opportunities to assist in our program office expansion of integrated palliative care include 1) meaningful elements of integration, 2) standardized caregiver depression intervention, 3) development of a specific performance measure and 4) communication of value to leadership</p> <p>More Specific:</p> <p>1) I especially appreciated the 1st paragraph of the introduction about palliative care can be provided at all stages of disease and is now the standard of care</p> <p>2) I also appreciate the reference to the American College of Surgeons' Commission on Care about requiring integration of palliative care into cancer centers as this specialty has been a barrier within VHA</p> <p>3) I need to learn more about the impact of palliative care on caregivers as the findings seem mixed (none in the JAMA meta-analysis, some here and perhaps in the Cochrane review) and GEC may be embarking on a BIG initiative to support caregivers</p> <p>4) Page 7, 2nd paragraph, 2nd sentence..."All Veterans in the United States have access to palliative care..." needs to be changed to "All enrolled Veterans in the US..."</p> <p>5) Is there strong evidence elsewhere that the more "integrated" care is according to the Integrated Practice Assessment Tool that care is improved?</p>	<p>Acknowledged, thank you.</p> <p>Acknowledged, thank you.</p> <p>Acknowledged, thank you.</p> <p>Acknowledged, thank you.</p> <p>The JAMA review (Kavalieratos 2016) used a vote counting approach and found caregiver satisfaction improved in 4 of 5 studies reporting this outcome, but QOL, mood and caregiver burden were improved in only the minority of studies. However, this review included a broader range of conditions (e.g. heart failure) and palliative care approaches (e.g., those without clear integration). The Cochrane review (Haun 2017) was restricted to early palliative care for advanced cancer and found no effect on caregiver burden and one study showing mixed effects on caregiver mood.</p> <p>This change has been made.</p> <p>This is an interesting question. To our knowledge the level of integration has been studied infrequently, and classifications such as the one we used in our study have not been evaluated</p>

Question Text	Comment	Response
	<p>6) Page 18, I'd be interested to know what the median intervention was for the studies (e.g., 4 outpatient visits as it was for Temel in 2010)? I also found it surprising that the Palliative Care Interventions did not specifically mention a social worker. Our program office did some analyses and found SW staffing correlated with improved family perception of the quality of care.</p> <p>7) Page 21, Figure 5, I'm a bit confused in the labelling of the x axis, didn't most of these studies show a benefit for palliative care whereas the axis favors the control group?</p> <p>8) Page 23, increased likelihood of dying at home is important as is the impact on mortality.</p> <p>9) Page 24, I'm a bit disheartened to see no impact from the telephone intervention trials but ask if I'm correct that telemedicine would be an entirely different intervention? Any evidence on this?</p> <p>10) Page 24 re reduced caregiver depressive symptoms would seem to have policy implications and perhaps a more standardized use of the intervention by our palliative care teams</p> <p>11) Page 30, I'm enticed by the comments about integration elements (suggestion that palliative and oncology teams that have interactive, routine communication and some degree of colocation) as our program office seeks to promote integration across our system</p> <p>12) Page 35, the use of a patient decision aid is enticing as I've heard of this being used to assist in promoting advance directives but had not heard of its effectiveness in promoting palliative care among patients (food for thought as oncologist could incorporate</p>	<p>previously for an association with intervention impact.</p> <p>The median intervention was 17 weeks in those with fixed duration; 3 studies continued the intervention until death. Two of the 9 eligible intervention studies included social workers, one as a facilitator of multidisciplinary sessions and one as part of the overall palliative care team. This information has been added to the results section.</p> <p>The x axis was mislabeled and has been corrected.</p> <p>We agree. These findings are highlighted in the key points and discussion.</p> <p>Telemedicine is defined broadly as using telecommunications technology to evaluate, diagnose and treat patients at remote locations. Only 1 of the 9 interventions studies used telephone interactions as the primary mode for delivering care. This study is identified and discussed in the results section. There is too little data to make any definitive conclusions on telemedicine as a delivery mode for palliative care</p> <p>Acknowledged, thank you.</p> <p>Acknowledged, thank you.</p> <p>Acknowledged, thank you.</p>

Question Text	Comment	Response
	<p>this at time of diagnosis)</p> <p>13) Any thoughts on why there was an impact on short term QOL but not longer term?</p> <p>14) Page 39, Performance measures were mentioned by VA leaders as needed to facilitate integrated palliative care whereas many senior VA leaders are seeking to reduce performance measures, somewhat of a conundrum.</p>	<p>There were fewer studies and fewer patients in the longer term QOL. Thus statistical power was lower for effects on longer compared with short-term QOL. There also may be clinical reasons for why long-term effects were less. As patients approach the terminal portion of illness with greater symptom burden and decreased functional status, palliative care interventions may become less effective.</p> <p>We agree with the reviewer that there is inconsistency regarding performance measures. The need for the development of performance measures emerged as a theme by all local leaders (Bekelman et al). However, it was incorrectly written in our summary as a potential facilitator of implementation. At this time, there are no standardized performance measures for patient-centered care and outcomes, so this is considered a barrier to outpatient palliative care implementation. The results and discussion have been updated.</p>
	<p>Some specific comments/questions to consider -</p> <p>p. 20 - long-term (6-12months) benefit of PC on QoL is less robust -</p> <p>Is a QoL benefit at 6-12 months an attainable/desirable goal? (this is also referenced in the summary on page 40); Isn't it likely that at 6-12 months, many of these patients would have significant disease progression/overall health decline/death (or alternatively a minority may have gotten over the worst of their cancer-related symptoms and be doing better)? Should we really expect a benefit at 6-12months? Maybe we would expect that more people would be referred to hospice and possibly have improved QoL from hospice if not deceased?</p> <p>p. 21 Figure 5 - bottom of figure - does negative SMD really favor control? When I read this, I wondered if the wording at the bottom was accurate or if the PC/control words needed to be switched.</p>	<p>Regarding p. 20, we agree with the reviewer's hypothesis that long-term QOL likely does not increase as disease progresses, and symptom burden increases as end of life draws near. We have added a sentence in the results in the first paragraph under the subheading "Effects on Functional Status, Overall Symptom Burden, and Psychological Symptoms" on p. 19 noting that the finding may be expected given patients' declining health. Additionally, because there is a lack of literature examining the appropriateness of QOL measures for use with individuals who are becoming increasingly ill and nearing death, we now note this limitation of the current literature under the Heterogeneity subheading of the Limitations section on p. 42 and as an area for future research in the "Outcomes" row of Table 9 Highest Priority Evidence Gaps on p. 44.</p> <p>The x axis was mislabeled and has been corrected.</p>



Question Text	Comment	Response
	<p>p. 25 yes (yet?) there may be disease-specific benefits (e.g. there may be more benefit for patients with malignancies that are more likely to have high symptom burden and low life expectancy)</p> <p>p. 30 if all trials studied (p. 30 paragraph 2) included co-location, then we aren't able to assess whether colocation itself affects the outcome, right? (If we are trying to understand whether having PC team co-located in oncology clinic improves care [possibly by making consultation easier for patient, staff, and by "normalizing" the process], wouldn't that require us to have a comparator group that does NOT have colocation?)</p>	<p>This is an interesting point, that patients with different malignancies and differing symptoms may experience differing effects from palliative care interventions. Because most studies enrolled patients with a range of malignancies and with 1 exception (Temel 2017) did not examine interaction effects, we are unable to evaluate this hypothesis but have raised it as an area for future research in the discussion.</p> <p>Regarding p. 30, the reviewer makes a great point. Because authors were only offered the option of a "yes/no" response to the question about whether the intervention was colocated in the same facility, we did not obtain data regarding degree of physical proximity (eg, same clinic vs same facility). It is possible that differences in physical proximity could have impacted the relation between the intervention and outcomes. Additionally, there was a further lack of variability in colocation because all study authors indicated that the interventions were colocated. Thus, the review did not include any study interventions that lacked colocation which could be an important comparator. These limitations and their potential impact on the findings are now explicitly addressed in the Limitations section.</p>
	<p>The report is well written with clear methods and procedures for analysis. The criteria for inclusion was very restrictive and thus only a few papers included but it is helpful to have details about papers excluded.</p>	<p>Thank you!</p>
	<p>The authors did an incredible job of systematically reviewing the literature on the benefits and harms of outpatient palliative care in advanced cancer. They developed targeted research objectives, used the appropriate quantitative and qualitative methods to synthesize the literature depending on the research question and available evidence, and went above and beyond to gather the relevant information necessary to answer their research objectives.</p> <p>There have been multiple prior peer-review publications that broadly synthesize the evidence on the impact of specialty</p>	<p>Thank you!</p>

Question Text	Comment	Response
	<p>palliative care; the authors decided therefore appropriately targeted their search to the outpatient arena, and subsequently focused their second and third objectives on important factors that hadn't been previously explored, including the features of palliative care that provide the greatest benefit as well as the most important barriers to implementation.</p> <p>Appropriately, they used primarily quantitative techniques, including conducting a meta analysis, for RCTs that met their inclusion criteria for objective 1. The results are timely and important, and they are appropriately cautious about over-interpreting the findings around quality of life, healthcare utilization, and survival.</p> <p>For Objective 2, the investigators went as far as to contact authors to obtain important information from the Integrated Practice Assessment Tool delivered by SAMHSA to measure the degree of integration of health care services.</p> <p>In Objective 3, they used a combination of quantitative and qualitative techniques appropriate to their review of the literature on barriers to implementation.</p> <p>The figures and tables were painstakingly detailed and easy to read and understand.</p> <p>They also rated the quality of the evidence, and went above and beyond by making an attempt to ascertain the degree of publication bias (turns out this was not possible due to the small number of studies that met inclusion).</p> <p>This is overall an outstanding job of evidence based synthesis - the authors did not take a one size fits all approach to the literature. They used a wide array of detailed assessment tools for systematic review of quantitative and qualitative evidence. They used a variety of methods depending on not only the research objective but also the available literature. I have no constructive comments!</p>	
	<p>Please correct the following errors in Figures 3 and 5.</p> <p>Figure 3, page 20. Temel 2010, used the FACT-L, not the FACT-G</p> <p>Figure 5, page 21. Temel 2010, the population studied was lung</p>	<p>Temel 2010 reported the FACT-L and the TOI index. We used the TOI for this analysis and this is reflected in the revised figure.</p> <p>Thank you. The original figure misidentified the population and has now been corrected.</p>

Question Text	Comment	Response
	not pancreatic cancer.	

APPENDIX H. STUDY CHARACTERISTICS FOR KEY QUESTIONS 1 AND 2

For full study citations, please refer to the report’s main reference list.

Study Location Total N	Intervention Setting Comparator Time Since Diagnosis	Mean Age in Years % Female Veteran?	% Cancer Type Severity or Prognosis	Outcomes Reported	ROB by Outcome Category
Bakitas, 2009 ¹² United States 322	Outpatient Usual care 8-12 weeks	Int: 64.7 Com: 65.4 Int: 40.4% Com: 43.5% Yes	Lung: 36-37% GI: 41-42% Breast: 10-11% GU: 11-12% Stage III or IV	<u>Patient</u> Mental status QOL Disease symptoms Survival Health services use	Objective: Low Patient-reported: Low
Bakitas, 2015 ⁴¹ United States 207	Home Delayed palliative care Within 30-60 days of diagnosis or recurrence	Int: 64.0 Com: 64.6 Int: 46.2% Com: 48.5% Yes	Lung: 41-44% GI: 23-25% Breast: 10-12% Other: 21-23% Advanced stage	<u>Patient</u> Mental status QOL Disease symptoms Survival Health services use	Objective: Unclear Patient-reported: Unclear
Clark, 2013 ⁴³ United States 138	Outpatient Usual care Within 12 months	Int: 58.7 Com: 59.9 Int: 37% Com: 32% No	Lung: 11-15%, GI: 36-39% Other: 46-53% Advanced stage ECOG range 0-2	<u>Patient</u> Mental status QOL <u>Caregiver</u> Experience (QOL)	Objective: NR/NA Patient-reported: High
Maltoni, 2016 ³⁹ Europe 207	Outpatient Standard care plus on demand PC Within 8 weeks	Int: 67 (median) Com: 66 (median) Int: 38.5% Com: 47.2% No	Pancreatic: 100% inoperable or metastatic >2 months	<u>Patient</u> Mental status QOL Disease symptoms Care experience Health service use	Objective: Unclear Patient-reported: High



Study Location Total N	Intervention Setting Comparator Time Since Diagnosis	Mean Age in Years % Female Veteran?	% Cancer Type Severity or Prognosis	Outcomes Reported	ROB by Outcome Category
McCorkle, 2015 ⁴⁰ United States 146	Outpatient Enhanced usual care Within 100 days	Int: 51.5% <age 65 Com: 71.3% <age 65 Int: 71.2% Com: 43.7% No	Intervention: Lung: 56.1% Gyn: 43.9% Comparator: GI: 66.2% Head/neck: 33.8% Late-stage	<u>Patient</u> Physical status Mental status QOL Disease symptoms	Objective: Unclear Patient-reported: High
Rummans, 2006 ⁴⁴ United States 115	Outpatient Usual care Within 12 months	Int: 59.7 Com: 59.4 Int: 40.8% Com: 31.5% No	Lung: 11-18% GI: 36-39%, Other: 45-50% Prognosis > 6 month	<u>Patient</u> Mental status QOL Caregiver: Experience (QOL)	Objective: NR/NA Patient-reported: Unclear
Temel, 2010 ¹⁴ United States 151	Outpatient Usual care Within 8 weeks	Int: 65.0 Com: 64.9 Int: 55% Com: 49% No	Lung: 100% Metastatic ECOG range 0-2	<u>Patient</u> Mental status QOL Survival Site of death Health service use	Objective: Low Patient-reported: Unclear
Temel 2017 ⁴⁵ United States 350	Outpatient Usual care Within 8 weeks	Int: 65.64 Com: 64.03 Int: 48% Com: 44% No	<u>Int</u> Lung: 54.3% GI: 20.6% Pancreatic: 25.1% <u>Com</u> Lung: 54.9% GI: 20.6% Pancreatic: 24.6% NR other than eligibility of "incurable"	<u>Patient</u> Mental status QOL	Objective: NR/NA Patient-reported: Low

Study Location Total N	Intervention Setting Comparator Time Since Diagnosis	Mean Age in Years % Female Veteran?	% Cancer Type Severity or Prognosis	Outcomes Reported	ROB by Outcome Category
Zimmermann, 2014 ⁴² Canada 461	Outpatient Usual care NR	Int: 61.2 Com: 60.2 Int: 59.6% Com: 53.6% No	Lung: 20-24% GI: 28-33% Gyn/GU: 25-39% Stage III or IV ECOG range 0-2	<u>Patient</u> QOL Disease symptoms Health service use <u>Caregiver</u> Family satisfaction with patient care	Objective: Low Patient-reported: Unclear

Abbreviations: Com=comparator; ECOG=Eastern Cooperative Oncology Group; GI=gastrointestinal; GU=genitourinary; Gyn=gynecologic; Int=intervention; NA=not applicable; NR=not reported; QOL=quality of life