Evidence-based Practice Center Mixed Methods Review
Protocol

Project Title: Mixed Methods Review - Integrating Palliative Care with Chronic Disease Management in Ambulatory Care

I. Background and Objectives for the Mixed Methods Review

Background

Most care for patients with serious life-threatening chronic illness or conditions occurs in ambulatory settings. Care for these patients can be complex, as they often face high symptom burden and decreased quality of life. Research has shown that patients and caregivers appreciate the integration of serious illness care into primary care.1, 2 Palliative care is defined as “care, services, or programs for patients with serious life-threatening illness and their caregivers, with the primary intent of relieving suffering and improving health-related quality of life, including dimensions of physical, psychological/emotional, social, and spiritual well-being”.3 Importantly, palliative care approaches are not based on prognosis and can be beneficial throughout the course of serious illness, not just at the end of life. Populations with serious life-threatening chronic illness of key interest for palliative care include, but are not limited to, those with advanced heart failure (New York Heart Association (NYHA) class III or IV), advanced chronic obstructive pulmonary disease (Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria III or IV), end-stage renal disease (on dialysis or choosing not to have dialysis and age 75 or older), and those with frailty or multiple serious chronic conditions.4 Cancer is also a key area of interest for palliative care, but given the large existing research base and existing systematic reviews about integrating palliative care into ambulatory oncology, this review will focus on other illnesses and conditions where more insights are needed.

A variety of types of interventions can be implemented to integrate palliative care into ambulatory care, as described below.

Intervention(s) and Comparator(s)

Approaches to identifying ambulatory patients who could potentially benefit from palliative care include triggers or predictive models or tools, some of which can be incorporated into the electronic medical record.5 These approaches may comprise patient or illness characteristics, recent hospitalizations, indicators of serious illness or worsening of illness such as worsening functional status, or frequent phone calls indicating uncontrolled symptoms. Predictive models are increasingly used in health systems for ambulatory care population health initiatives in conjunction with case management programs for patients at high risk for health care utilization such as hospitalizations. Prediction tools for potential life-shortening illness include measures such as the Palliative Performance Scale, web-based tools (e.g., eprognosis.ucsf.edu) or brief clinician questions to identify those that may have a serious life-threatening condition such as the validated question6 recommended by the American College of Physicians4 to define, "Would I be surprised if
this patient were to die in the next 12 months?” Triggers could include health care utilization such as hospitalizations, or patient-reported measures to identify patients who may have needs that could be addressed with palliative care approaches. Guidelines and position statements may be available through key US palliative care organizations (e.g., the National Consensus Project for Quality Palliative Care) and health care professional primary and palliative care organizations (e.g., the American College of Physicians).

For patient and caregiver education about palliative care, educational materials such as pamphlets and videos may be available from a variety of organizations, particularly those in the National Coalition for Hospice and Palliative Care (e.g., the Center to Advance Palliative Care), as well as government agencies (e.g., the National Institute for Nursing Research, the Health Resources and Services Administration) and organizations focusing on specific conditions (e.g., the Alzheimer’s Association). Many of these materials are proprietary. Some evidence supports the effectiveness of patient-oriented educational approaches for increasing patient acceptance of specialty palliative care.

Shared decision-making tools for palliative care approaches address domains such as goals of care communication or symptom management. The American College of Physicians defines communication about serious illness care goals, also known as advance care planning, as a key task in ambulatory care that should occur throughout the course of a serious illness. Recent systematic reviews have addressed shared decision-making tools for advanced care planning (ACP). Tools include ACP guides, which may include advance directive forms, patient and clinician educational materials, and web- and video-based interventions. To date, these interventions have mainly demonstrated effectiveness for improving documentation about ACP and patient-surrogate congruence for preferences; evidence for integration into ambulatory settings or improving patient/caregiver outcomes is limited. For patients with serious life-threatening chronic illness, palliative care approaches go beyond traditional ACP to discuss current goals of care and patient preferences in the face of serious illness.

For clinician education, National Coalition for Hospice and Palliative care (e.g., the Center to Advance Palliative Care) and health care professional primary care and specialty organizations (e.g., the American College of Physicians) have developed various training and education materials to educate clinicians about use of palliative care and how to integrate palliative care approaches into care. Educational materials and trainings for clinicians have often been studied with other interventions, such as triggers decision support tools, in multimodal interventions. Key barriers to integrating these in ambulatory settings include lack of clinician time and support or services to address patients’ needs related to palliative care. Real-time clinician access to useful information and changing attitudes and culture through addressing clinicians’ needs can also be helpful components of interventions.

A number of reviews have addressed how palliative care can be incorporated into different models of care in the ambulatory setting and what may contribute to their success. A recent rapid review on elements of successful palliative care models found that integrating palliative care specialist expertise with primary and other ambulatory care services was key to model success. Successful models ideally addressed complexity of care and increasing patient comorbidity and longevity with serious illness and coordination with complex health systems and their interactions. Key models include consultative care (where patients are referred to specialty palliative care when appropriate for their needs), shared care (where palliative care clinicians work alongside other ambulatory clinicians to meet patients’ palliative care needs), and stepped care (where non-palliative care ambulatory clinicians are trained to meet and systems support common palliative
care needs, and patients are referred to specialty palliative care when needs are more complex or are not being met). Other types of models include supplementary telephone nurse coaching and integrating social workers into ambulatory care practices. As primary care moves more to interdisciplinary team-based care and capitated care models with new federal and state policy initiatives, these may influence what palliative care models can be implemented and how they can be financed and supported.

Finally, a variety of Centers for Medicare and Medicaid Services (CMS) and other payor payment models and innovations are relevant to the topic of this review, including the integration of palliative care into primary care and other emerging ambulatory care models, such as CMS’s 2019 Primary Care First and Serious Illness Population initiative (https://innovation.cms.gov/initiatives/primary-care-first-model-options/) and Blue Cross Blue Shield’s palliative care initiatives (www.blueshieldca.com/palliativecare).

Purpose of this Review

The aim of this mixed methods review is to evaluate the evidence for integrating palliative care approaches into ambulatory chronic illness care, both through improving provision of palliative care in chronic illness services as well as the appropriate use of specialty palliative care services. The key decisional dilemma for clinicians, patients and caregivers is, “How can people with serious life-threatening chronic illness or conditions best receive ambulatory care that integrates appropriate palliative care approaches or educational services, materials, or shared decision-making tools?

The key audiences for this mixed methods review include primary care, geriatrics, nephrology, pulmonology, cardiology, and neurology providers and their professional organizations; payors, health systems, and government organizations involved in developing programs and training the workforce in ambulatory care of those with serious chronic illness; and patients and caregivers. AHRQ is the primary partner and this review is part of its support of learning health systems in that this information will be valuable to health systems to deliver quality care to patients with serious illnesses. Our Health Resources and Service Administration partner hopes to highlight the latest evidence to help train the primary care workforce, and needs a report of the available evidence to support that training. Our National Institute for Nursing Research partner is the primary government lead for palliative care research at the National Institutes of Health. They will use the evidence synthesis to inform their up-coming five-year strategic plan and to help inform national committees and other scientific initiatives, to identify gaps, research priorities and future funding opportunities, and to help provide the background for guidelines and educational materials for the public.

II. Key Questions

We are addressing five questions about the integration of palliative care in ambulatory care:

1. How can we identify those patients who could benefit from palliative care in ambulatory care settings?
2. What educational resources are available for patients and caregivers in ambulatory care about palliative care?
3. What palliative care decision making tools are available for clinicians, patients and caregivers in ambulatory care?
4. What educational resources are available for non-palliative care clinicians about palliative care in ambulatory settings?
5. What are the models for integrating palliative care into ambulatory settings?

For each of these questions we are addressing three parts:
- What is available? (part a of questions)
- What is the effectiveness? (part b of questions)
- How is it implemented? (part c of questions)

The following are the Key Questions to be addressed in this mixed methods review:

KQ 1:
- **KQ1a.** What prediction models, tools, triggers and guidelines and position statements are available about how to identify when and which patients with serious life-threatening chronic illness or conditions in ambulatory settings could benefit from palliative care?
- **KQ1b.** What is the effectiveness of prediction models, tools and triggers for identifying when and which patients with serious life-threatening chronic illness or conditions in ambulatory settings could benefit from palliative care?
- **KQ1c.** How have prediction models, tools and triggers for identifying when and which patients with serious life-threatening chronic illness or conditions in ambulatory settings could benefit from palliative care been implemented? What is the evidence for how, when and for which patients they could best be implemented in care?

KQ 2:
- **KQ2a.** What educational materials and resources are available about palliative care and palliative care options for patients with serious life-threatening chronic illness or conditions in ambulatory settings and their caregivers?
- **KQ2b.** What is the effectiveness of educational materials and resources about palliative care and palliative care options for patients with serious life-threatening chronic illness or conditions in ambulatory settings and their caregivers?
- **KQ2c.** How have educational materials and resources about palliative care and palliative care options for patients with serious life-threatening chronic illness or conditions and their caregivers in ambulatory settings been implemented? What is the evidence for how, when and for which patients and caregivers they could best be implemented in care?

KQ 3:
- **KQ3a.** What palliative care shared decision-making tools are available for patients with serious life-threatening chronic illness or conditions in ambulatory settings and their caregivers?
- **KQ3b.** What is the effectiveness of palliative care shared decision-making tools for patients with serious life-threatening chronic illness or conditions in ambulatory settings and their caregivers?
- **KQ3c.** How have palliative care shared decision-making tools been implemented for patients with serious life-threatening chronic illness or conditions in ambulatory settings and their caregivers? What is the evidence for how, when and for which patients and caregivers they could best be implemented in care?

KQ 4:
- **KQ4a.** What palliative care training and educational materials are available for non-palliative care clinicians caring for patients with serious life-threatening chronic illness or
conditions in ambulatory settings?

KQ4b. What is the effectiveness of palliative care training and educational materials (with or without other intervention components) for non-palliative care clinicians caring for patients with serious life-threatening chronic illness or conditions in ambulatory settings?

KQ4c. How have palliative care training and educational materials (with or without other intervention components) for non-palliative care clinicians caring for patients with serious life-threatening chronic illness or conditions in ambulatory settings been implemented? What is the evidence for how, when and for which clinicians they could best be implemented in care?

KQ 5:

KQ5a. What models (i.e., stepped care, consultative care, shared care, collaborative care, coaching, integrating social workers into practice, and palliative care approaches provided by non-palliative care specialists) for integrating palliative care have been developed for patients with serious life-threatening chronic illness or conditions in ambulatory settings?

KQ5b. What is the effectiveness of models (i.e., stepped care, consultative care, shared care, collaborative care, coaching, integrating social workers into practice, and palliative care approaches provided by non-palliative care specialists) or multimodal interventions for integrating palliative care for patients with serious life-threatening chronic illness or conditions in ambulatory settings?

KQ5c. What are components of models for integrating palliative care in ambulatory settings? What models have been implemented for key subpopulations? What components and characteristics of these models contribute to their effective implementation? What is the evidence for how, when and for which patients they could best be implemented in care?

PICOTS Inclusion Criteria

The PICOTS inclusion criteria for all Key Questions are provided here:

- **Population(s)**
  - Adults age 18 or older with serious life-threatening chronic illness or conditions (other than those adults only with cancer) and their caregivers, being seen in ambulatory settings (KQ 1, 2, 3, 5)
  - Clinicians practicing in ambulatory settings listed below (KQ 4)

- **Interventions:**
  - KQ1: prediction models, tools or triggers to identify patients for palliative care in ambulatory settings
  - KQ2: educational materials and resources for patients and/or caregivers about palliative care in ambulatory settings
  - KQ3: palliative care shared decision-making tools and resources for clinicians and patients and/or caregivers in ambulatory settings
  - KQ4: palliative care training or educational materials for non-palliative care clinicians in ambulatory settings
  - KQ5: models for integrating palliative care in ambulatory settings

- **Comparators (for part (b) KQ):**
  Comparators between:
KQ1: prediction models, tools or triggers to identify patients for palliative care in ambulatory settings
KQ2: educational materials and resources for patients and/or caregivers about palliative care in ambulatory settings
KQ3: palliative care shared decision-making tools and resources for clinicians and patients and/or caregivers in ambulatory settings
KQ4: palliative care training or educational materials for clinicians in ambulatory settings
KQ5: models for integrating palliative care or multimodal interventions in ambulatory settings
As well as with usual care for all KQs

Outcomes (for part (b) KQ):
- Intermediate (Excludes clinician self-report)
  - Knowledge (clinicians, patients, caregivers) (KQ2, KQ4)
  - Awareness (clinicians, patients, caregivers) (KQ2, KQ4)
  - Skills (clinicians) (KQ4)
- Final (All apply to all KQ) (In hierarchy from patient-centered to clinician to health system. All patient or caregiver-reported outcomes must be measured by a validated instrument. All outcomes must relate to components of care relevant to serious, life-threatening chronic illness or conditions)
  - Patient or caregiver satisfaction
  - Patient or caregiver health-related quality of life
  - Patient or caregiver symptoms of depression or anxiety or psychological well-being
  - Caregiver burden, caregiver impact or caregiver strain
  - Patient symptoms or symptom burden (includes multidimensional symptom tools and key symptoms of pain, dyspnea, fatigue). This must include patient-reported symptom measurement (or caregiver-reported for patients unable to report).
  - Concordance between patient preferences for care and care received
  - Clinician job satisfaction or burnout, perceptions of teamwork
  - Healthcare utilization (use and length of hospice care, hospitalizations, advance directive documentation) and costs and resource use (use of outpatient clinician services, including palliative care)
- Adverse effects
  - Medication side effects
  - Dropouts

Timing
- Any timing

Settings
- Ambulatory primary and specialty care, including geriatrics, nephrology, pulmonology, cardiology, and neurology
- US-based studies, as systems of care differ in other countries

III. Analytical Framework

Figure 1. Analytic framework for integrating palliative care with chronic disease management in ambulatory care.
IV. Methods

The protocol is divided into sections by methods for the search and data abstraction (grey literature search, systematic review of the published literature) and synthesis methods to answer each part ((a), (b) and (c)) of each of the Key Questions.

A. Search and Data Abstraction Methods: Grey literature

To identify resources that have not been evaluated or have no published evaluation we will conduct a search of the grey literature.

i. Criteria for Inclusion/Exclusion of Grey Literature Documents: Criteria for inclusion and exclusion of documents are based on the Key Questions and are briefly described in the previous PICOTS section and below in Table 1.

Table 1. Specific inclusion criteria for Grey Literature Review

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Relevant to any of the interventions listed in KQ and PICOTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Content</td>
<td>As described above in PICOTS section</td>
</tr>
<tr>
<td>Population</td>
<td>Grey literature developed or updated in past 5 years</td>
</tr>
<tr>
<td>Language/ Country</td>
<td>English/ United States</td>
</tr>
</tbody>
</table>

ii. Grey Literature Search to Identify Relevant Documents: We will search key websites from health care professional organizations relevant to primary care, included specialties and palliative care, and other established relevant federal government and national US nonprofit and patient organization web resources. We will limit the search to grey literature that has been developed or updated within the last 5 years. Websites to search are in Table 2.
<table>
<thead>
<tr>
<th>Proprietary</th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Key palliative care organizations</strong></td>
<td></td>
</tr>
<tr>
<td>National Coalition for Hospice and Palliative Care (NCHPC) <a href="http://www.nationalcoalitionhpc.org">www.nationalcoalitionhpc.org</a></td>
<td>Clinician training and educational materials; Patient/caregiver educational materials/resources</td>
</tr>
<tr>
<td>Center to Advance Palliative Care (CAPC) <a href="http://www.capc.org">www.capc.org</a></td>
<td>Clinician training and educational materials; Patient/caregiver educational materials/resources; Shared decision-making tools</td>
</tr>
<tr>
<td>Hospice and Palliative Nurses Association <a href="http://www.advancingexpertcare.org">www.advancingexpertcare.org</a></td>
<td>Clinician training and educational materials; Guidelines and position statements</td>
</tr>
<tr>
<td>American Academy of Hospice and Palliative Medicine (AAHPM) <a href="http://aahpm.org/">aahpm.org/</a></td>
<td>Clinician training and educational materials; Guidelines and position statements</td>
</tr>
<tr>
<td>Social Work Hospice &amp; Palliative Care Network (SWHPN) <a href="http://www.swhpn.org/">www.swhpn.org/</a></td>
<td>Clinician training and educational materials; Guidelines and position statements</td>
</tr>
<tr>
<td>Council on Social Work Education (CSWE) <a href="http://www.cswe.org">www.cswe.org</a></td>
<td>Clinician training and educational materials; Guidelines and position statements</td>
</tr>
<tr>
<td>Physician Assistants in Hospice and Palliative Medicine (PAPHM) <a href="http://www.pahpm.org">www.pahpm.org</a></td>
<td>Clinician training and educational materials; Guidelines and position statements</td>
</tr>
<tr>
<td>Society of Pain and Palliative Care Pharmacists (SPPCP) <a href="http://www.palliativepharmacist.org">www.palliativepharmacist.org</a></td>
<td>Clinician training and educational materials; Guidelines and position statements</td>
</tr>
<tr>
<td>National Hospice and Palliative Care Organization <a href="http://www.nbpc.org/education/">www.nbpc.org/education/</a></td>
<td>Clinician training and educational materials; Patient/caregiver educational materials/resources</td>
</tr>
<tr>
<td>National Consensus Project for Quality Palliative Care <a href="http://www.nationalcoalitionhpc.org/ncp/">www.nationalcoalitionhpc.org/ncp/</a></td>
<td>Guidelines and position statements</td>
</tr>
<tr>
<td><strong>Key primary care health care professional organizations</strong></td>
<td></td>
</tr>
<tr>
<td>American College of Physicians <a href="http://https://www.acponline.org/">https://www.acponline.org/</a></td>
<td>Clinician training and educational materials, Guidelines and position statements</td>
</tr>
<tr>
<td>Society of General Internal Medicine <a href="http://www.sgim.org">www.sgim.org</a></td>
<td>Clinician training and educational materials, Guidelines and position statements</td>
</tr>
<tr>
<td>American Academy of Family Physicians <a href="http://www.aafp.org/home.html">www.aafp.org/home.html</a></td>
<td>Clinician training and educational materials, Guidelines and position statements</td>
</tr>
<tr>
<td><strong>Key specialty health care professional organizations</strong></td>
<td></td>
</tr>
<tr>
<td>American Geriatrics Society <a href="http://www.americangeriatrics.org">www.americangeriatrics.org</a></td>
<td>Clinician training and educational materials, Guidelines and position statements</td>
</tr>
<tr>
<td>American Thoracic Society <a href="http://www.thoracic.org/">www.thoracic.org/</a></td>
<td>Clinician training and educational materials; Patient/caregiver educational materials/resources</td>
</tr>
<tr>
<td>American Society of Nephrology <a href="http://www.asn-online.org/">www.asn-online.org/</a></td>
<td>Clinician training and educational materials</td>
</tr>
<tr>
<td>American Nurses Foundation <a href="http://www.nursingworld.org/foundation/">www.nursingworld.org/foundation/</a></td>
<td>Clinician training and educational materials</td>
</tr>
<tr>
<td>Gerontological Advanced Practice Nurses Association <a href="http://www.gapna.org/">www.gapna.org/</a></td>
<td>Clinician training and educational materials</td>
</tr>
<tr>
<td>National Association of Social Workers (NASW) <a href="http://www.socialworkers.org">www.socialworkers.org</a></td>
<td>Clinician training and educational materials</td>
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<tr>
<td><strong>Widely-used curricula</strong></td>
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<tr>
<td>End-of-Life Nursing Education Consortium (ELNEC) <a href="http://www.aacnnursing.org/ELNEC">www.aacnnursing.org/ELNEC</a></td>
<td>Clinician training and educational materials</td>
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<tr>
<td>EPEC: Education in Palliative and End of Life Care</td>
<td>Clinician training and educational materials</td>
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### Non-Proprietary

Key US federal government organizations

<table>
<thead>
<tr>
<th>Organization</th>
<th>Types of Materials Available</th>
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<tbody>
<tr>
<td>National Institute of Nursing Research (NINR)</td>
<td>Clinician training and educational materials; Patient/caregiver educational materials/resources</td>
</tr>
<tr>
<td><a href="www.ninr.nih.gov">www.ninr.nih.gov</a></td>
<td></td>
</tr>
<tr>
<td>National Institute on Aging</td>
<td>Clinician training and educational materials; Patient/caregiver educational materials/resources</td>
</tr>
<tr>
<td><a href="www.nia.nih.gov/">www.nia.nih.gov/</a></td>
<td></td>
</tr>
<tr>
<td>Health Resources and Services Administration</td>
<td>Clinician training and educational materials</td>
</tr>
<tr>
<td><a href="www.hrsa.gov/">www.hrsa.gov/</a></td>
<td></td>
</tr>
<tr>
<td>Center for Medicare and Medicaid Services</td>
<td>Models of care</td>
</tr>
<tr>
<td><a href="www.cms.gov">www.cms.gov</a></td>
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</table>

Key national US foundations with major focus in palliative care

<table>
<thead>
<tr>
<th>Foundation</th>
<th>Types of Materials Available</th>
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</thead>
<tbody>
<tr>
<td>John A. Hartford Foundation</td>
<td>Clinician training and educational materials</td>
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<tr>
<td><a href="www.johnahartford.org/">www.johnahartford.org/</a></td>
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<tr>
<td>Cambia Health Foundation</td>
<td>Clinician training and educational materials</td>
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<tr>
<td>Cambiahealthfoundation.org</td>
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<tr>
<td>Gordon and Betty Moore Foundation</td>
<td>Clinician training and educational materials</td>
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<tr>
<td><a href="www.moore.org">www.moore.org</a></td>
<td></td>
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<tr>
<td>Pew Charitable Trusts</td>
<td>Clinician training and educational materials</td>
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<tr>
<td><a href="www.pewtrusts.org/en">www.pewtrusts.org/en</a></td>
<td></td>
</tr>
<tr>
<td>Henry J. Kaiser Family Foundation</td>
<td>Patient/caregiver educational materials/resources</td>
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<tr>
<td><a href="https://www.kff.org/">https://www.kff.org/</a></td>
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Key patient organizations

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<thead>
<tr>
<th>Organization</th>
<th>Types of Materials Available</th>
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<tbody>
<tr>
<td>Alzheimer’s Association</td>
<td>Clinician training and educational materials; Patient/caregiver educational materials/resources</td>
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<tr>
<td><a href="www.alz.org">www.alz.org</a></td>
<td></td>
</tr>
<tr>
<td>American Heart Association</td>
<td>Clinician training and educational materials; Patient/caregiver educational materials/resources</td>
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<tr>
<td><a href="www.heart.org">www.heart.org</a></td>
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</tr>
<tr>
<td>American Lung Association</td>
<td>Clinician training and educational materials; Patient/caregiver educational materials/resources</td>
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<tr>
<td><a href="www.lung.org/">www.lung.org/</a></td>
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<tr>
<td>National Kidney Foundation</td>
<td>Patient/caregiver educational materials/resources</td>
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<tr>
<td><a href="www.kidney.org">www.kidney.org</a></td>
<td></td>
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<tr>
<td>Coalition for Supportive Care of Kidney Patients</td>
<td>Patient/caregiver educational materials/resources</td>
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<tr>
<td><a href="https://www.kidneysupportivecare.org/">https://www.kidneysupportivecare.org/</a></td>
<td></td>
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<tr>
<td>AARP</td>
<td>Patient/caregiver educational materials/resources</td>
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<td><a href="www.aarp.org">www.aarp.org</a></td>
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<tr>
<td>National Alliance for Caregiving</td>
<td>Patient/caregiver educational materials/resources</td>
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<td><a href="www.caregiving.org">www.caregiving.org</a></td>
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### iii. Data Abstraction and Data Management

We will use standardized and pilot tested forms to extract information about the resources identified, such as target audience, date developed, and availability/how to access. We will list the types of materials available from each grey literature source.
B. Search and Data Abstraction Methods: Systematic review of the published quantitative literature

i. Criteria for Inclusion/Exclusion of Studies in the Systematic Review of published quantitative literature: The criteria for inclusion and exclusion of studies for the systematic review of the quantitative literature are described in Table 3.

Table 3. PICOTS: Inclusion and exclusion criteria for quantitative studies

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
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<tbody>
<tr>
<td><strong>Population</strong></td>
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<tr>
<td>Patients (age ≥18 years of age) with serious life-threatening chronic illness or conditions (others than those only with cancer) and their caregivers, being seen in ambulatory settings (KQ 1,2,3,5)</td>
<td>Studies with only cancer patients Studies not focusing on ambulatory populations</td>
</tr>
<tr>
<td>Clinicians practicing in ambulatory settings (KQ4)</td>
<td>Studies of clinicians caring only for cancer patients Studies focusing on trainees</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
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</tr>
<tr>
<td>• KQ1: prediction models, tools or triggers to identify patients for palliative care in ambulatory settings</td>
<td>Studies that report no intervention of interest</td>
</tr>
<tr>
<td>• KQ2: educational materials and resources for patients and/or caregivers about palliative care in ambulatory settings</td>
<td></td>
</tr>
<tr>
<td>• KQ3: palliative care shared decision-making tools and resources for clinicians and patients and/or caregivers in ambulatory settings</td>
<td></td>
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<tr>
<td>• KQ4: palliative care training or educational materials for ambulatory settings</td>
<td></td>
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<tr>
<td>• KQ5: models for integrating palliative care or multimodal interventions in ambulatory settings</td>
<td></td>
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<tr>
<td><strong>Comparisons</strong></td>
<td></td>
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<tr>
<td>• KQ1: prediction models, tools or triggers to identify patients for palliative care in ambulatory settings</td>
<td>Studies that do not report the comparisons of interest</td>
</tr>
<tr>
<td>• KQ2: educational materials and resources for patients and/or caregivers about palliative care in ambulatory settings</td>
<td></td>
</tr>
<tr>
<td>• KQ3: palliative care shared decision-making tools and resources for clinicians and patients and/or caregivers in ambulatory settings</td>
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<td>• KQ4: palliative care training or educational materials for ambulatory settings</td>
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<tr>
<td>• KQ5: models for integrating palliative care or multimodal interventions in ambulatory settings</td>
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<tr>
<td>• Usual care for all KQs</td>
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<tr>
<td><strong>Outcomes</strong></td>
<td></td>
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<tr>
<td>Intermediate</td>
<td></td>
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<tr>
<td>• Knowledge (clinicians, patients, caregivers) (KQ2, KQ4)</td>
<td>Studies that do not report the outcomes of interest Excludes clinician self-report for intermediate outcomes</td>
</tr>
<tr>
<td>• Awareness (clinicians, patients, caregivers) (KQ2, KQ4)</td>
<td></td>
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<tr>
<td>• Skills (clinicians) (KQ4)</td>
<td></td>
</tr>
<tr>
<td>Final (All apply to all KQ) (In hierarchy from patient-centered to clinician to health system. All patient or caregiver-reported outcomes must be measured by a validated instrument\textsuperscript{17}. All outcomes must relate to components of care relevant to serious, life-threatening chronic illness or conditions)</td>
<td></td>
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<tr>
<td>• Patient or caregiver satisfaction</td>
<td></td>
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<tr>
<td>• Patient or caregiver health-related quality of life</td>
<td></td>
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<tr>
<td>• Patient or caregiver symptoms of depression, anxiety or psychological well-being</td>
<td></td>
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<tr>
<td>• Caregiver burden, caregiver impact or caregiver strain</td>
<td></td>
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<tr>
<td>• Patient symptoms or symptom burden (includes multidimensional symptom tools and key symptoms of)</td>
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</table>
pain, dyspnea, fatigue). This must include patient-reported symptom measurement (or caregiver-reported for patients unable to report).

- Concordance between patient preferences for care and care received
- Clinician job satisfaction or burnout, perceptions of teamwork
- Healthcare utilization (use and length of hospice care, hospitalizations, advance directive documentation) and costs and resource use (use of outpatient clinician services, including palliative care)

Adverse effects
- Medication side effects
- Dropouts

**Type of Study**
- Randomized controlled trials
- Non-randomized studies with concurrent or historical controls
- Articles published prior to year 2000
- Non-English publications
- Case reports or case series
- Publications with no original data (e.g., editorials, letters, comments, reviews)
- Full text not presented or unavailable, abstracts only

**Timing and Setting**
- Any timing
- Ambulatory care settings
- US-based studies
- Hospital setting
- Oncology setting
- Emergency department
- Nursing home and long-term care facilities

**ii. Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions:** We will search the following databases for primary quantitative studies: PubMed, CINAHL, and the Cochrane Central Register of Controlled Trials. We will develop a search strategy for PubMed, based on an analysis of the medical subject headings (MeSH) terms and text words of key articles identified a priori. The searches will be updated during the peer review process.

We will hand search the reference lists of included articles and relevant systematic reviews. We will also seek relevant studies during our search of websites (part a). Additionally, we will search clinicaltrials.gov to identify any relevant ongoing trials. We will use DistillerSR (Evidence Partners, 2010) to manage the screening process. DistillerSR is a web-based database management program that manages all levels of the review process. Unique citations identified by the search strategies will be screened in the following manner:

i. Abstract screening: Two reviewers will independently review abstracts, which will be excluded if both reviewers agree that the article meets one or more of the exclusion criteria listed in Table 3. Differences between reviewers regarding abstract eligibility will be tracked and resolved through consensus adjudication.

ii. Full-text screening: Citations promoted on the basis of abstract review will undergo another independent parallel review using full-text of the articles. The differences regarding article inclusion will again be tracked and resolved through consensus adjudication.

**iii. Data Abstraction and Data Management:** We will use standardized forms for data extraction and pilot test them. Each article will undergo a double review for data abstraction. The second reviewer will confirm the first reviewer’s data abstraction for completeness and accuracy. Articles
referring to the same study will be abstracted on a single review form if reporting the same data or on separate forms if necessary, with clear information that the results should be interpreted as from the same study. For all articles, reviewers will extract information on general study characteristics (e.g., study design, study period and follow-up), study participants, eligibility criteria, interventions and their characteristics, details about their implementation, outcome measures and the method of ascertainment, and the results of each outcome, including measures of variability.

iv. Assessment of Methodological Risk of Bias of Individual Studies: The assessment of risk of bias of included trials will be conducted independently and in duplicate using the Cochrane Risk of Bias Tool. For nonrandomized studies, we will use the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ROBINS-I tool). Differences between reviewers will be resolved through consensus adjudication.

C. Search and Data Abstraction Methods: Systematic review of the published qualitative, mixed-methods and process evaluation literature

i. Criteria for Inclusion/Exclusion of Qualitative, Mixed-Methods and Process Evaluation Studies: The criteria for inclusion and exclusion of qualitative and mixed methods studies will be based on the Key Questions and are described in the previous PICOTS section and below in Table 4. Note that all other criteria are the same as for the quantitative studies.

Table 4. Inclusion and exclusion criteria for integrative review of qualitative, mixed-methods and process evaluation studies

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Inclusion</th>
<th>Exclusion</th>
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<tbody>
<tr>
<td>Comparison</td>
<td>No comparison group needed</td>
<td></td>
</tr>
<tr>
<td>Type of study</td>
<td>• Systematic reviews of qualitative studies</td>
<td>Qualitative studies: observation or artifact analysis</td>
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<td></td>
<td>• Qualitative or mixed-methods studies: include studies that use a formal</td>
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<td></td>
<td>qualitative data collection method such as interviews, focus groups,</td>
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<td></td>
<td>or ethnography and analysis methods such as phenomenological, grounded</td>
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<td>theory, ethnographic and thematic analysis studies</td>
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<td></td>
<td>• Process evaluation studies (type of implementation studies) including</td>
<td>Process evaluation studies focusing only on research issues (e.g. fidelity,</td>
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<td>studies that address in results:</td>
<td>participant recruitment, intervention quality, participant engagement)</td>
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<td></td>
<td>▪ Identifying/addressing barriers/facilitators</td>
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<td></td>
<td>▪ Populations to target</td>
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<td></td>
<td>▪ Mechanisms for success/ failure</td>
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<tr>
<td>Sample size</td>
<td></td>
<td>Analysis of interest includes fewer than 10 participants</td>
</tr>
</tbody>
</table>

ii. Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions: The databases will be the same as for the quantitative studies. We will revise the search strategies from the quantitative searches to have additional focused searches for this section. For example, for Key Question 5c, we will include studies summarized in recent relevant reviews\textsuperscript{12-16} and from supplemental searches that describe the types of integrated models for palliative care that are in use in the US and their key components. We will also search for studies focusing on details of models and what they include, how they address patients’ palliative care-related needs, when
they may be appropriate (e.g., for which populations and settings), and what may contribute to their effective implementation.

iii. Key Informant Input Strategies: We will engage two separate groups of key informants of end users to provide input on our approach and our findings: one for patients and caregivers, and one for practicing clinicians, relevant professional and consumer organizations, purchasers of health care, representatives of learning health systems, and others with experience in making health care decisions. We will engage each group of key informants twice: once while identifying and developing the categories (i.e., categories may include themes from qualitative studies or characteristics of interventions or studies) to summarize the qualitative, mixed-methods and process evaluation literature, and once after the evidence has been summarized. In the first set of key informant interviews, we will solicit input on the categories into which the qualitative, mixed-method and process evaluation literature should be summarized and will discuss issues around applicability. For the second set of key informant interviews, we will solicit additional input based on the categories identified to refine and interpret results and address gaps not identified from the literature reviews.

We will create an interview guide as a framework on which to base the informant discussions. The guide will follow a semi-structured format, with the interviewer asking the informants the main questions first and then following up with secondary questions as needed. This framework will provide informants flexibility to comment on the examples provided and speak broadly on their relevant knowledge of the topics. Then, if particular points of interest were not covered in the informants’ initial responses, we will ask directed follow-up questions. We will audiorecord and take notes on key informant interviews. We will compile key issues brought up in the interviews and use these to inform the synthesis of results from the integrated analysis of the qualitative, mixed-methods and process evaluation literature.

iv. Data Abstraction and Data Management: We will follow the same process as for the systematic review of the quantitative literature. Reviewers will extract information from included studies on general study characteristics (e.g. study design, study period and follow-up), study participants, eligibility criteria, and interventions when applicable. In addition, we will abstract information on relevant categories for each key question.

v. Assessment of Quality of Individual Studies: Methodologic risk of bias is not relevant for qualitative research, so we will conduct quality assessment of systematic reviews and studies. For systematic reviews of qualitative research we will use the Confidence in the Evidence from Reviews of Qualitative research approach (CERQual)\(^21\). For individual qualitative and mixed methods studies we will modify the Joanna Briggs Institute Checklist\(^22, 23\) to address elements specific to our key questions.

D. Synthesis Methods

Our mixed methods review, having completed separate searches for each type of literature, will then combine these to answer each of the key questions and conduct a final integration step; considering the different types of evidence will allow for fully answering all parts of the key questions.\(^19\)

i. Part (a) key questions synthesis methods (“what is available?”)

To address the part (a) questions we will develop a matrix of (i) what is available but has not been
evaluated from the grey literature search, (ii) what has been evaluated for effectiveness from the
grey literature or published literature, and (iii) what has been evaluated for implementation.

ii. Part (b) key questions methods (“what is the effectiveness?”)
To address the part (b) questions, we will use systematic review methods for evaluating studies of
effectiveness (from the grey literature search and search of the quantitative literature).

a. Data Synthesis: For part (b) of each Key Question, we will create a set of detailed evidence
tables containing all information extracted from eligible studies. These tables will include details of
what is included in the interventions; for example, for models of care, they will include what
disciplines are involved, schedules of visits and assessments, and any standard elements such as
symptoms or psychosocial assessment or provision of advance directives. Tables will also include
details of implementation of the interventions as described in these studies, such as clinician
training provided and changes in clinic processes. All studies will be summarized qualitatively. We
will conduct meta-analyses when there are sufficient data (at least three studies) and studies are
sufficiently homogeneous with respect to key variables (population characteristics, study duration,
and intervention). Randomized controlled trials and nonrandomized studies will be analyzed
separately. Statistical significance will be set at a two-sided alpha of 0.05. We will evaluate for
statistical heterogeneity among studies using an $I^2$ statistic and anticipate statistical heterogeneity.
If substantial heterogeneity is found, we will conduct sensitivity analyses, when applicable, as well
as a meta-regression analysis if covariate information is available. For continuous outcomes, we
will calculate a standardized mean difference using a random-effects model with DerSimonian and
Laird formula. In a situation where dichotomous outcomes are presented, we will calculate a
pooled effect estimate of relative risk between trial arms of RCTs, also using a random-effects
model with DerSimonian and Laird formula. For sparse data meta-analysis, we will employ the
Peto Odds ratio method when event rates are less than 1 percent. When event rates are between 5-
10%, substantial differences between the N of two arms, or when effect size is large, dichotomous
data will be meta-analyzed using the Mantel-Haenszel method without continuity correction.
Dichotomous data with zero values in both arms will not be included in meta-analyses. All meta-
analyses will be conducted using STATA (College Station, TX).

Results will be presented by the Key Questions with the critical outcomes listed below presented
first. We will synthesize characteristics of included interventions and their implementation. Where
possible we will also present synthesis by key illnesses and conditions of interest. These include
advanced heart failure, advanced chronic obstructive pulmonary disease, end-stage renal disease,
frailty and multiple serious chronic conditions.

b. Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes: At the
completion of our systematic review, we will grade the strength of evidence on critical outcomes
by using the grading scheme recommended by the Methods Guide for Conducting Comparative
Effectiveness Reviews. The critical outcomes are defined as those most important for making
decisions and were identified a priori with input from the Technical Expert Panel.

The critical outcomes include:

- Patient health-related quality of life
- Patient symptom burden
- Patient symptoms of depression
- Patient satisfaction
- Caregiver satisfaction
Advance directive documentation

Following this standard EPC approach, for each critical outcome, we will assess the number of studies, their study designs, the study limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence to the Key Questions, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, and the overall findings across studies. Based on these assessments, we will assign a strength of evidence rating as being either high, moderate, or low, or insufficient evidence to estimate an effect. Investigators writing each section will complete the strength of evidence grading. The team members will review the assigned grade and conflicts will be resolved through consensus.

c. Assessing Applicability: We will consider elements of the PICOTS framework when evaluating the applicability of evidence to answer our key questions as recommended in the Methods Guide for Comparative Effectiveness Reviews of Interventions. We will consider important population and contextual characteristics that may cause heterogeneity of effects and affect the generalizability of the findings.

iii. Part (c) key questions methods (“how is it implemented?”)

To address the part (c) questions, we will use integrative review methods for evaluating studies of implementation (from the quantitative, qualitative, mixed-methods, and process evaluation literature).

a. Data Synthesis: We will create evidence tables summarizing all information abstracted from included studies. We will summarize the results of the qualitative, mixed-methods and process evaluation studies into categories for each KQ. These categories will be informed by discussions with the KIs and might include components of what is included in the integrated palliative care approach (e.g., addressing symptoms), or factors related to how, when and for which patients integrated approaches could best be implemented in care (e.g., characteristics of the patients or setting). Where possible we will also present synthesis by key illnesses and conditions of interest. These include advanced heart failure, advanced chronic obstructive pulmonary disease, end-stage renal disease, frailty and multiple serious chronic conditions.

b. Integrative synthesis methods:

We will conduct an integrative review of quantitative, qualitative and mixed-methods studies to address mechanisms and context (including patient and population issues and settings) for part (c) of each KQ. Methods are based on the 2017 Cochrane guidance, Qualitative and Implementation Methods Group Guidance Paper 5: Methods for integrating qualitative and implementation evidence within intervention effectiveness reviews and Joanna Briggs Institute methods for mixed methods systematic reviews. The Cochrane guidance defines the integrative review as “combining the findings from different types of studies to produce a more comprehensive synthesis of the evidence on ‘what works’”, recognizing that a variety of contextual factors, such as characteristics of the local population or setting, are key to intervention implementation and effectiveness (under “real world” conditions). Through incorporating qualitative and mixed methods research, the integrative review process can incorporate the patient and caregiver perspective, which is critical for palliative care, and the practicing clinician and health system perspective, which is critical for the integration of palliative care in the ambulatory setting.
Through incorporating process evaluation research, the integrative review can examine information on mechanisms (how and why something can be successfully implemented) and contextual issues (population, setting, barriers and facilitators).20

We will juxtapose the findings from the grey literature (key questions part (a) in each question) with the systematic review (key questions (part (b) in each question) with the identified categories from the integrative review of qualitative, mixed-methods and process evaluation studies (part c of each question). The matrix will provide a visualization of categories of what is available (e.g., components of what is included in integrated palliative care interventions) from qualitative, mixed-methods and process evaluation studies with evidence from effectiveness studies, informed by Key Informant input. This will help to address in particular the elements of the part (c) questions on why and how some types of interventions may be effective and others are not, when and which patients may benefit from these interventions, and how the palliative care approaches can best be integrated into ambulatory care.

V. References

VI. Definition of Terms
The following definitions are being used in this project.

**Ambulatory settings:** Includes settings such as hospital outpatient departments and clinicians’ offices, particularly primary care, but also including geriatrics, nephrology, pulmonology, cardiology and neurology

**Chronic illness:** An illness that lasts one year or more and requires ongoing medical attention and/or limits activities of daily living.

**Collaborative care model:** The collaboration of primary care and specialty care providers to develop and adjust treatment plans based on the measurement of symptom-related outcomes. 24

**Consultative care model:** Specialized care undertaken upon referral from a primary care provider.

**Disease management:** Includes key elements such as a coordinated system of care, delivery system support, support for patient self-care, identification of at-risk populations, a feedback loop between patients and care providers, measures of clinical and other outcomes, and the goal of improving health-related quality of life and health outcomes.25

**Guidelines and position statements:** Clinical practice guidelines and position statements from key US health care professional and other organizations relevant to serious illness chronic care and palliative care.

**Integrative review:** This method allows for the combination of diverse methodologies.26 We use this approach to examine qualitative and process evaluation literature (such as interviews with patients and families and implementation studies) to address how interventions work and evidence for how they should best be included in care, and to integrate this with the effectiveness literature. Combining the findings from different types of studies to produce a more comprehensive synthesis
of the evidence on ‘what works’ and how.\textsuperscript{18}

\textbf{Palliative care:} Care, services, or programs for patients with serious life-threatening illness and conditions and their caregivers, with the primary intent of relieving suffering and improving health-related quality of life, including dimensions of physical, psychological/emotional, social, and spiritual well-being.\textsuperscript{3} Note that other terms, such as supportive care, may be similarly used. Hospice care is a type of palliative care but is not included in this review as it is not delivered in ambulatory care.

\textbf{Patient education:} This can be conducted either individually or as part of a group or community, including through methods such as in-person, telephone, online or other electronic, print or audiovisual educational materials.\textsuperscript{27}

\textbf{Prediction models:} Modeling of patient and illness factors to predict the likelihood of patient outcomes, such as hospitalizations.

\textbf{Primary palliative care:} Care in palliative care domains for relevant populations provided by non-palliative care specialists, such as by primary care clinicians.\textsuperscript{28}

\textbf{Process evaluation} (also type of implementation study): Research focusing on mechanisms (how and why something can be successfully implemented) and contextual issues (population, setting, barriers and facilitators).\textsuperscript{18} Process evaluation studies include process studies that report on why and how interventions work with similar interventions, health conditions and contexts.\textsuperscript{29} They may be:

- conducted alongside effectiveness studies
- conducted after the effectiveness study on the same groups
- unrelated to effectiveness studies

\textbf{Provider education:} Used to describe a variety of interventions including educational workshops, meetings (e.g., traditional Continuing Medical Education [CME]), lectures (in person or computer-based), educational outreach visits (by a trained representative who meets with providers in their practice settings to disseminate information with the intent of changing the providers' practice). The same term also is used to describe the distribution of educational materials (electronically published or printed clinical practice guidelines and audio-visual materials).\textsuperscript{27}

\textbf{Stepped care model:} A model of care where the intensity of specialty professional care is augmented for patients who do not achieve an acceptable outcome with lower levels of care.\textsuperscript{30}

\textbf{Shared care model:} A model of care in which the collaboration among practitioners of different disciplines or with different skills and knowledge allows for the delivery of patient care by the most appropriate health care practitioner.\textsuperscript{31}

\textbf{Shared decision-making tools:} These are tools (also sometimes called decision aids) to help clinicians and patients make decisions that reflect medical evidence and patient goals for care relevant to palliative care, such as advance care planning tools to aid with decisions about treatment options and preferences for future care.\textsuperscript{32}

\textbf{Triggers:} Also known as screening criteria; indicators that someone may benefit from palliative care services. These may include patient or disease characteristics, palliative care needs, functional status decline or persistent or worsening symptoms, or high health care needs.
VII. Summary of Protocol Amendments
None.

VIII. Review of Key Questions
N/A

IX. Key Informants
We will include Key Informants for the part (c) Key Questions.

Key Informants are the end users of research; they can include patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into the decisional dilemmas and help keep the focus on Key Questions that will inform health care decisions. Key Informants are not involved in writing the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The AHRQ Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

A TEP for the systematic review portion of this mixed methods review will be convened. TEP input will hone and re-affirm methods in the draft protocol, including perspectives on proposed KQ and PICOTS changes, approaches to new data integration, managing challenges and reporting to enhance usability and inform meaningful presentation of the report. We will also solicit input about additional web resources that we should include for the part (a) questions.
XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. HHSA290201500006I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XIV. Registration

This protocol will be posted on the AHRQ website.