Evidence Report/Technology Assessment
Number 110

End-of-Life Care and Outcomes

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-02-0003

Prepared by:
Southern California Evidence-Based Practice Center
RAND Corporation, Santa Monica, CA

Principal Investigators
Karl Lorenz, MD
Joanne Lynn, MD

Director
Paul G. Shekelle, MD, PhD
Senior Statistician/Co-Director
Sally C. Morton, PhD
Project Manager/Policy Analyst
Margaret Maglione, MPP
Reviewers
Sydney Dy, PhD
Ronda Hughes, PhD, MHS, RN
Richard Mularski, MD
Lisa Shugarman, PhD
Virginia Sun, RN
Anne M. Wilkinson, PhD

Programmer/Analyst
Lara Hilton, BA
Database Manager
Shannon Rhodes, MFA
Research Assistant
Hsien Seow, BS
Staff Assistant
Cony Rolón, BA

AHRQ Publication No. 05-E004-2
December 2004
This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

AHRQ is the lead Federal agency charged with supporting research designed to improve the quality of health care, reduce its cost, address patient safety and medical errors, and broaden access to essential services. AHRQ sponsors and conducts research that provides evidence-based information on health care outcomes; quality; and cost, use, and access. The information helps health care decisionmakers—patients and clinicians, health system leaders, and policymakers—make more informed decisions and improve the quality of health care services.
Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This report was requested and funded by the National Institute of Nursing Research, National Institutes of Health (NIH). The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.gov.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Patricia A. Grady, Ph.D., R.N., F.A.A.N.
Director
National Institute of Nursing Research, NIH

Kenneth S. Fink, M.D., M.G.A., M.P.H.
Director, EPC Program
Agency for Healthcare Research and Quality

Ronda G. Hughes, R.N., M.H.S., Ph.D.
EPC Program Task Order Officer
Agency for Healthcare Research 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 of a particular drug, device, test, treatment, or other clinical service.
Structured Abstract

Context: The “end-of-life” refers to a prolonged, difficult period for patients and caregivers. Nine-tenths of Medicare-insured elderly live with a serious, chronic condition before death. Due to our aging population, Americans will increasingly face such challenges.

Objectives: Focusing on the outcomes patient and family satisfaction; pain, dyspnea, depression and anxiety and behavioral problems in dementia; continuity; caregiving burden other than bereavement; and advance care planning, we conducted a systematic review to evaluate the following:

1. The scope of the end-of-life population.
2. Outcome variables that are valid indicators of the quality of the end-of-life experience for the dying person and surviving loved ones.
3. Patient, family, and healthcare system associated with better or worse outcomes at end-of-life.
4. Processes and interventions associated with improved or worsened outcomes.
5. Future research directions for improving end-of-life care.

Data Sources: MEDLINE®, Database of Reviews of Effects (DARE), the National Consensus Project for Quality Palliative Care, Toolkit of Instruments to Measure End-of-life Care (TIME), and citations recommended by an international expert panel.

Study Selection: We focused on studies in the Western literature related to adult patient or caregiver end-of-life outcomes published between 1990 and April 2004, excluding studies of chemotherapy, radiotherapy, and similar technical care.

Data Extraction: We identified a total of 24,423 citations from all sources; 5,216 went on to abstract review, of which 911 articles were considered for detailed review including 95 systematic reviews, 134 intervention, and 682 observational studies.

Data Synthesis: Evidence is strongest in cancer, reflecting the degree to which palliative care has been integrated into oncology practice. Studies demonstrate strong associations between satisfaction and communication, pain control, practical support, and enhanced caregiving. We identified high-quality measures of quality of life, satisfaction, quality of care, and symptoms. Strong evidence undergirds cancer pain and depression treatment, and small studies suggest that opioids benefit dyspnea. Caregiving studies demonstrated inconsistent effects and focused on dementia. Strong evidence supports interventions to improve continuity in cancer and congestive heart failure (CHF), although CHF studies lack generalizability and palliative outcomes. Inconsistent evidence supports advance care planning, although studies often measure utilization rather than patient and family-centered outcomes.

Conclusions: We identified a number of priorities including a need to (1) characterize the implications of alternative definitions of the “end-of-life”; (2) test measures in diverse settings and populations; (3) in studies of satisfaction, emphasize specific process, especially those less-studied (e.g., non-pain symptoms, spiritual support, and continuity); (4) address methodological
challenges in measurement; (5) conduct studies of the epidemiology and clinical significance of symptoms in non-cancer conditions; (6) conduct larger studies of interventions for dyspnea; (7) conduct studies of short- as well as long-term treatment of depression; (8) conduct studies of caregiving in populations other than cancer and dementia; (9) evaluate economic and social dimensions of caregiving; (10) in continuity research, emphasize common settings (e.g., ambulatory care) and studies of nursing home-hospital continuity and involving multiple providers; and (11) in studies of continuity in CHF, incorporate palliative domains and ensure that studies are generalizable to the sickest patients.
Contents

Chapter 1. Introduction ....................................................................................................................1
  Background and Context.............................................................................................................1
  Framework for the Systematic Review......................................................................................1
    Pain, Dyspnea, Depression and Anxiety, and Behavioral Symptoms in Dementia.............2
    Caregiver Experience..........................................................................................................3
    Continuity of Care..............................................................................................................3
    Advance Care Planning......................................................................................................4
  Summary....................................................................................................................................4

Chapter 2. Methods..........................................................................................................................5
  Task Order Questions ..............................................................................................................5
  Overview....................................................................................................................................5
  Technical Expert Panel—Scope and Approach to the Report...................................................6
  Table 1. Report Section by Key Question .................................................................................8
  Analytic Framework ..............................................................................................................9
  Evidence Sources and Searches...............................................................................................9
    Literature Searches.................................................................................................................9
    Database of Abstracts of Reviews of Effectiveness ..........................................................10
    National Consensus Project ...............................................................................................10
    Major Recent Systematic Reviews of Palliative Care .......................................................10
    Gray Literature....................................................................................................................11
  Title Screening, Abstract Review, and Selection of Individual Studies ..................................11
  Procedures to Reduce Bias, Enhance Consistency, and Check Accuracy...............................13
  Summarizing the Evidence (Key Questions 1–3).....................................................................14
    Previous Systematic Reviews—Definitions ........................................................................14
    Screening of Reviews .........................................................................................................14
    Implicit Quality Assessment of Systematic Reviews .........................................................15
    Intervention and Observational Studies ..............................................................................16
    Assessment of Quality—Intervention and Observational Studies ......................................16
    Qualitative Data Analysis ...................................................................................................17
  Review of Articles Relevant to the Scope of “End of Life” ...................................................18
  Peer Review Process..............................................................................................................18

Chapter 3. Results ..........................................................................................................................19
  Results of the Literature Search.............................................................................................19
  Table 2. Study design by Topic Area.......................................................................................20
  Figure 1. Article Flow.............................................................................................................21
  A. Key Question 1a. What individual outcome measures are most strongly associated with overall satisfaction with end-of-life care? .................................................................22
    Systematic Reviews and Satisfaction with End-of-Life Care.............................................22
    Table 3. Systematic Reviews for Patient and Family Satisfaction with End-of-Life Care......22
    Additional Interventional Studies and Satisfaction with End-of-Life Care.........................25
    Observational Studies Evaluating Satisfaction in Palliative Care .......................................28
    Qualitative Studies Evaluating Satisfaction with Palliative Care .......................................30
Summary of the Relationship of Satisfaction to Other Measures of Process and Outcome...31

B. Key Question 1b. What is the reliability and validity of specific instruments for measuring quality of life or quality of care at end of life? .................................................................32
Measurement of Patient and Family Outcomes........................................................................32
Literature Review of Measures .................................................................................................33
Multidimensional Measures: Quality of Life, Quality of Care and Satisfaction .......................33
  Measures of Quality of Life ............................................................................................33
  Measures of Quality of Care and Satisfaction ..................................................................35
Measures Related to Other Specific Domains ..........................................................................37
  Measures of Pain and Other Symptoms .........................................................................37
  Measures of Emotional and Cognitive Symptoms..........................................................39
  Measures of Functional Status ......................................................................................39
  Measures of Survival Time and Aggressiveness of Care ..................................................40
  Measures of Advance Care Planning .............................................................................40
  Measures of Continuity of Care ....................................................................................40
  Measures of Spirituality ...............................................................................................40
  Measures of Grief and Bereavement ............................................................................41
  Measures of Caregiver Well-Being ...............................................................................41
  Other Measures ..........................................................................................................42
  Summary of Measures ..................................................................................................42

C. Key Questions 2 and 3
2. What patient, family, and healthcare system factors are associated with better or worse outcomes at end of life?
3. What processes and interventions are associated with improved or worsened outcomes?

Elements Associated with Patient Experience: Symptoms of Pain, Dyspnea, Depression and Anxiety, and Behavioral Issues in Dementia ..........................................................44

Table 4. Systematic Reviews for Symptoms: Pain, Dyspnea, Depression/Anxiety, Behavior in Dementia .........................................................................................................................45
Pain ....................................................................................................................................45
  Systematic Reviews and Pain ......................................................................................45
  Additional Interventional Studies of Pain .......................................................................48
Dyspnea ...............................................................................................................................50
  Systematic Reviews of Dyspnea ..................................................................................50
  Additional Interventional Studies of Dyspnea ..............................................................52
Depression and Anxiety .......................................................................................................54
  Systematic Review of Depression and Anxiety ............................................................54
  Additional Interventional Studies of Anxiety and Depression .......................................55
Behavioral Issues in Dementia ..............................................................................................57
  Systematic Reviews of Behavioral Issues in Dementia .................................................57
  Additional Interventional Studies of Behavioral Problems in Dementia .......................58
Observational Studies and Symptoms ..................................................................................59

D. Key Questions 2 and 3
2. What patient, family, and healthcare system factors are associated with better or worse outcomes at end of life?
3. What processes and interventions are associated with improved or worsened outcomes?

Elements associated with family experience, especially caregiving ...............................................61
Table 5. Systematic Review—Caregivers ................................................................................62
Systematic Reviews and Caregiver Burden ...........................................................................62
Additional Interventional Studies and Caregiver Burden .........................................................66
Observational Studies and Caregiver Burden ......................................................................70
Outcomes at Transitions (Placement or Death) .......................................................................72
Caregiving for Non-Cancer, Non-Alzheimer’s Disease .........................................................74

E. Key Question 2 and 3

2. What patient, family, and healthcare system factors are associated with better or worse outcomes at end of life?

3. What processes and interventions are associated with improved or worsened outcomes?

Elements Associated with Healthcare System Performance, Especially Continuity of Services ................................................................................................................................76
Introduction ...............................................................................................................................76
Systematic Reviews ..................................................................................................................77
Table 6. Systematic Reviews for Continuity/Coordination ......................................................77
Table 7. Summary of Results from Systematic Reviews Relevant to Continuity ....................78
Additional Interventional Studies and Continuity ....................................................................79
  Information/Record Continuity .......................................................................................79
  Management Continuity ...............................................................................................79
  Relational Continuity .......................................................................................................81
Specific Populations ..................................................................................................................81
  Heart Failure .................................................................................................................81
Table 8. Systematic Reviews Relevant to Continuity/Coordination in Heart Failure ..............81
Additional Interventional Studies and Continuity in CHF .......................................................82
Observational Studies in Continuity .........................................................................................83

F. Key Question 2 and 3

2. What patient, family, and healthcare system factors are associated with better or worse outcomes at end of life?

3. What processes and interventions are associated with improved or worsened outcomes?

Elements Associated with Decision-Making, Especially Advance Care Planning ...............85
Systematic Reviews .................................................................................................................85
Table 9. Systematic Review for Advance Care Planning ........................................................86
Additional Interventional Studies of Advance Care Planning ..............................................87
Prospective Cohort Observational Studies on Advance Care Planning ..................................91
Additional Cross Sectional and Retrospective Observational Studies ...................................93

G. Summary Regarding Outcome Variations Among Populations (by Patient, Family, and Health System Characteristics) .....................................................................................94
Table 10. Systematic Review of Outcome Variation ...................................................................94

H. Summary Regarding Effectiveness of Intervention .............................................................96
Satisfaction .................................................................................................................................96
Pain, Depression and Anxiety, and Behavioral Symptoms in Dementia ..................................96
Caregiving Burden..................................................................................................................97
Continuity .................................................................................................................................98
Advance Care Planning .............................................................................................................98

Chapter 4. Research Recommendations .................................................................................101
Overview .....................................................................................................................................101
Limitations .................................................................................................................................101
Definition of the “End of Life” Population Needed ..................................................................102
Measures and Satisfaction with Care and the of the End-of-Life Experience .........................103
Pain, Dyspnea, Depression and Anxiety, and Behavioral Symptoms in Dementia ..............104
Caregiving .....................................................................................................................................105
Continuity of Services ...............................................................................................................106
Advance Care Planning .............................................................................................................106

References ....................................................................................................................................109

Appendixes
Appendix A. Scope of End-of-Life Population
Appendix B. Search Strategies
Appendix B1. NLM Initial Search Strategy
Appendix B2. Q2-Trajectories Search Strategy
Appendix B3. DARE Search Strategy
Appendix B4. RAND Search Strategy
Appendix C. Summary of Health Canada Literature
Appendix D1. Sample—Abstract Screening Form
Appendix D2. Sample—Systematic Reviews Screening Form
Appendix E. Intervention Studies Evidence Tables
Appendix F. TEP and Peer Reviewers
Appendix G. Cambridge Ballot
Appendix H1. Methodological Issues in Measurement
Appendix H2. Table H-2 Reliability and Validity Measures
Appendix I. Bibliography of Excluded Abstracts
Appendix J. Bibliography of Excluded Articles
Appendix K. Peer Reviewer Comments
Appendix L. Observational Studies Evidence Tables
Appendix M. Included Studies

The Appendixes and Evidence Tables cited in this report are provided electronically at
Overview

To evaluate progress in the field of end-of-life care and clarify research priorities, the National Institute of Nursing Research (NINR), with the Agency for Healthcare Research and Quality (AHRQ), commissioned this evidence report as the basis for a State-of-the-Science Conference in December 2004. The need for such an assessment is clear. More than 75 percent of Americans now live past age 65, and 83 percent of Americans now die while covered by Medicare. In 2000, the average life expectancy for Americans was 80 years for women and 74 years for men, compared to just 49 years in 1900. By 2050, life expectancy for women and men will likely increase to 84 and 80, respectively. A century ago, death came to most Americans suddenly. Today, many Americans live their last years with a chronic health condition, and about 40 million people, 15 percent of the adult U.S. population, are limited in activities from such a condition. Population aging patterns suggest that in the coming decades, larger numbers of Americans will be coping with serious impairments late in life. For the relatively healthy, a care system focused on curing acute intermittent illness is adequate. For persons living with advanced, chronic disease, neither prevention nor cure are ordinarily possible. Instead, patients and families struggling with serious illness have other concerns, including managing pain and other symptoms, coordinating care among multiple providers and settings, ensuring that treatments reflect preferences and balance benefits and harms as well as medical appropriateness, achieving empathic communication and care, fostering well-being (including spiritual concerns), maintaining function, and practically supporting family and caregivers through illness and bereavement.

Reporting the Evidence

This report addresses the following key questions:

1. What outcome variables are valid indicators of the quality of the end-of-life experience for the dying person and for the surviving loved ones?
   a. What individual outcome measures are most strongly associated with overall satisfaction with end-of-life care?
   b. What is the reliability and validity of specific instruments for measuring quality of life or quality of care at the end-of-life?

2. What patient, family, and health care system factors are associated with better or worse outcomes at end of life?
   a. What individual patient factors (e.g., age, gender, race/ethnicity, underlying illness, education, etc.) are associated with better or worse outcomes at end of life?
   b. What family factors (e.g., relationship to patient, race/ethnicity, etc.) are associated with better or worse outcomes at end of life, including both outcomes reported by the family and how the family affects outcomes experienced by the patient?
   c. What health care system factors (e.g., site of care, type of provider, support services, etc.) are associated with better or worse outcomes?
3. What processes and interventions are associated with improved or worsened outcomes?
   a. What is the effectiveness of specific healthcare interventions for improving specific outcomes in patients at the end of life?
   b. Does effectiveness of specific interventions vary among different populations?

4. What are future research directions for improving end-of-life care?

Methodology

A multidisciplinary Technical Expert Panel (TEP) was formed to assist the Southern California Evidence-based Practice Center with its review and to guide the evidence report. The TEP included leading scientists and clinicians in nursing, gerontology, and palliative medicine, and others with a broad knowledge of relevant research and policy issues in both the United States and Europe. Research reviewers included an oncology nurse, an intensivist (a physician who specializes in the care of critically ill patients), a general internist, palliative care physicians, and gerontologists.

The sponsors decided to focus only on adults and identified as a priority the evaluation of interventions related to managing symptoms, enhancing communication, enhancing spirituality, withdrawing technology, facilitating family caregiving, and enhancing grief resolution. A decision was also made to focus on three clinical common, representative conditions. Thus, as an organizing principle, our analysis deliberately highlighted evidence that illuminated the end of life as lived with cancer, chronic heart failure, or dementia. Cancer patients experience a somewhat predictable decline and are often served by hospice in their final weeks. In contrast, patients with organ system failure (e.g., congestive heart failure [CHF], chronic obstructive pulmonary disease [COPD]) may experience stable but impaired function punctuated by unpredictable, severe illness and rather sudden death and are rarely served by hospice. In further contrast, patients with dementia have prolonged declines and often reside in nursing homes.

TEP members were asked to prioritize potential topics for the report based on relative importance at the end of life, relationship to patient experience, feasibility, relevance to care and policy, the availability of recent reviews on the topic, ability of the topic to illuminate differences in the strength of research in important clinical areas of palliative care, and modifiability in clinical practice and policy. With the TEP’s assistance, we decided to focus on the following topics:

- Satisfaction with care.
- As patient-centered concerns, the symptoms of pain, dyspnea, depression, anxiety, and behavioral symptoms associated with dementia.
- As family and caregiver concerns, caregiver burden excluding bereavement.
- As health system concerns, continuity of care.
- As a concern that requires coordinated action among patients, caregivers, and the healthcare system, advance care planning (ACP).

Literature Search and Review

A comprehensive search of the medical literature was conducted to identify studies addressing the key questions. Staff reviewed relevant articles, compiled tables of study characteristics and results, appraised the methodological quality of the controlled trials, and summarized results.

Sources for our review included MEDLINE®, the Cochrane Database of Reviews of Abstracts of Effects (DARE), the National Consensus Project for Quality Palliative Care, and several recent systematic reviews from both Health Canada and National Institute for Clinical Excellence (NICE), United Kingdom. We also used the 2000 Toolkit of Instruments to Measure End of Life Care (TIME). Additional studies were identified primarily through searches by U.S. National Library of Medicine (NLM) staff, complemented by RAND library searches. The searches were limited to published articles in the English language, appearing in journals between the years 1990 through 2004, involving human subjects, and did not include individual case reports. NLM staff conducted the first search of PubMed® in April 2004.

At the title screening stage, citations that clearly met the following criteria were excluded: studies that enrolled only a pediatric population (age 18 years and under); those that were case studies with fewer than 30 cases; those that did not consider palliative care; those that enrolled a non-Western population or were published in a non-English journal; reviews that were not systematic; clinical trials of chemotherapy, radiotherapy, stent, laser, endoscopy, or surgery (unless effects of the interventions were considered beyond effects on the primary disease process); descriptions of ethical, legal, or regulatory issues; descriptions of research processes; editorials, histories, personal narratives, and other descriptive non-clinical articles; articles about professional education (unless clinical or patient outcomes described); articles about organ transplantation or donation; articles that presented data only from prior to the mid 1980s; and studies in which the outcomes were lab or radiological tests or other physiological indicators. Approved titles moved on to an abstract screening phase.
The Report

Studies that satisfied the inclusion criteria are summarized in the evidence tables. The evidence tables provide detailed information about the study design, patient characteristics, inclusion and exclusion criteria, interventions evaluated, and the outcomes. The study sample size offers a measure of the weight of the evidence. Within the report, summaries of systematic reviews and intervention studies appear in an abbreviated form in tables, using summary measures of the main outcomes. Narrative text summarizes the findings and provides qualitative analysis in response to the key questions for each topic area.

Peer Review

Nine peer reviewers and TEP members reviewed our report. We compiled the comments and made appropriate changes to the report.

Findings

Literature Review

Of the 21,745 titles identified through literature searches, 5,563 were considered to be of possible relevance and subject to abstract review. The literature search of the DARE abstracts identified 92 titles; 62 were considered potentially relevant to our topic areas and proceeded to abstract review. Another 71 were added to the library of abstracts from the NICE guidelines, the Health Canada reports, the Toolkit of Instruments to Measure End of Life Care, and the files of our content experts. After eliminating duplicates and considering only citations for which an abstract was available, a total of 5,165 abstracts were reviewed.

Responses to Questions

Key Question 1a. What individual outcome measures are most strongly associated with overall satisfaction with end-of-life care?

Key Question 1b. What is the reliability and validity of specific instruments for measuring quality of life or quality of care at the end of life?

We identified 10 systematic reviews, 12 intervention studies, and 17 observational studies on the subject of end-of-life care and patient or caregiver satisfaction. The preponderance of the interventional and observational literature supports the effectiveness of palliative care for improving both patient and caregiver satisfaction. Subjective measures of the end-of-life care experience include both satisfaction and quality-of-care measures, and these tools overlap significantly. Satisfaction or quality-of-care instruments that assess focused aspects of end-of-life care have been most useful in demonstrating the effects of interventions. Nonspecific satisfaction instruments or studies that use measures not specifically adapted for or developed for palliative care settings have often demonstrated ceiling effects. Possibly for that reason, effects of interventions on satisfaction have been somewhat inconsistent.

Measures of satisfaction that are more specific and strongly related to explicit intervention aims or processes (e.g., communication, pain control, practical support and enhanced caregiving) have demonstrated greater sensitivity to change and support a process-outcome relationship among these variables. The relationship of other processes or attributes of care (e.g., treatment of symptoms other than pain, spiritual support, continuity and coordination of care) to satisfaction is less evident in the literature, although such relationships are supported qualitatively. The ability to demonstrate relationships between these aspects of care and satisfaction may be partially related to challenges in defining spiritual support as an intervention and measuring spiritual support and continuity of care.

With regard to measures, our review identified one high-quality, widely recognized resource (Toolkit of Instruments to Measure End of Life Care) available on the World Wide Web at www.chcr.brown.edu/pcoe/bibliographies.htm that systematically reviewed and compiled recommended instruments for end-of-life research up to the year 2000. We updated and superceded this review, identifying 48 new measures to supplement the 35 existing recommended measures within the Toolkit. Measure development is most advanced for cancer populations or mixed populations that consist largely of cancer patients. The largest number of measures evaluated quality of life, quality of care, and symptoms. The literature documents many measurement challenges including proxy respondents, timing of interviews, and cognitive thresholds.

Key Question 2a: What individual patient factors are associated with better or worse outcomes at the end of life?

Key Question 3a: What is the effectiveness of specific healthcare interventions for improving specific outcomes in patients at the end of life?

As our outcomes, we considered the specific symptoms of pain, dyspnea, depression and anxiety, and behavioral effects of dementia, as well as caregiver burden. We reviewed 27 systematic reviews or meta-analyses because they addressed selected symptoms of a palliative care population. Of those 27, we identified 12 that addressed the project questions and met implicit quality criteria. Two of the reviews included here focused specifically on a cancer population, one focused on patients with COPD, three focused on patients with dementia, and another six did not limit their reviews to only one disease...
dementia, it is not clear what proportion of the populations in other on mixed disease). SSRI’s have been shown to be effective the intervention literature regarding depression treatment in non-cancer conditions. We identified one extensive review of Reuptake Inhibitors [SSRIs]) or the treatment of depression in studies evaluating interventions for behavioral problems in dementia are clearly near the end of life. The literature addresses many symptoms including aggressive/disruptive behavior, agitation, wandering, and mood lability. These studies suggest that a variety of non-pharmacologic therapies may be effective. Pharmaceutical interventions were the subject of only a few studies we identified and produced mixed results. Because the literature on dementia is beset by many methodological limitations, it is difficult to make definitive statements about the best treatment for these patients.

With regard to burdens of caregiving other than bereavement, we identified eight systematic reviews and meta-analyses that were relevant to family or informal caregiving. Three dealt with outcomes of caregivers for patients with dementia or other chronic illness, while five dealt with cancer patients or other life-threatening illnesses. We identified 13 additional studies assessing interventions and caregiver burden and 18 observational studies. Of these, seven studies evaluated the effect of caregiving interventions on terminally ill patients, nine studies investigated the impact of two critical transitions faced by many caregivers (nursing home placement or the death of the care recipient, and only two studies examined the needs of terminally ill non-cancer patients and their caregivers.

In general, a variety of interventions were studied for a broad range of caregivers (e.g., spouses, adult children, others), primarily caregivers to dementia patients. Palliative care caregiver interventions were studied mostly in terminal cancer patient caregivers, usually as a supplement to clinical palliative care services being provided to the terminally ill patient. Most studies, whether on dementia or end-of-life caregiver interventions, focused on caregiver burden (objective and subjective burden) as the main outcome measure, but outcomes also included psychological distress (stress, depression), anxiety, coping skills, life satisfaction, health related quality of life, satisfaction with services or care, morale, rate of patient home death, rates of patient institutionalization, and costs.

Two kinds of interventions were used to address caregiver burden: individual and group interventions. The interventions included education, counseling, support groups, home health, hospice, or palliative care services to caregivers, singly, or in some combination. For the most part, intervention studies have reported inconsistent results. Larger treatment effects have been found for individual interventions, although group interventions predominate in the literature. Multi-component interventions and some respite services have shown positive (though small) impacts on caregiver burden. The inconsistencies in the literature may be attributable to the differences in the caregiver outcome measurement, research design, and analytical methods used.

With regard to continuity of care, we identified 9 systematic reviews that potentially dealt with the subject of continuity. We identified an additional 20 intervention studies and 17 relevant observational studies that met our criteria. A preponderance of evidence from systematic reviews and interventions support the efficacy of interventions to improve continuity of palliative treatment.
cancer care. In addition, we found some lower quality evidence that palliative HIV care could improve continuity of care. Interventions embody a variety of successful approaches including aspects of management, informational, and interpersonal continuity as well as comprehensive integrated care such as palliative care services. We found evidence for the effectiveness of interventions targeting care at multiple levels—provider, patient, provider/patient interface, and multiple settings but particularly home and hospital. Our review is limited in that it identified no evidence related to improving continuity across multiple sites of care.

Although we identified many effective interventions for improving continuity in CHF care, few of these explicitly addressed or reported patient-centered palliative outcomes (e.g., improvement in dyspnea, greater advance care planning, caregiving impact). However, interventions that improved continuity (often measured as hospital re-admission) share features of successful interventions in general, including longer intervention periods, coordination among providers, and regular, structured home assessment. Many CHF interventions specifically excluded patients who were ‘terminally ill,’ limiting their generalizability. Most interventions have targeted re-admission to the hospital or other kinds of high cost care, but interventions are needed to understand how to improve continuity in other settings as well.

The usual practice of advance directives and advance care planning is supported by little reliable scientific evidence of efficacy in improving outcomes. Improved communication and planning has some tendency toward improved patient and family satisfaction, and certainly anecdotes and small series point to patient and family frustration and disappointment with seriously flawed communication. Nevertheless, high-quality research designs have not often been applied to these questions and, when applied, have shown quite modest effects, even upon increasing the rate of making decisions in advance. Whether improved advance care planning actually improves the experience for patients and their families has only thin and equivocal evidence.

**Recommendations and Future Research**

Our literature review identified a very large and diverse body of literature reflecting the tremendous growth and importance of the field of end-of-life care over the last decade. This review of the scientific evidence underlying key parts of the field of end-of-life care illuminates strengths of the field as well as opportunities for research. We identified evidence supporting the association of satisfaction and quality of care with pain management, communication, practical support and enhanced caregiving. The literature review identified evidence to support the effectiveness of interventions to improve satisfaction; ameliorate cancer pain, relieve depression in cancer, non-pharmacologic interventions for behavioral problems in dementia, and foster continuity in cancer and CHF care. Evidence is strongest in cancer reflecting the degree to which palliative care has already been integrated into the research agenda and clinical practice of oncology.

We also identified several opportunities for future research to strengthen the evidence base for end-of-life care. Our recommendations are as follows:

1. Research would benefit from characterizing the implications of alternative conceptual and operational definitions of the “end of life,” particularly for important conditions. Efforts to define populations with specific symptoms, informational and caregiver needs, and risks of discontinuity are needed.
2. Further measure development should emphasize testing the highest quality measures in important settings (e.g., hospital, nursing home, hospice, and ambulatory care). These measures need to be evaluated in diverse populations (e.g., racial/ethnic groups, non-cancer conditions).
3. Studies evaluating satisfaction should use specific measures that reflect processes of care, and studies should examine the relationship of satisfaction to less studied processes such as non-pain symptoms, spiritual support, and continuity.
4. Methodological challenges in measurement require focused research. Strengthened research infrastructure including collaborative networks should be considered.
5. Symptoms have been relatively well-characterized in cancer, but high-quality studies of the incidence and epidemiology of pain and other symptoms, the relationship among symptoms, and the clinical significance of symptoms are needed in non-cancer conditions.
6. Small, high-quality studies suggest the effectiveness of interventions to alleviate dyspnea. Larger studies of interventions to alleviate dyspnea in cancer and non-cancer conditions are needed.
7. Studies that evaluate short- as well as long-term treatment of depression in palliative care settings are needed.
8. Research supports the effectiveness of interventions for cancer and dementia caregiving. High-quality studies in other populations are needed. These studies need to pay special attention to methodologic issues such as careful, specific measurement of outcome variables.
9. The economic and social dimensions of caregiving need additional research.
10. Substantial evidence supports interventions to improve continuity between home and hospital. Continuity research needs to look at other settings in which most patients are cared for, e.g., ambulatory care. Additional study of nursing home-hospital continuity and studies that incorporate multiple settings and providers are needed.

11. Studies of continuity in CHF and other conditions should incorporate the palliative domains described above (e.g., physical and psychological symptoms, caregiver burden, advance care planning) and need to be more generalizable to the sickest patients. Such studies need to include patients with multiple comorbidities.

12. Rigorous research in advance care planning is needed to understand how to best achieve patient and family goals (as opposed to evaluating resource allocation), and such research needs to address fundamental processes of care planning.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Southern California Evidence-based Practice Center, under Contract No. 290-02-0003. It is expected to be available in December 2004. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 110, End-of-Life Care and Outcomes. In addition, Internet users will be able to access the report and this summary online through AHRQ’s Web site at www.ahrq.gov.

Suggested Citation


References


Chapter 1. Introduction

Background and Context

Only a century ago, death was common at every age and dying usually quickly followed the onset of disease or injury. Now, public health measures and health care prevent or cure many previously fatal illnesses or injuries, allowing most Americans to live into old age. Medications and treatments now often allow prolonged survival with serious chronic conditions. More than 75% of Americans now live past age 65,¹ and 83% of Americans now die while covered by Medicare.² In 2000, the average life expectancy was 80 years for women and 74 years for men, compared to just 49 years in 1900.³ By 2050, life expectancy for women and men will likely increase to 84 and 80, respectively.³

Rather than a brief, well-defined period, the “end of life” today refers to a prolonged, uncertain period of difficulty because many Americans today live their last years with a advanced, chronic illness. In fact, such conditions affect 15% of the adult U.S. population.⁴, ⁵ Of these, one-twelfth have severe cognitive impairments,⁶ almost one-third have difficulty walking,⁷ and one-fifth have impaired vision.⁸ With advancing age, the likelihood of disability increases dramatically.⁹ After age 85, only one person in twenty reports being fully mobile.¹⁰ Age and disability are strongly associated with further declines in functioning, recurrent hospitalization, institutionalization, and death, even after accounting for other risk factors.¹¹, ¹²

An important group of chronic conditions consists of those that typically worsen and eventually cause death (e.g., cancer; chronic heart, lung, liver, or renal disease; dementia; and stroke). Nine-tenths of the elderly insured by Medicare live with one or more of these conditions in the year before death.¹ Most Americans will have a substantial period of serious illness before dying, with onset months or years before death. Already, half of Americans who live to be 85 years have major memory loss in their final years.¹³ By 2030, persons over 80 years of age will increase from approximately 3% to over 5% of the population, numbering 19 million.¹⁴ Trends in the rates of late-life disability are uncertain,¹⁵ but the growing size of the aging population suggests that many Americans will face chronic illness and impairment when the baby boomers grow old.

Over the past several decades, analyses underscored the cost of caring for chronic illness during the last years of life. For example, more than one-third of lifetime expenditures are still ahead of a person who is alive at age 85, and more than half are still ahead of a person at age 65.¹⁶ Reports have consistently and repeatedly demonstrated that the last year of life consumes about 30% of lifetime Medicare expenditures.¹, ¹⁷-¹⁹ The length of time a person lives is relatively unimportant in predicting total costs, and lifetime medical expenditures are similar for those who start retirement healthier and those who start more disabled, because even healthier persons eventually reach the disabled state at the end of life, and that period of time is very costly.²⁰

Framework for the Systematic Review

For persons living with advanced, chronic disease, neither prevention nor cure is ordinarily possible. Rather than a simple, straightforward aim like survival, which makes sense as a priority for most of life, people who are living with advanced and eventually fatal illness have complicated priorities like living well as long as possible but not suffering unduly, and being
close to and cared for by family but also not being a weighty burden on them. In this phase of life, care must serve multiple and complex goals and is affected by patient, caregiver, and healthcare system factors. A comprehensive description of the experience of patients living with advanced illness and their caregivers requires consideration of a range of conceptually overlapping measures including satisfaction, quality of care, quality of dying, and quality of life.21,22

Both expert opinion and research on the end-of-life experiences of patients, caregivers, and providers inform a description of the major domains for evaluating the end-of-life experience. These core considerations arise from the experience of both patients and caregivers and include23-31

- pain and other symptom prevention and treatment
- adequate support for families and caregivers including bereavement
- continuity of health care
- treatment consistent with patient and family preferences and medical knowledge
- effective, empathic communication about diagnoses, prognosis, and care plans
- well-being, including addressing existential and spiritual concerns
- function and self-determination
- length of survival.

For this report, we addressed several categories among these outcomes that are relevant to particular aspects of the patient’s and family’s experience, and healthcare system concerns. To examine the patient’s experience, we focused upon symptoms, particularly pain, dyspnea, depression and anxiety, and behavioral issues in dementia. To examine the family’s experience, we focused on caregiving (excluding bereavement). To examine on the healthcare system’s performance, we focused on continuity of care. The joint endeavor of decision-making and providing care consistent with preferences focused on advance care planning.

**Pain, Dyspnea, Depression and Anxiety, and Behavioral Symptoms in Dementia**

When a person is living with advanced illness and coming to the end of life, effective prevention and relief of symptoms becomes a high priority. Symptoms are subjective indicators of distress and the primary reason patients seek care, and they remain important in and of themselves even when the underlying causes of illness are increasingly difficult to modify.

Effective pain management is a palliative focus for many conditions, and pain is among the most debilitating and feared symptoms that patients and families face. Studies demonstrate a pain prevalence of 70–100% among cancer patients,32-34 and an Institute of Medicine conference recently named pain in advanced cancer as one of five high-leverage targets for national reform.35 Undertreatment and inequitable access to pain treatment have been described among many cancer patients presenting with pain.36,37 Pain is also prevalent among patients with advanced health conditions other than cancer38-40 underscoring the importance of evaluating the scientific evidence relevant to pain in both cancer and non-cancer conditions.
Dyspnea, or shortness of breath, is an especially troublesome symptom that is characteristic of conditions including advanced chronic obstructive lung disease (COPD) and congestive heart failure (CHF). The Institute of Medicine also named improving palliative care for CHF and COPD as one of five national priority areas for quality improvement. Understanding and treating dyspnea better would represent important progress in these priority conditions. Dyspnea is also an important symptom in cancer—in primary malignancies (e.g., lung), metastatic disease (e.g., metastasis to the lung), and as a consequence of treatment or progressive disease (e.g., associated with anemia).

Depression has increasingly come to attention as a cause of suffering in advancing illness. Similarly, the suffering that anxiety causes might well be mitigated with better care arrangements and medications. These and other behavioral symptoms such as wandering are especially important as manifestations of dementia. Such symptoms create difficulties for caregivers of demented patients, including nursing homes where Americans increasingly reside during their final years. Certain approaches to these symptoms (e.g., restraints) can be particularly harmful, and disseminating effective alternatives could improve palliative care in nursing homes and other settings for these patients.

Caregiver Experience

Families and other informal caregivers are essential in meeting an individual’s physical and psychosocial needs and in accomplishing treatment goals. Caregivers provide substantial amounts of assistance with daily living tasks, watching over symptoms and general health, monitoring and administering medications, and coordinating care among health and social service providers, as well as through emotional support. This is particularly true when patients live with prolonged illness such as dementia, which has a median life expectancy of 3.5 years according to a large, recent prospective cohort study. Caregiver responsibilities do not end with admission to a nursing home because caregivers continue to provide significant personal support even in the nursing home.

Families and other caregivers face emotional, physical, and economic consequences as a result and may lack reliable support for their responsibilities. Emanuel surveyed nearly 1000 caregivers and found that 35% reported substantial care needs that consumed time, money, and affected employment and borrowing, and that financial and nonfinancial caregiving burdens were related to depression as well as thoughts about physician-assisted suicide and euthanasia. Almost half of personal bankruptcy is associated with medical illness, and adverse financial circumstances may affect family decision-making. Caregiver stresses do not diminish even after institutional placement.

Continuity of Care

Continuity is an important goal that is mostly the responsibility of healthcare providers to foster. When a patient has complex illness, care is often characterized by multiple providers and settings, and continuity is important and elusive. A recent review identified irreducible elements of continuity including a focus on the individual patient and a concern with care delivery over time. Aspects of continuity include a patient’s having an ongoing relationship with specific providers, standardizing approaches to care so that services are delivered in an integrated, consistent fashion, and ensuring that information about the disease process or the preferences and values of the individual follow the patient into every setting of care.
Evidence suggests that discontinuity is a significant but addressable problem at the end of life. Discontinuity has been demonstrated in communicating treatment preferences, and in events related to late transfers among settings of care.\textsuperscript{56-58} Hospice might be effective in promoting continuity—family members of hospice patients are less likely to report that providers do not know enough about a family member’s clinical situation to provide the best care.\textsuperscript{59} Important aspects of care related to continuity include record keeping, various settings of care, and effective planning for the acute problems and symptoms patients face when they are near the end of life.

**Advance Care Planning**

Advance care planning (ACP) depends upon forecasting the challenges that the patient and family will face due to illness, medical treatment, and other concerns. When an important decision can be anticipated, the decision-making process is usually envisioned as including a prediction of the situation, awareness of alternative care plans, elicitation of preferences, and a final melding of preferences and alternatives into a coherent plan. Closely related issues include the need to make advance care plans available when patients need them and across settings, implementing advance care plans, and understanding their overall effects.

The early emphasis of advance care planning was on legal initiatives, although the concept has been broadened to emphasize the need to plan ahead and shape the course of care.\textsuperscript{60} The 1990 Patient Self-Determination Act (PSDA) required states to articulate their statutory provisions and healthcare providers to inform patients of their rights and record any advance directives (ADs). The legalistic origins of ADs emphasized protecting patients’ rights by granting them enforceable authority to make their own decisions. A broader construction of ACP recognizes that concerned parties are allied to discern what course best serves the patient and to ensure specific steps to make that course more likely. In addition to ADs, this requires practical arrangements (e.g., having the right medications in place). A number of authors have suggested that ACP should be targeted based on age, medical conditions, the patient’s health status, social circumstances, and beliefs.\textsuperscript{60, 61}

**Summary**

Given these significant concerns, the present offers an opportune time to conduct a systematic review to inform the research agenda for palliative care. Research to target gaps in knowledge will facilitate the quality, effectiveness, and affordability of care as well as access to care for patients and caregivers living with advanced illness. Thus, in order to evaluate progress and to propose research priorities the National Institute for Nursing Research, with the Agency for Healthcare Research and Quality, commissioned this Evidence Report as the basis for a State of the Science Conference in December 2004.
Chapter 2. Methods

Task Order Questions

The National Institute on Nursing Research, National Institutes of Health, requested this systematic review in preparation for a State of the Science conference to be held in December 2004. The following key questions were originally posed in the Request for Task Order (RFTO):

1. What outcome variables are valid indicators of the quality of the end-of-life experience for the dying person and for the surviving loved ones?
   a. What individual outcome measures are most strongly associated with overall satisfaction with end-of-life care?
   b. What is the reliability and validity of specific instruments for measuring quality of life or quality of care at end of life?

2. What patient, family, and healthcare system factors are associated with better or worse outcomes at end of life?
   a. What individual patient factors (e.g., age, gender, race/ethnicity, underlying illness, education) are associated with better or worse outcomes at end of life?
   b. What family factors (e.g., relationship to patient, race/ethnicity) are associated with better or worse outcomes at end of life, including both outcomes reported by the family and how the family affects outcomes experienced by the patient?
   c. What healthcare system factors (e.g., site of care, type of provider, support services) are associated with better or worse outcomes?

3. What processes and interventions are associated with improved or worsened outcomes?
   a. What is the effectiveness of specific healthcare interventions for improving specific outcomes in patients at end of life?
   b. Does effectiveness of specific interventions vary among different populations?

4. What are future research directions for improving end-of-life care?

Overview

In order to proceed with the task order, we assembled a team of clinical and methodological experts and staff and worked closely with the directors and staff of the Southern California Evidence Based Practice Center. Dr. Karl Lorenz led the day-to-day work of the review and writing teams with the close assistance and regular involvement of Drs. Joanne Lynn, Paul Shekelle, and Sally Morton. Our team included eight literature reviewers (with Dr. Lorenz) whose interests span broad concerns in palliative care and represented nursing, medicine, and gerontology. Reviewers possessed diverse clinical experience and included an oncology nurse, one intensivist, and two general internist/palliative care physicians. Our gerontologist reviewers possess special expertise in nursing home and hospice issues. The overall team met weekly to review and refine the methodology of the task order. Meetings and teleconferences of the SCEPC staff with technical experts helped specify issues central to this report within the framework of the key questions provided by AHRQ and NINR. The SCEPC conducted a comprehensive search of the medical literature to identify studies addressing the key questions. Staff reviewed relevant articles, compiled tables of study characteristics and results, appraised the methodological quality of the controlled trials, and summarized results.
Technical Expert Panel—Scope and Approach to the Report

In consultation with our Agency for Healthcare Research and Quality (AHRQ) Task Order Officer and the NIH Conference Panel Chair, we created a Technical Expert Panel (TEP) to guide the evidence report. We invited a multidisciplinary group of leading scientists and clinicians with expertise in nursing, gerontology, and palliative medicine and a broad knowledge of research and policy issues in the field of palliative care in both the United States and Europe to participate. The list of potential technical experts and their curriculum vitae were submitted to the Task Order Officer for approval, and a list of members is included in Appendix F.

Project staff worked closely with AHRQ, the Chair of the State of the Science Conference, and the TEP to refine the research questions and focus on the relevant outcomes in the topic areas. Before the contract was awarded, the sponsors had decided not to focus upon children or drugs used in palliative care. In considering the scientific literature that our review might address, we found it necessary to further focus and narrow the research questions.

One consideration was to represent the field by focusing on important, representative clinical conditions. We wanted to address important settings of care and also to illuminate important aspects of the patient and caregiver experience. Cancer patients experience a somewhat predictable decline, and are often served by hospice in their final weeks.1 In contrast, patients with organ system failure (e.g., CHF, COPD) may experience stable but impaired function punctuated by unpredictable, severe illness and rather sudden death62-64 and are less often served by hospice. Patients with dementia have prolonged declines and often reside in nursing homes.9, 65 As an organizing principle, our analysis deliberately highlighted evidence that illuminated the experience of living through the end of life with

- cancer
- chronic heart failure
- dementia.

A second consideration in approaching the topic is that the category “end of life” has been undergoing substantial changes in recent years, and the lack of a settled definition has greatly limited the coherence of the research literature.21 Previous systematic reviews concerned with end-of-life care have focused on well-bounded disease states (e.g., cancer), clinical conditions, (e.g., pain), or specific treatments (e.g., palliative services).66-69 In organizing a review around the “end of life” population, George observed variation among operational definitions used in research, including diagnosis; prognostic criteria including diagnosis; symptom expression; functional capacity; provider, patient, and family estimates of life expectancy; or particular healthcare settings (e.g., ICU).21

These varying operational approaches reflect a few clinically relevant distinctions. Some investigators may use “end of life” to mean the last few days or hours, roughly corresponding to what hospice nurses call “active dying.” Others mean a larger group of people who would be eligible for hospice with the six-month prognosis required for hospice admission or some other arbitrary prognostic interval. The broadest approach uses “end of life” to denote the part of life when a person is impaired with an eventually fatal condition, even if the prognosis is ambiguous. We did not distinguish among these approaches in our review and implicitly accepted the
broadest definition—of a period of time when a person and his or her family are living with the challenges of advanced illness.

The first of a series of calls was held April 28, 2004 with our Chair and the TEP, and we narrowed the scope in a fashion consistent with the sponsor’s priorities not to include chemotherapy, radiotherapy, stents, surgery, and other similar medically invasive or technically complex procedures. The TEP and the project sponsor also added a preliminary question of the evidence underlying various potential definitions of the field. For that reason, in addition to the task order questions, we also examined a preliminary question (Appendix A) of prognostication within the end-of-life literature.

Furthermore, since the RFTO was organized around outcomes in the end-of-life literature, we discussed considerations related to specific outcomes with the TEP and conducted a modified Cambridge ballot (see Appendix G) to prioritize those outcomes for inquiry. TEP members rated aspects of end-of-life care, on the basis of

- relative importance
- relationship to patient experience
- feasibility
- relevance to clinical care and healthcare policy
- the availability of recent reviews on the topic
- ability to illuminate differences in the strength of research
- modifiability in clinical practice and policy.

Each potential topic that included pain, affective symptoms, other symptoms, quality of life, spiritual or existential well-being, caregiver well-being and satisfaction, provider communication, advance care planning, continuity and coordination, utilization of services, and site of death was rated independently by each TEP member on each of the above attributes on a scale of 0–10. We totaled the score for each topic area and discussed the findings with TEP members, asking them to reflect on their rankings. The TEP and the sponsors agreed that the EPC search would not include grief and bereavement, spiritual issues, highly technical care (defined as surgery, stents, laser therapy, chemotherapy, and radiation therapy and similar technological innovations), or general issues of communication including giving bad news. Keeping in mind the sponsor’s priorities of focusing on aspects of the patient and family experience, and healthcare system concerns, this process resulted in our final decision to focus on the following topic areas in addition to satisfaction with care (specified in Question 1a).
• The patient’s experience, focused on Symptoms, particularly
  • Pain
  • Dyspnea (shortness of breath)
  • Depression or anxiety
  • Behavioral issues in dementia.
• The family’s experience, focused on Caregiving (excluding bereavement).
• The healthcare system’s performance, focused on Continuity.
• The joint endeavor of decision-making and providing care consistent with preferences, focused upon Advance Care Planning.

Table 1 illustrates the task order questions and how we organized the report to address the sponsor’s priorities of the patient and family’s experience, and the healthcare system’s performance.

**Table 1. Report Section by Key Question**

<table>
<thead>
<tr>
<th>Key Question</th>
<th>Section of Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preliminary</td>
<td>The scope of the population (Appendix A)</td>
</tr>
<tr>
<td>Q 1a</td>
<td>Chapter 3 A. Better and worse outcomes, especially patient and family satisfaction</td>
</tr>
<tr>
<td>Q 1b</td>
<td>Chapter 3 B. Measurement of outcome elements for the patient and family</td>
</tr>
<tr>
<td>Q 2 and 3</td>
<td>Chapter 3 C. The patient experience, especially symptoms</td>
</tr>
<tr>
<td></td>
<td>Chapter 3 D. The family experience, especially caregiving</td>
</tr>
<tr>
<td></td>
<td>Chapter 3 E. Health-care system performance, especially continuity of services</td>
</tr>
<tr>
<td></td>
<td>Chapter 3 F. Decision-making, especially advance care planning</td>
</tr>
<tr>
<td>Q2 Q3</td>
<td>Chapter 3 G. Summary of patient, family, and health system factors associated with better or worse outcomes</td>
</tr>
<tr>
<td></td>
<td>Chapter 3 H. Summary of the effectiveness of interventions</td>
</tr>
<tr>
<td>Q 4</td>
<td>Chapter 4. Future research directions for improving end-of-life care</td>
</tr>
</tbody>
</table>

The reader will note that this implements a general strategy of including a broad scope, but also providing focus on a specific important issue within each dimension of that scope. This strategy deliberately leaves some important issues incompletely addressed or not addressed at all. In addition to the exclusion of children and drugs mentioned earlier, this strategy means that this report does not address, except in passing, such issues as spirituality, bereavement, rehabilitation, withdrawal of life support, or any of an array of additional symptoms (fatigue, seizures, delirium, hallucinations, pressure ulcers, and so on). The report also does not focus on many important illnesses such as HIV/AIDS, multi-organ system failure, end-stage renal disease, chronic obstructive lung disease, frailty of old age, or neurological degenerative conditions other than dementia. Finally, articles on advanced illness but which did not include the search terms we used related to “end of life” in the title, abstract, or indexing terms were not are likely not to be included, except by nomination of one of the expert reviewers.
Analytic Framework

Donabedian’s quality-of-care framework structures our examination of the associations among outcomes considered by the project. Donabedian described the relationship between outcomes, processes, and structure of care.\textsuperscript{71} Quality of care, quality of dying, quality of life, and satisfaction are various distal outcomes that apply in varying degrees to both patients and caregivers.\textsuperscript{21, 22} Other topics we chose to examine (e.g., pain and symptoms, advance care planning, caregiver burdens, and continuity/coordination) could be considered as both processes of care related to these more global outcomes or as outcome themselves. In addition, some of these concerns may be understood as processes that affect other considerations as outcomes (e.g., improved pain and symptom management could reduce caregiver anxiety or improved continuity could improve pain management).

Evidence Sources and Searches

Literature Searches

Sources for our review included Medline, the Database of Reviews of Effects (DARE), the National Consensus Project for Palliative Care, and several recent unpublished systematic reviews from National Institute for Clinical Excellence (NICE) and Health Canada. National Library of Medicine (NLM) staff performed most of the searches, complemented by RAND library searches. Members of the project team worked closely with the TEP and librarians at NLM to decide how to refine the search strategy. We limited the searches to published articles in the English language, appearing in journals between the years 1990 through 2004, involving human subjects, and excluding individual case reports. The first search of PubMed was conducted by NLM staff in April 2004. The main search strategy included an extensive list of terms intended to identify all research publications associated with

- palliative or end-of-life care
- both overall (e.g., quality of life, quality of care, quality of death, satisfaction) and specific outcomes (e.g., pain and other symptoms) of interest
- measures and measurement
- individual, family or caregiver, and health system factors
- the full scope of healthcare settings relevant to end-of-life care.

The initial search strategy can be found in Appendix B1.

RAND and NLM created supplemental search strategies (Appendix B2) one week after the initial searches to enrich the initial set of citations. One revised search included terms on psychological and physical symptoms (i.e., pain, depression, anxiety) and specific healthcare services (i.e., nursing homes, hospice, home care) related to end-of-life care. The other new search focused on our three exemplary clinical conditions: cancer, heart failure, and dementia. Given the large number of citations identified through Medline, additional searches of other electronic databases simply were not possible within the resources and time constraints of the project.
Database of Abstracts of Reviews of Effectiveness

DARE contains structured abstracts of high-quality systematic reviews published in the scientific literature. DARE also contains references to other reviews which may be useful for background information. The reviews are identified by searching through key medical journals, bibliographic databases, and less widely available “gray literature.” DARE includes papers that review the effectiveness of healthcare interventions or organization. The quality of the database content relies upon ensuring that all reviewers work to specified guidelines, and that independent checks on the review process are carried out. DARE is produced by the Centre for Reviews and Dissemination (CRD) at the University of York, UK. Full information about the database is available on the DARE website at http://york.ac.uk/inst/crd/darehp.

As displayed in Appendix B3, we searched for systematic reviews on cancer, heart failure, dementia, palliative care, and the topics we focused on for this review. One of us (KL) searched DARE using relevant terms and conducted an implicit title review of the resulting citations.

National Consensus Project

In February 2004, the National Consensus Project (NCP) for quality palliative care published guidelines to improve the delivery of palliative care in the United States. NCP conducted a search of the end-of-life literature that, although not strictly systematic, was extensive and gathered the input of clinical, research, and policy leaders in palliative care selected through a national nomination process. Five palliative care organizations oversaw the National Consensus Project including the American Academy of Hospice and Palliative Medicine (www.aahpm.org), the Center to Advance Palliative Care (www.capc.org), the Hospice and Palliative Nurses Association: (www.hpna.org), the National Hospice and Palliative Care Organization (www.nhpco.org), and the Last Acts Partnership (www.lastactspartnership.org). We incorporated the entire reference list, eliminated duplicates, and screened studies that were not otherwise identified through our computerized searches.

Major Recent Systematic Reviews of Palliative Care

In addition to systematic review citations identified via DARE and Medline, the project identified several unpublished but important reviews (listed chronologically by recency) of the end-of-life literature relevant to our task order directives and topics. These were evaluated for quality, and those accepted as high-quality reviews (see below) were key sources for certain topics of the review.

2003 NICE Systematic Review of Supportive Care for Cancer. TEP member Prof. Irene Higginson provided a systematic review on Improving Supportive and Palliative Care for Adults with Cancer that was conducted for the National Institute for Clinical Excellence (NICE) in 2003. This recently published review (available at http://www.nice.org.uk/page.aspx?o=110005) evaluated studies from Medline, EMBASE, CINAHL, Cochrane Registry of Controlled Clinical Trials (CENTRAL), Cochrane Database of Systematic Reviews, and an Effective Practice and Organization of Care (EPOC) specialist register published from 1966 to 2003, and was organized around a wide variety of supportive interventions in oncology including coordination of care, patient activation, communication, information provision, psychological support, social support, spiritual support, palliative care services, rehabilitation, complementary therapies, and family and caregiver support. Of 5263 studies reviewed, 443 potentially eligible studies were accepted after abstract review.
2003 Health Canada Reports. Health Canada, Canada’s federal department of health provided an unpublished review that evaluated studies from nine databases (Medline, EMBASE, CINAHL, AHMED, PsychInfo, Eric, HealthStar, Sociological Abstracts, and Cochrane and covered the period 1987–2003). This Health Canada project generated 32 recent reports on a wide variety of topics, our review by two project investigators identified 14 of these as relevant to our task order directive and principal topic areas. Titles of all 32 reports are listed in Appendix C.

2000 Toolkit of Measures for End of Life Care (TIME). TEP member Dr. Joan Teno published the Toolkit, which arose from a review of over 928 articles identified from 1967 through 2000 and which selected 293 measures as potentially relevant to end-of-life care research. The Toolkit review through 2000 recommended 35 unique measures based on the criteria that (1) measures should be patient-focused, family-centered, clinically meaningful, and manageable in their application; (2) measures should strive for reliability, validity, and responsiveness; (3) measures should be user-friendly and relevant to quality evaluation and improvement; (4) measures should incorporate both the patient and family perspectives; and (5) measures should examine both the process and the outcomes of care. The website, www.chcr.brown.edu/pcoc/bibliographies.htm, gives an extensive summary of the Toolkit. The Toolkit is a well-known and widely used resource within the palliative care community and served as a foundation for our review of measurement.

Gray Literature

We sought supplemental publications from experts on our team and others involved in the review process, including the occasional “gray literature.” We did not make an exhaustive effort to solicit this information however because a recent and well-conducted systematic review that evaluated the efficacy of palliative care teams demonstrated that the gray literature did not affect the results.

Title Screening, Abstract Review, and Selection of Individual Studies

Eight researcher reviewers, six with clinical backgrounds in palliative care and all with established research careers in the area, conducted the study selection process. We trained the group in the critical analysis of scientific literature. The principal investigators resolved any questions or needs for clarification that arose throughout the literature review. Reviewers screened all titles found through our NLM searches or the NCP database or that were submitted by content experts for pertinence to the key questions and therefore their relevance to this project. We established screening criteria to facilitate the identification of articles concerning patient, caregiver, or health system factors related to patient and family-centered outcomes. At the title screening stage, we marked for exclusion citations that were

- exclusively pediatric (<18 years of age)
- case studies with <30 cases
- not on palliative care content (e.g., not about people who are living with serious illness or not an appropriate outcome)
• exclusively non-Western (i.e., North America, Europe, Australia/New Zealand)—either the population or the journal of origin
• nonsystematic review articles
• clinical trials about chemotherapy, radiotherapy, stent, laser, endoscopy, surgery
• descriptive of ethics, legal, or regulatory issues (nonclinical discussions)
• descriptive of the process of research
• editorials, history, personal narrative or other descriptive, nonclinical articles
• about palliative care professional education (unless effects on clinical, patient outcome(s) are described)
• about organ transplantation and/or organ donation
• clearly discussing research data only from before 1990
• studies in which the outcome was a lab, radiological test, or physiologic indicator (articles about strictly medical/technical outcomes even in the appropriate population).

We only eliminated citations at the title screening stage that clearly met any of the above criteria; we generally retained ambiguous citations. Some of the exclusions warrant explanation. Of the above criteria, as noted, we took the broadest possible view of the “end of life” population. We did not accept articles from the non-Western literature or those that focused exclusively on non-Western populations because (a) health systems and cultural factors are known to vary profoundly, limiting their applicability, and (b) these studies have qualitatively made little to no contribution to major recent systematic reviews of palliative care.72, 74 We did not include clearly nonsystematic reviews in the title stage because so many citations fell into this category and we searched secondary sources (e.g., DARE) to supplement systematic reviews of relevant topics in the most efficient fashion. We excluded articles arising from data before 1990 because George21 found that articles published before 1990 constituted just 10% of her unlimited review and articles more than fifteen years old are harder to locate in a short time. We decided to limit on the basis of when the data were generated, rather than when the article was published, since articles can take varying times to be published. We eliminated small case reports because one of the principal investigators (KL) reviewed a random sample of 30 such citations and corresponding reports and determined that they would add little substantive information, even descriptively, to understanding the issues in this review.

Approved titles moved on to the abstract screening phase. We designed a one-page data collection instrument specifically for this project and pilot-tested it with all reviewers after training conducted by SCEPC staff. This abstract screener (see Appendix D1) contained questions about outcomes, population, age, location, design, research topics, and diseases studied. The abstract screener phase included the same exclusion criteria as the title review stage. We added additional exclusion criteria based on the outcomes within the scope of the review that were chosen in consultation with our TEP and Conference Chair. Therefore, we excluded abstracts that clearly dealt with topics other than
• “good death” or “quality of dying”
• patient or family satisfaction
• measures
• family or informal caregiver concerns (other than bereavement alone)
• advance care planning
• continuity and coordination
• ain
• dyspnea
• depression or anxiety
• behavioral issues in dementia.

We provided definitions of these topics that were consistent with the general approach and definitions articulated in the field (see Introduction). Articles that focused on background or prognosis were marked for separate examination, as described below. Project staff entered data from the forms into an electronic database and tracked all studies through the screening process. We ordered all articles that were accepted after abstract screening and sent them out for further review based on topic area.

Procedures to Reduce Bias, Enhance Consistency, and Check Accuracy

Because of the very large number of citations to be evaluated and the short time to completion, we determined that the EPC’s usual method of dual independent reviews of all titles was not feasible. Therefore, we used single review of titles and abstracts and employed the following techniques to improve the reliability and accuracy of our method.

• Reviewers were trained in principles of citation review and use of a “training set” for title review to encourage consistent application of the definitions and criteria of the project.

• One of the principal investigators (KL) served as the “gold standard reviewer.” Outlier sets were identified by a second abstraction of a random subset of titles within each reviewer’s citation set, and the proportion of retained titles was compared. Dr. Lorenz subjected high and low outlier title sets to a second review.

• Specific definitions were used for both exclusion criteria and categorization of abstracts as described above. These criteria were similar at the title and abstract review stages.

• Reviewers were instructed that in any situations where they were not certain of their categorization to request a “second review” of abstracts, both to facilitate reviewer learning and enhance concordance with the ‘gold standard’ reviewer.
• A second review of a random subset of abstracts from all reviewers was conducted.

Following title and abstract review, accepted articles were reviewed by topic teams. The teams of at least two reviewers reached consensus on inclusion of final article sets for each topic area as well as consensus on data abstraction from these articles. Because of the large number of articles and the short time for our review, in practice articles were not dual-abstracted even though team members worked together closely, but abstraction results and findings were reviewed by the principal investigators for accuracy.

**Summarizing the Evidence (Key Questions 1–3)**

**Previous systematic reviews—Definitions**

As described above, we had three sources of reviews: our DARE search, experts, and titles identified in broad library searches that abstract review identified as systematic reviews or meta-analyses, using the definitions above (nonsystematic reviews were excluded). Before we begin discussion of the screening and assessment of reviews, we note the definitions that we used:75, 76

- **Review:** A review article that summarizes a number of different studies and may draw conclusions about a particular intervention. The methods used to identify, select, and appraise the studies are not systematic or necessarily reproducible. The summary in a review is generally narrative.

- **Systematic review:** A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review. Statistical methods are NOT used to analyze and summarize the results of the included studies.

- **Meta-analysis:** A systematic review that uses statistical methods to integrate the results of the individual studies. A meta-analysis contains at least one estimate formed by pooling results across individual studies, i.e., an overall odds ratio.

We applied these definitions in the following manner. If a publication addressed a number of studies, then it was a review. If it was a review, then we assessed if the methods (search methods, inclusion/exclusion criteria, quality assessment, etc.) were systematic. If it was a systematic review, then we assessed if it produced a pooled estimate, i.e., applied meta-analytic procedures. If a review was clearly not a systematic review or meta-analysis, then we simply called it a review.

**Screening of Reviews**

We assessed all resulting reviews using a Systematic Review Screener (Appendix D2). Mostly, we relied upon the abstract; but, if an abstract was not available, we obtained the original article for screening. We excluded all that were not true reviews (i.e., did not address more than one study); were not systematic reviews or meta-analyses; or were not appropriate to our topics (using the same exclusion criteria as on the general screener above). Generally, reviews were not appropriate if they did not address palliative care.
All systematic reviews and meta-analyses that passed screening were sent to the appropriate topic team. For example, if the review addressed symptoms and advanced care planning, it was sent to both the symptoms and advanced care planning teams. The topic teams read each review with particular attention to the team’s specific topic. They recorded the publication date and the date that the search for literature ended. Using these dates as well as the topic the review addressed, they assessed how relevant the review was to their topic. All reviews that were considered “highly” or “possibly” relevant were then assessed for quality.

**Implicit Quality Assessment of Systematic Reviews**

Two reviewers (PS and SM) reviewed all highly or possibly relevant systematic reviews or meta-analyses for quality independently. They then discussed their findings and reached consensus on the quality determination. No situations arose in which consensus could not be reached.

The reviewers categorized each review as either good, fair or poor quality. Good and fair reviews were acceptable to be used by the topic teams as evidence. The quality assessment was implicit. In this assessment the reviewers considered several characteristics of the review, drawing upon guidelines for assessing the quality of systematic reviews and meta-analyses.\(^77, 78\) Good systematic reviews and meta-analyses met almost all of the standards below, and fair systematic reviews or meta-analyses met the majority:

- The search should be comprehensive, systematic and reproducible. Publication bias should be minimized, its existence assessed, and its possible impact on the conclusions discussed.
- The inclusion/exclusion criteria for studies should be clear, reproducible, and defensible, and a flowchart of studies should be provided.
- The study quality assessment criteria and process should be described and evidence-based.
- Data abstraction should be done by two independent readers with a consensus process, or by one reader after a reliability test.
- Individual study characteristics should be presented and possible causes for study heterogeneity considered and investigated.
- If the review is a meta-analysis, the pooling methods should be described and appropriate.
- The results of the review should follow from the evidence presented. Potential biases in the review process and their possible impact on the conclusions should be evaluated and discussed.

All systematic reviews assessed as good or fair quality were summarized by the topic area teams with a narrative description including an in-text table.
**Intervention and Observational Studies**

Intervention studies included a variety of designs, and we included all types in our report, being sure to emphasize study design and quality in the narratives. We used the following definitions:

*Randomized controlled trial (RCT)*: A trial in which the participants (or other units) are definitely assigned prospectively into either “control” or “study” groups using a process of random allocation (e.g., random number generation, coin flips). “Study” groups receive a specific procedure, maneuver, or intervention.

*Controlled clinical trial (CCT)*: A trial in which participants (or other units) are either

a) definitely assigned prospectively to one (or more) “control” or “study” groups using a quasi-random allocation method (e.g., alternation, date of birth, patient identifier) OR

b) possibly assigned prospectively to one (or more) “control” or “study” groups using a process of random or quasi-random allocation.

*Intervention trial with comparison group but not RCT/CCT*: A trial in which the participants (or other units) receive one of two (or more) forms of health care; some or all participants are either:

a) not assigned to one of two (or more) forms of health care by the investigator, OR

b) are not assigned prospectively to one of two (or more) forms of health care (e.g., historical control).

*Intervention study without comparison group*. A trial in which all participants (or other units) receive the same form of health care (e.g., pre-post).

*Observational studies*. We also evaluated a variety of other observational designs employed in nonexperimental studies. These designs may be retrospective, cross-sectional, or prospective.

**Assessment of Quality—Intervention and Observational Studies**

To evaluate the quality of the individual intervention studies, we collected information on the study design, withdrawal/dropout rate, method of random assignment (and blinding), and method for concealment of allocation (the attempt to prevent selection bias by concealing the assignment sequence prior to allocation) consistent with requirements for ODS-OMAR-supported EPC evidence reports. The elements of design and execution (randomization, blinding, and withdrawals) have been aggregated into a summary score developed by Jadad. The Jadad score rates studies on a 0 to 5 scale, based on the answer to three questions:

1. Was the study randomized?

2. Was the study described as double-blind?

3. Was there a description of withdrawals and dropouts?

One point is awarded for each “yes” answer, and no points are given for a “no” answer. Additional points are awarded if the randomization method and method of blinding were described and were appropriate. A point is deducted if the method is described but is not
appropriate. Empirical evidence in other clinical settings has shown that studies scoring 2 or fewer points show larger apparent differences between treatment groups than do studies scoring 3 or more.\textsuperscript{79, 80}

Observational studies were assessed using ODS-OMAR procedures. Because of the extremely large number of observational studies identified, we were forced to limit our review of observational studies by definitely accepting only those that met the following criteria consistent with the task order goals:

a) If the study dealt with the topic of race / ethnicity as a single description of a racial group OR in the results reports racial differences, THEN it was included. If it did not do that AND it did not meet other criteria (b or c), then it was rejected.

b) If the study dealt with a setting of care other than hospice or compared settings of care, then it was included. If it did not do that AND it did not meet other criteria (a or c) then it was rejected.

c) If the study deals with the topic of CHF or dementia it is included, OR if it dealt with a comparison of a non-cancer disease state with cancer, then it was included. If it did not do that AND it did not meet other criteria (a or b), then it was rejected.

We defined a \textit{cohort} as \textquote{a group of people who share a common experience or condition.} For example, a birth cohort shares the same year of birth; a cohort of smokers has smoking as the common experience.\textsuperscript{81} We also distinguished prospective cohorts as those that were forward looking or longitudinal in design and in which the measurement of exposure preceded the measurement of the outcome. We included all prospective cohorts that met criteria a–c. Selected observational studies were included in the evidence tables at the implicit discretion of our expert reviewers if they addressed an important aspect of the topic even if they did not meet criteria a–c.

Qualitative research studies were included only in the discussion of satisfaction and its relationship to other outcomes (question 1a). These studies were reviewed by a single reviewer (KL) to examine common themes in the literature. Most qualitative studies involved focus groups or unstructured individual interviews.

\textbf{Qualitative Data Analysis}

We report the evidence in several forms. First, the evidence tables (in Appendix E—Interventions and Appendix L—Observational Studies) offer a detailed description of the studies that we identified, addressing each of the topic areas. At the end of the printed report, summary tables report on systematic reviews and intervention studies in an abbreviated form, using summary measures of the main outcomes. Narrative text summarizes the findings and provides qualitative analysis of the key questions as they relate to the topic area. The synergistic impact of multiple or sequential interventions is not considered with this methodology.

The evidence tables provide detailed information consistent with ODS-OMAR criteria about the study design, patient characteristics, inclusion and exclusion criteria, interventions evaluated, and the outcomes. The study sample size offers a measure of the weight of the evidence. (In general, larger studies provide a more precise estimate of the effect in question, although patient population governs more the applicability of any given study.) Again, we graded the quality of the studies according to the Jadad scale; this is also presented in the evidence tables. The
evidence tables are condensed into in-text summary tables to provide a concise overview of study results. Summarizing the data in such a way allows for ease of comparison among studies.

**Review of Articles Relevant to the Scope of “End of Life”**

Starting with the articles that the core literature review had identified as related to background and prognosis, and supplemented by articles pointed out by experts and other reviewers, three reviewers examined the titles and abstracts for this preliminary task of defining the scope of “end of life” care. They then categorized the articles into potentially useful categories and implicitly reviewed them for research quality. Then, the team categorized the articles and qualitatively described the implications for defining the “end of life” as a target for care. This work was essential to our overall effort but lies outside the scope of the RFTO and we have summarized it completely in Appendix A. Because this issue as a whole is also relevant to how we understood the literature, some of the insights from this preliminary task are discussed in Chapter 4.

**Peer Review Process**

We identified potential peer reviewers through project staff, the TEP and AHRQ. Based on these inquiries we contacted 12 individuals with wide expertise in the field and with deep knowledge of the literature, 9 of whom provided recommendations in addition to our TEP members. We selected reviewers because of their international stature, knowledge of both the North American and European literature, and research experience. The list of peer reviewers and their affiliations can be found in Appendix F.

A copy of the draft evidence report was mailed to each peer reviewer and TEP member. All reviewers were asked to respond with their comments. We compiled the peer reviewer comments and made appropriate changes to the draft report, based on these comments. The reviewer comments and the EPC’s responses are provided in Appendix K.