National Clinical Guideline Centre

Full Appendices

Care of dying adults in the last days of life

Care of dying adults in the last days of life

Clinical guideline NG31

Appendices A – Q

December 2015

FINAL

Commissioned by the National Institute for Health and Care Excellence

Royal College of Physicians
The Royal College of Surgeons of England
RCGP Royal College of General Practitioners
Royal College of Nursing
NICE accredited
www.nice.org.uk/accreditation

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and, where appropriate, their guardian or carer.

Funding
National Institute for Health and Care Excellence

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Appendix A: Scope

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SCOPE

1 Guideline title

Care of the dying adult: Clinical care of the dying adult in the last days of life.

2 The remit

The Department of Health has asked NICE 'to develop a guideline on the care of the dying adult'.

3 Need for the guideline

a) Death is a natural part of the life cycle. In some cases, such as cancer or other forms of progressive illness, clinicians can become aware that death may be approaching fast, but there is time for clinical services to adapt the aims and level of care in the last days. Less frequently, sudden death occurs from rapid-onset illness or major trauma, such as road accidents, and the time to prepare for this event is limited.

b) Caring for people who are thought likely to be dying in a matter of days, and providing support to their families, or those of importance to them, at this time, is of profound importance. Death may take place in a variety of settings, depending on choice and individual needs. Recognising that someone is likely to be dying imminently is vital to ensure that both dying people and their families or those important to them can prepare for death and make all relevant plans and preparations that they wish to. As death approaches, the

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clinical care provided should maximise the dying person's comfort and aim to reduce pain, anxiety and other symptoms and minimise disturbance and unnecessary intervention.

c) The likely time of death is often difficult to anticipate or predict, especially in people with chronic non-cancer conditions. Progressive weakness with no obviously reversible cause, altered breathing, increased periods of sleep and a general reduction in communication and participation in daily life may indicate that death is imminent.

d) Patient-centred multi-professional care provides the means to identify individual needs and make suitable care personalised plans for dying people (and their families and carers), regardless of the underlying causes or the setting in which care is provided. The recognition and the assessment of factors that may indicate that the person is in the last days or hours of his or her life are complex and subtle. It is important that these decisions and any changes to the care plans are conveyed to all people involved. However, healthcare professionals, the people who are dying and their relatives and friends may all feel uncomfortable about having frank discussions and may therefore avoid them. This avoidance needs to be overcome in order to plan and share the individual's care.

e) Individualised care of people who are dying encompasses physical symptoms (such as pain, increasing fatigue and breathlessness), psychological symptoms (such as anxiety and depression), social and spiritual needs. Good communication and advance planning is necessary to ensure that people are appropriately involved in the decision-making process about the care they or their loved ones

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receive and that patients and families are treated with respect to maintain their dignity.

3.1 Epidemiology

Approximately 500,000 people die in England each year and, because of the ageing population, that number is predicted to rise. Most people want to die with family and others important to them nearby, to feel cared for, to be free from symptoms and to have medical or nursing support available when it is needed. It is estimated that 70% of the population would prefer to die at home. Despite this, about 60% of people currently die in hospital and this figure is predicted to rise to approximately 65% by 2030. A variety of factors, including clinical needs, availability of family carers, local palliative care resources and cultural beliefs, may influence the choice of and actual place of dying and the level of support needed at the actual time of death.

3.1.1 Current practice

a) Until July 2014, NHS care in the last days of life was delivered and coordinated in many places by the use of end of life care pathways such as the Liverpool Care Pathway (LCP) or its local derivatives. The LCP was intended to ensure that people thought to be in the last 2 or 3 days of life, regardless of their setting, died free of distressing symptoms and with dignity, by transferring the model of care as practised in hospices to other healthcare settings. However, there has been criticism about how some elements of the LCP have been implemented. These include issues about how patients were selected to be placed on the LCP; communication with patients and families; the appropriateness of withholding or withdrawing hydration, nutrition and some medication; injudicious

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use of pain-killers or tranquillisers leading to undue sedation; and the lack of research-based evidence. More care, less pathway, the report of an independent review panel on the use of the LCP recommended that it should be phased out of practice by July 2014 in the UK. The challenge for the NHS is to provide a framework and culture that ensures that care provided to people in the last days and hours of life is evidence-based, of high quality and is based on individual needs.

b) The Royal College of Physicians (RCP) and the Marie Curie Palliative Care Institute published its National care of the dying audit of hospitals in May 2014. The audit found significant variations in care across hospitals in England. It showed that, although there are examples of excellent care, major improvements need to be made to ensure better care for people who are dying and better support for their families and others important to them.

c) A 'Leadership Alliance for the Care of Dying People' (LACDP) was set up following the 'More care, less pathway' report, with the aim of gathering consensus on the way forward after the withdrawal of the LCP. The LACDP published a report, 'One chance to get it right', in June 2014. It contained 5 new priorities for care to succeed the LCP as the new basis for caring for someone at the end of their life.

d) Recognising when a person is likely to be entering the last hours or days of their life is a challenge for even experienced clinicians in specialist palliative care. It is important to provide guidance that supports clinicians in all settings to make an assessment that death is likely within days and to communicate the prognosis sensitively, effectively and in a timely manner. Because of the long experience

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of palliative care in people with cancer, the approach of death in cancer is a relatively easier path to predict. For those people dying as a result of chronic conditions such as chronic obstructive pulmonary disease or heart failure, from which temporary remissions occur, anticipating dying may be more difficult. More challenging still is anticipating dying in those with dementia, cognitive impairment or frailty because people in these circumstances may live for a long time, even with a reduced level of function and because palliative care services have less experience with these groups. Just as important as recognising when a person is likely to be dying is being able to monitor bodily and mental changes that may suggest the person is recovering and may need a different course of management to live for a longer time.

e) The provision of medically assisted hydration, for some patients and those important to them, can be an important and comforting aspect of care in the last days of life. However, for some people, assisted hydration may be unnecessary or, if medical drips are applied without due care, harmful. The decision to initiate, continue, withhold or withdraw assisted hydration should be made on an individual basis, as the General Medical Council's guidance for doctors advises. Apart from the clinical considerations, the ethical and cultural issues related to providing or withholding hydration remain controversial.

f) Managing symptoms such as pain, breathlessness, nausea and vomiting, troubling respiratory secretions, anxiety and agitation is key to a peaceful death. Current practice for managing these symptoms includes assessing for and treating any reversible causes. It is recognised that it is sometimes necessary to use sedative doses of medications such as opioids, benzodiazepines

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and major tranquillisers (antipsychotics or neuroleptics) to control refractory symptoms and 'terminal agitation'. However, the independent review of the LCP 'More care, less pathway', identified concern about injudicious use of such drugs, for example, starting them too early or using inappropriately high doses, leading to undue sedation. This may prevent communication in the final days and cause more distress for the person who is dying and their families or those important to them.

g) In the UK, a key approach to improving symptom control in end of life care in all settings (particularly the community) is the use of 'anticipatory' or 'just in case' prescriptions. This allows clinicians such as district nurses to alleviate distressing symptoms of pain, nausea, vomiting, troublesome respiratory secretions and breathlessness or increasing anxiety, promptly without the additional delay of obtaining a new prescription and the dispensing of medication, especially out of hours. However, there has been some criticism of the arrangements for storing and disposing of such medication in the community. Furthermore, there have been reports that family members perceive that these drugs, if started too early or without good justification and communication, can hasten death.

h) More care, less pathway highlighted that frequently the decision that a person is dying is left to individual 'out-of-hours' clinicians without the support of an experienced team. The report also emphasised the importance of clear communication with patients, carers and families. Consideration of the timeliness and quality of multi-professional team clinical decision-making relating to the provision of care is vital and ideally this should involve both the person who is dying and those important to them.

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i) It is recognised that for some people in the last days of life the ability to make decisions about their care may be limited because of reduced conscious level. The Mental Capacity Act is designed to protect people who can't make decisions for themselves or lack the mental capacity to do so and clinicians need to consider these issues when making decisions about care.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

Adults (aged 18 years and over) in whom death is expected within a few days

4.1.2 Groups that will not be covered

Infants, children and young people aged under 18 years.

4.2 Setting

All settings where NHS funded care is received, including:

a) Care homes (with or without nursing).

b) Hospices.

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c) Hospitals.

d) Hostels.

e) Places of detention

f) Private residences.

4.3 Management

4.3.1 Key issues that will be covered

a) How clinicians recognise whether or not people are likely to be in their final hours or days of life; and how they recognise that the patient may be improving and recovering. How uncertainties regarding both situations are communicated and managed.

b) Multi-professional shared decision-making about the possibility of dying, and communicating this message.

c) Anticipatory prescribing in the last days of life.

d) Clinical effectiveness of assisted hydration

e) Pharmacological management of pain, anxiety, breathlessness, terminal agitation, nausea, vomiting and respiratory secretions.

4.3.2 Issues that will not be covered

a) Service delivery (for example out-of-hours availability of staff or how services are structured).

b) Palliative care or end of life care before the last few days or hours of life.

c) Care after death (care of the body, certification and bereavement).

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d) Case notes review for recognition of dying

e) The usefulness of laboratory and other biological evidence.

f) Multi-professional team structure.

g) Clinically assisted nutrition.

4.4 *Main outcomes*

a) Subjective rating of pain, breathlessness, anxiety, terminal agitation, nausea and vomiting and respiratory secretions.

b) Subjective and objective evidence of unwanted sedation, nausea or other side-effects as a result of pharmacological management of the symptoms above.

c) Family members' and carers' views about the care that was provided.

d) Correct recognition of being in the last days and hours of life.

e) Length of wait for medication for symptom control to be administered after the reporting of symptoms.

f) Symptoms such as pain, breathlessness, anxiety, terminal agitation, nausea, vomiting and respiratory secretions.

4.5 *Review questions*

Review questions guide a systematic review of the literature. They address only the key issues covered in the scope, and usually relate to interventions, diagnosis, prognosis, service delivery or patient experience. Please note that these review questions are draft versions and will be finalised with the Guideline Development Group.

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a) What signs and symptoms indicate that adults are likely to be entering the last days of life; or that they may be recovering? How should uncertainties about either situation be dealt with?

b) How are decisions about clinical care most effectively shared and communicated between health care professionals, adults in the last days of life, their families, carers and others important to them?

c) What is the role of anticipatory prescribing in the clinical care of adults in the last days of life?

d) Is medically assisted hydration effective in improving quality of care for adults in the last days of life?

e) What is the role of pharmacological treatment in the management of pain, anxiety, terminal agitation, breathlessness, nausea, vomiting and respiratory secretions whilst minimising unwanted levels of sedation in adults who are in the last days of life?

4.6 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), although this may not be appropriate for the clinical context of this guideline. The costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in The guidelines manual.

4.7 Status

4.7.1 Scope

This is the final scope.

4.7.2 Timing

The development of the guideline recommendations will begin in October 2014.

5 Related NICE guidance

5.1.1 Published guidance

- Prostate cancer. NICE clinical guideline 175 (2014).
- Intravenous fluid therapy in adults in hospital. NICE clinical guideline 174 (2013).
- Neuropathic pain – pharmacological management. NICE clinical guideline 173 (2013).
- Idiopathic pulmonary fibrosis. NICE clinical guideline 163 (2013).
- Neutropenic sepsis. NICE clinical guideline 151 (2012).
- Opioids in palliative care. NICE clinical guideline 140 (2012).
- Patient experience in adult NHS services. NICE clinical guidance 138 (2012).
- Colorectal cancer. NICE clinical guideline 131 (2011).
- Ovarian cancer. NICE clinical guideline 122 (2011).
- Lung cancer. NICE clinical guideline 121 (2011).
- Chronic heart failure. NICE clinical guideline 108 (2010).
- Chronic obstructive pulmonary disease. NICE clinical guideline 101 (2010).
- Motor neurone disease. NICE clinical guideline 105 (2010).
- Metastatic malignant disease of unknown primary origin. NICE clinical guideline 104 (2010).

- Advanced breast cancer. NICE clinical guideline 81 (2009).
- Metastatic spinal cord compression. NICE clinical guideline 75 (2008).
- Prophylaxis against infective endocarditis. NICE clinical guideline 64 (2008).
- Acutely ill patients in hospital. NICE clinical guideline 50 (2007).
- Dementia. NICE clinical guideline 42 (2006).
- Service guidance for improving outcomes for people with brain and other central nervous system tumours. NICE cancer service guidance (2006).
- Parkinson's disease. NICE clinical guideline 35 (2006).
- Improving supportive and palliative care for adults with cancer. NICE cancer service guidance (2004).
- Improving outcomes in haemato-oncology cancer. NICE cancer service guidance (2003).
- Guidance on the use of gemcitabine for the treatment of pancreatic cancer. NICE technology appraisal guidance 25 (2001).
- Multiple sclerosis. NICE clinical guideline 186. (2014).

5.1.2 Published quality standards

- Supporting people to live well with dementia. NICE quality standard 30 (2013).
- End of life care for adults. NICE quality standard 13 (2011).
- Breast cancer. NICE quality standard 12 (2011).
- Chronic obstructive pulmonary disease. NICE quality standard 10 (2011).
- Dementia. NICE quality standard 1 (2010).

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5.2 *Guidance under development*

NICE is currently developing the following related guidance (details available from the NICE website):

- Bladder cancer. NICE clinical guideline. Publication expected February 2015.
- Motor neurone disease. NICE clinical guideline. Publication expected February 2016.
- Transition between inpatient hospital settings and community or care home settings for adults with social care needs. Social Care guideline. Publication expected November 2015.
- Major trauma. NICE clinical guideline. Publication expected April 2016.
- Transition between inpatient mental health settings and community and care home settings for people with social care needs. Social care guideline. Publication expected August 2016.
- Acute medical emergency. NICE clinical guideline. Publication date to be confirmed.
- End of life care for infants, children and young people. Publication date to be confirmed.

6 Further information

Information on the guideline development process is provided in the following documents, available from the NICE website:

- How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS: 5th edition
- The guidelines manual.

Information on the progress of the guideline will also be available from the NICE website.

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Appendix B: Declarations of interest

The October 2008 version of the NICE code of practice for declaring and dealing with conflicts of interest policy was applied to this guideline.

B.1 Sam Ahmedzai – Chair (Consultant Palliative Care Physician)

Guideline Committee meeting	Interest declared	Type of Interest	Decision Taken
Initial declaration (application)	Lecture fees for Pain Forum lecture tour – SE Asia and Brazil – March and April 2014.	Personal non-specific pecuniary interest	Declare and participate
	For all of the following, fees have gone to University department – Lecture fees from pharmaceutical companies, charities, and academic groups. Fees from pharmaceutical companies for advisory boards. Fees from pharmaceutical companies for drug trial consultancies. Research grant from pharmaceutical company for fMRI and drug study. Fees for attending charity advisory boards and research committees. Research grant from HTA.	Non-personal non-specific pecuniary interest	Declare and participate
Guideline Committee meeting 1 and 2 30 October 2014 31 October 2014	Lecture fees for Pain Forum lecture tour – SE Asia and Brazil – March and April 2014. Total fee £10,000. Travelling expenses and hotel accommodation covered. Lectures – 1. Adequacy of Opioid Analgesic Consumption at Country, Global, and Regional Levels To provide an analysis for the adequacy of the consumption of opioid analgesics for countries and World Health Organisation regions in 2010 as compared with 2006.	Personal non-specific pecuniary interest	Declare and participate

Guideline Committee meeting	Interest declared	Type of Interest	Decision Taken
	Examples of countries that improved their parameters as a result of good practices. 2. Assessing & Treating Pain in Patients with Substance Abuse Concerns Distinguish tolerance, physical dependence, addiction, and aberrant behaviour. Differentiate the usefulness of the SOAPP-R, ORT, and COMM screening instrument. Universal Precautions in clinical practice Abuse deterrent formulations of opioids. 3. 75 min – Case presentation - 7 cases Assessing and Treating Persistent Non-malignant Pain / Neuropathic Cancer Pain / Palliative Care / Neuropathic Pain Case Presentations		
	For all of the following, fees have gone to the University department – Lecture fees from pharmaceutical companies, charities, and academic groups. Fees from pharmaceutical companies for advisory boards. Fees from pharmaceutical companies for drug trial consultancies. Research grants from pharmaceutical companies Fees for attending charity advisory boards and research committees. Section 1: Advisory boards and consultancy (See explanatory notes below) Date | Meeting | Type | Organisation | Travel, £ | Honorarium, £ 17.10.13 | Target Ovarian Cancer Advisory | Charity | TOC | 34.70	Non-personal non-specific pecuniary interest	Declare and participate

Guideline Committee meeting	Interest declared						Type of Interest	Decision Taken
		Board						
	30.10.13	Maggie's Scientific + Advisory Boards	Charity	Maggie's	221.00			
	06.11.13	HPAD AGM	Charity	Health Professionals for Assisted Dying	165.00			
	12.11.13	Grunenthal Advisory Board (new pain drug)	Pharma	Grunenthal	239.50	1,200.00		
	14.11.13	Myeloma Education Day	Charity	Myeloma UK	166.70			
	27.11.13	Meeting re Sativex (cannabis drug)	Pharma	Bayer plc		440.00		
	30.11.13	Nurses opposed to Euthanasia	Charity	Teresa Lynch	141.00			
	Section 2 - Academic research grants							
	Date	Meeting	Type	Organisation	Travel, £	Honorarium, £		
	01.01.14 to	Holistic needs	Charity	Prostate Cancer UK	34.70	£249,008 (Chief		

Guideline Committee meeting	Interest declared						Type of Interest	Decision Taken
	31.12.16	assessment in prostate cancer				Investigator)		
	01.03.14 to 30.06.18	RCT of early referral to palliative care for advanced non-small cell lung cancer	Special	NIHR	HTA	£1,591,728 (Chief Investigator)		
	01.04.13 to 31.03.16	RCT of Saracatanib for bone cancer pain	Charity	MRC		£1,051,966 (Co-applicant)		

Section 3 - Consultancies with pharma associated with research (Sam Ahmedzai as Chief Investigator)

Study		From	To	Value
Neuro-imaging study of neuropathic pain in myeloma patients	Pfizer	01/09/10	30/08/14	£105,000
Trial of standardised laxatives in opioid-induced constipation (SLT4501)	Mundipharma	01/12/13	30/04/14	£11,000
Drug trial for new oral analgesic for cancer pain (KF6005/09)	Grunenthal	15/06/13	01/06/18	£8,189.66
Observational study on burden of opioid-	AstraZeneca	10/03/13	01/06/15	£22,000

Guideline Committee meeting	Interest declared	Type of Interest	Decision Taken
	induced constipation		
Guideline Committee meeting 3 5 December 2014	As part of his role as Chair of the NCRI Clinical Studies Group for supportive care trials, SA met with a company (Chugai Pharma Ltd) to discuss their offering of a product to the NCRI for cancer research purposes. It is a product for cancer cachexia to help with unintentional weight loss in ambulatory cancer patients. This is not something that the CODA Committee are looking at and is at a much earlier stage than the last few days of life. He has not been personally involved in this research but met with the company in order to determine the suitability of their product for NCRI involvement and will direct them to the people who would conduct future research.	Non-personal non-pecuniary interest	Declare and participate
Guideline Committee meeting 4 16 January 2015	Appointed as RCP clinical lead for the national end-of-life care audit. The RCP has obtained a grant from NHS England to do an independent audit. This is future planned activity so not relevant for the current meeting.	n/a	-
Guideline Committee meeting 5 23 February 2015	Interest declared related to attending a meeting on 23rd February with representatives from a pharmaceutical company (Chugai Pharma Ltd.). In his role as chair of the supportive and palliative care clinical studies group of the NCRI, part of his responsibility is keeping industry in touch with researchers within the NCRI. In this case, he was directive the representatives to researchers for 2 drugs; early stage cancer prevention of cancer cachexia (weight loss) and a second line drug for multiple myeloma.)		
Guideline Committee meeting 6 24 February 2015	No change in declaration		
Guideline Committee meeting 7 26 March 2015	No change in declaration		
Guideline Committee meeting 8 27 March 2015	No change in declaration		

Guideline Committee meeting	Interest declared	Type of Interest	Decision Taken
Guideline Committee meeting 9 5 May 2015	No change in declaration		
Guideline Committee meeting 10 6 May 2015	No change in declaration		
Guideline Committee meeting 11 17 June 2015	No change in declaration		
Guideline Committee meeting 12 7 October 2015	No change in declarations		

B.2 Adrian Blundell – Consultant Geriatrician

Guideline Committee meeting	Interest declared	Type of Interest	Decision Taken
Initial declaration (application)	None	-	-
Guideline Committee meeting 1 and 2 30 October 2014 31 October 2014	Due to receive royalties from publication of a textbook on geriatric medicine due to be published in April 2015. Royalties would not be paid until December 2015.	n/a	
	Wife is a GP who is lead for palliative care at her practice.	Personal family interest non-pecuniary	Declare and participate
	Joint organiser of an annual GP refresher course which has pharmaceutical sponsorship. No personal payments.	Non-personal pecuniary interest	Declare and participate
	Non-trustee on board of Nottinghamshire Age UK	Personal non-pecuniary interest	Declare and participate
	Geriatrician representative on the Nottinghamshire End of Life Care Strategy Group	Personal non-pecuniary interest	Declare and participate
	Non-funded educational presentations about end of life in frailty	Personal non-pecuniary interest	Declare and participate
Guideline Committee meeting 3 5 December 2014	No change in declaration	-	-
Guideline Committee meeting 4 16 January 2015	No change in declaration	-	-
Guideline Committee meeting 5 23 February 2015	No change in declaration	-	-
Guideline Committee	No change in declaration	-	-

Guideline Committee meeting	Interest declared	Type of Interest	Decision Taken
meeting 6 24 February 2015			
Guideline Committee meeting 7 26 March 2015	No change in declaration	-	-
Guideline Committee meeting 8 27 March 2015	No change in declaration	-	-
Guideline Committee meeting 9 5 May 2015	No change in declaration	-	-
Guideline Committee meeting 10 6 May 2015	No change in declaration	-	-
Guideline Committee meeting 11 17 June 2015	No change in declaration	-	-
Guideline Committee meeting 12 7 October 2015	No change in declarations		

B.3 Maureen Carruthers – Community Matron/Advanced Nurse

Guideline Committee meeting	Interest declared	Type of Interest	Decision Taken
Initial declaration (application)	No interests declared	-	-
Guideline Committee meeting 1 30 October 2014	Did not attend	-	-
Guideline Committee meeting 2 31 October 2014	No change in declaration	-	-
Guideline Committee meeting 3 5 December 2014	No change in declaration	-	-
Guideline Committee meeting 4 16 January 2015	No change in declaration	-	-
Guideline Committee meeting 5 23 February 2015	No change in declaration	-	-
Guideline Committee meeting 6 24 February 2015	No change in declaration	-	-
Guideline Committee meeting 7 26 March 2015	Did not attend	-	-
Guideline Committee meeting 8 27 March 2015	Did not attend	-	-
Guideline Committee meeting 9	Did not attend	-	-

Guideline Committee meeting	Interest declared	Type of Interest	Decision Taken
5 May 2015			
Guideline Committee meeting 10 6 May 2015	Did not attend	-	-
Guideline Committee meeting 11 17 June 2015	No change in declaration	-	-
Guideline Committee meeting 12 7 October 2015	No change in declarations		

B.4 Susan Dewar – District Community Nurse

Guideline Committee meeting	Interest declared	Type of Interest	Decision Taken
Initial declaration (application)	None	-	-
Guideline Committee meeting 1 and 2 30 October 2014 31 October 2014	Member of the Clinical Advisory Board for Macmillan. This group meets about 3 times a year SD does not get paid for attending just for travel expenses. The model developed by the Midhurst Macmillan Specialist Palliative Care Service is being piloted by Macmillan and SD is paid on Bank nurse rate if she attends any of the meetings.	Personal non-pecuniary interest n/a	Declare and participate
Guideline Committee meeting 3 5 December 2014	No change in declaration	-	-
Guideline Committee meeting 4 16 January 2015	No change in declaration	-	-
Guideline Committee meeting 5 23 February 2015	Declaration made relating to being asked to sit on a new Cancer Strategy Taskforce in April 2015.	Personal non-pecuniary interest	Declare and participate
Guideline Committee meeting 6 24 February 2015	No change in declaration	-	-
Guideline Committee meeting 7 26 March 2015	No change in declaration	-	-
Guideline Committee meeting 8	No change in declaration	-	-

Guideline Committee meeting	Interest declared	Type of Interest	Decision Taken
27 March 2015			
Guideline Committee meeting 9 5 May 2015	No change in declaration	-	-
Guideline Committee meeting 10 6 May 2015	No change in declaration	-	-
Guideline Committee meeting 11 17 June 2015	No change in declaration	-	-
Guideline Committee meeting 12 7 October 2015	No change in declarations		

B.5 David Edwards – Palliative care nurse

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Initial declaration (application)	None	-	-
Guideline Committee meeting 1 and 2 30 October 2014 31 October 2014	Member of the Royal College of Nursing Ethics Committee Member of Public Health England Quality Assurance Group for the End of Life Care Communication Standard Member of the National Council for Palliative Care Ethics Forum Member of the combined Birmingham Cross City Clinical Commissioning Group & Birmingham South Central Clinical Commissioning Group, End of Life Care	Personal non-pecuniary interest	Declare and participate

Guideline Committee meeting	Declaration of interest	Classification	Action taken
	Clinical Advisory Group.		
	Care Quality Commission Specialist Advisor on End of Life Care (This is to participate as a member of inspection teams. Employing organisation is paid for DE time doing this work)	Non-personal pecuniary interest	Declare and participate
Guideline Committee meeting 3 5 December 2014	No change to declaration	-	-
Guideline Committee meeting 4 16 January 2015	No change to declaration	-	-
Guideline Committee meeting 5 23 February 2015	No change to declaration	-	-
Guideline Committee meeting 6 24 February 2015	No change to declaration	-	-
Guideline Committee meeting 7 26 March 2015	No change to declaration	-	-
Guideline Committee meeting 8 27 March 2015	Did not attend	-	-
Guideline Committee meeting 9 5 May 2015	Did not attend	-	-
Guideline Committee meeting 10	Did not attend	-	-

Guideline Committee meeting	Declaration of interest	Classification	Action taken
6 May 2015			
Guideline Committee meeting 11 17 June 2015	No change to declaration	-	-
Guideline Committee meeting 12 7 October 2015	No change in declarations		

B.6 Adam Firth – General Practitioner

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Initial declaration (application)	GP Principal at Bracondale Medical Centre, Stockport. Employed in a post joint funded by the RCGP and Marie Curie Cancer Care. Not subject to any specific direction with regards to the provision of End of Life Care from these organisations.	Personal non-pecuniary interest	Declare and participate
	Wife is a Physiotherapist employed by Salford Royal Foundation Trust.	Personal family interest	Declare and participate
	A member of the Royal College of General Practitioners. A member of the International Primary Palliative Care Network. Not subject to any specific direction with regards to the provision of End of Life Care from these organisations.	Personal non-pecuniary interest	Declare and participate
Guideline Committee meeting 1 30 October 2014	Self employed as a GP in a practice. Employed in a post jointly funded by the Royal College of GPs (RCGP) and Marie Curie Cancer Care. Not subject to any specific direction within this role.	n/a	Declare and participate
	Received <£1000 royalties from a book (an education resource for GPs in training helping them to pass training exams) that includes a palliative care scenario (published in September 2012).	Personal pecuniary non-specific interest	Declare and participate
	£200 honoraria received from RCGP for an advance care planning e-learning resource developed for GPs in their first 5 years following completion of training.	Personal pecuniary non-specific interest	Declare and participate
	Locality Vice-Chair for Stockport CCG receiving backfill payment to cover time away from practice – no specific	Non-personal pecuniary non-specific interest	Declare and participate

Guideline Committee meeting	Declaration of interest	Classification	Action taken
	remit around palliative care currently but this may develop in the future with work to develop DNAR policy.		
	Primary Care Medical Educator, responsible for a group of 30 GPs in Stockport. Some areas of palliative care are covered but not specifically EOL care. It is funded by Health Education North West deanery.	Non-pecuniary non-specific interest	Declare and participate
	RCGP representative for the Care Quality Commission thematic review of inequalities in End of Life Care – reasonable travel expenses received from RCGP to attend.	Personal pecuniary non-specific interest	Declare and participate
	RCGP representative on the expert advisory committee for the Summary Care Record – reasonable travel expenses received from RCGP to attend	Personal pecuniary non-specific interest	Declare and participate
	A member of the RCGP, Society of Academic Primary Care (SAPC) and the International Primary Palliative Care Network (IPPCN), an international palliative care network with a focus on research – not funded and not subject to any direction.	Personal non-pecuniary non-specific interest	Declare and participate
	Director of a charity, Ivy Manchester Limited, which runs a Christian Church in Manchester, but does not actively provide any services for EOL care in this role.	Personal non-pecuniary non-specific interest	Declare and participate
	Wife is employed in an NHS trust as a physiotherapist (not delivering EOL care).	Personal family interest	Declare and participate

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Guideline Committee meeting 2 31 October 2014	No change to declaration	-	-
Guideline Committee meeting 3 5 December 2014	Sits on the Editorial Board of the British Journal of General Practice- travel reasonable expenses received from the RCGP.	Personal pecuniary non-specific interest	Declare and participate
Guideline Committee meeting 4 16 January 2015	In CCG role, has now been tasked with reviewing the DNAR policy. This is only in the Stockport area and does not have any direct impact on this work. RCGP representative for the End of Life Care Ambitions partnership hosted by NHS England. Attended initial meeting 14/1/15. No direct impact on guideline and no further meeting attendance likely prior to guideline submission.	Non pecuniary interest	Declare and participate
Guideline Committee meeting 5 23 February 2015	No change to declaration	-	-
	No change to declaration	-	-
	No change to declaration	-	-
Guideline Committee meeting 6 24 February 2015	No change to declaration	-	-
Guideline Committee meeting 7 26 March 2015	No change to declaration	-	-

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Guideline Committee meeting 8 27 March 2015	No change to declaration	-	-
Guideline Committee meeting 9 5 May 2015	No change to declaration	-	-
Guideline Committee meeting 10 6 May 2015	Did not attend	-	-
Guideline Committee meeting 11 17 June 2015	No change to declaration	-	-
Guideline Committee meeting 12 7 October 2015	No change in declarations		

B.7 Annette Furley – Lay member

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Initial declaration (application)	None	-	-
Guideline Committee meeting 1 30 October 2014	A Trustee of Clare House Children's Hospice Wirral. Acts as a voluntary business advisor to charity, Living Well, Dying Well (supporting people at end of life) currently discussing potential partnership work with Baronesses Finley and Neuberger re: palliative care.	Personal non-pecuniary interest	Declare and participate
Guideline Committee meeting2	No change to declaration		

Guideline Committee meeting	Declaration of interest	Classification	Action taken
31 October 2014			
Guideline Committee meeting 3 5 December 2014	No change to declaration	-	-
Guideline Committee meeting 4 16 January 2015	Will be talking to 2nd and 3rd year palliative care health students at Manchester University about the work of a Doula at end of life. Honoraria will be received for this role.	Personal pecuniary non-specific interest	Declare and participate
Guideline Committee meeting 5 23 February 2015	No change to declaration	-	-
Guideline Committee meeting 6 24 February 2015	No change to declaration	-	-
Guideline Committee meeting 7 26 March 2015	No change to declaration	-	-
Guideline Committee meeting 8 27 March 2015	No change to declaration	-	-
Guideline Committee meeting 9 5 May 2015	No change to declaration	-	-
Guideline Committee meeting 10 6 May 2015	No change to declaration	-	-
Guideline Committee meeting 11	No change to declaration	-	-

Guideline Committee meeting	Declaration of interest	Classification	Action taken
17 June 2015			
Guideline Committee meeting 12 7 October 2015	No change in declarations		

B.8 Mike Grocott – Professor of Anaesthesia and Critical Care Medicine

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Initial declaration (application)	Paid in my salary: Director, National Institute of Academic Anaesthesia Health Services Research Centre, Royal College of Anaesthetists Clinical Lead, Division 6, Wessex Clinical Research Network Professor, University of Southampton Consultant in Critical Care, University Hospital Southampton NHS Foundation Trust	n/a	Declare and participate
	Paid separately: Consultant in Critical Care, Spire Hospital Southampton Joint Editor-in-chief, Extreme Physiology and Medicine Journal (BioMed Central) Chair, Evidence Based Perioperative Medicine Meetings Group	Personal pecuniary non-specific interest	Declare and participate
	Locum Consultant, University Hospital Southampton NHS Foundation Trust (wife)	n/a	Declare and participate
	All unrestricted research support. Industry: Smith's Medical Ltd Deltex Medical Ltd Cortex GmBh LidCo Ltd Ely Lily Critical Care Ltd Rolex Foundation	Non-personal pecuniary interest	Declare and participate

Guideline Committee meeting	Declaration of interest	Classification	Action taken
	The London Clinic BOC Medical (Linde)		
	Philanthropic: John Caudwell	Personal non-pecuniary interest	Declare and participate
	Grant giving body/charitable: National Institute of Health Research Medical Research Council Intensive Care Foundation National Institute of Academic Anaesthesia Special Trustees of the Royal Free Hospital NHS FT UCL Institute of Sports Exercise and Health Special Trustees of the UCLH NHS FT Association of Anaesthetists of Great Britain and Ireland Sir Halley Stuart Trust Frances and Augustus Newman Foundation National Blood Transfusion Service The Down Syndrome Trust	Personal non-pecuniary interest	Declare and participate
	Elected member, Board, Faculty of Intensive Care Medicine (FICM), UK Board and Research Council, National Institute of Academic Anaesthesia Currently writing an article (collaboratively) for the BMJ about issues around end-of-life care, patient choice and resource limitation in relation to critical	Personal non-pecuniary	Declare and participate

Guideline Committee meeting	Declaration of interest	Classification	Action taken
	care. Not related to the topics under review for this guideline.		
Guideline Committee meeting 1 30 October 2014	Receives occasional honoraria for a group of meetings he is involved with organising with a group of 4 other people – 10 meetings throughout the year. The subject is intensive care and anaesthesia in general that occasionally touches on end of life care every 2 – 3 years. The group has never been directly sponsored for this. End of life care has not been discussed for the past year.	Personal pecuniary non-specific interest	Declare and participate
Guideline Committee meeting 2 31 October 2014	No change to declaration	-	-
	Chairs various meetings and is on editorial boards but not directly related to end of life care. Travel expenses only are received for these roles.	Personal non-pecuniary interest	Declare and participate
	Involved in 2 social enterprise companies but does not receive payment from either of these. One looks after a bio resource for a large research consortium and the other is about medical innovation but neither relates to end of life care.	Personal non-pecuniary interest	Declare and participate
Guideline Committee meeting 3 5 December 2014	Involved in a Translational Research Partnership – a paid study on lung injury and vascular leak, with no direct links to end of life care.	Personal non-pecuniary interest	Declare and participate
Guideline Committee meeting 4 16 January 2015	No change to declaration	-	-

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Guideline Committee meeting 5 23 February 2015	Did not attend	-	-
Guideline Committee meeting 6 24 February 2015	Did not attend	-	-
Guideline Committee meeting 7 26 March 2015	No change to declaration	-	-
Guideline Committee meeting 8 27 March 2015	No change to declaration	-	-
Guideline Committee meeting 9 5 May 2015	No change to declaration	-	-
Guideline Committee meeting 10 6 May 2015	Did not attend	-	-
Guideline Committee meeting 11 17 June 2015	Did not attend	-	-
Guideline Committee meeting 12 7 October 2015	No change in declarations		

B.9 Gwen Klepping – Specialist Palliative Care Pharmacist

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Initial declaration (application)	None	-	-
Guideline Committee meeting 1 30 October 2014	Oxford Handbook of Clinical Pharmacy – update for 3rd edition due Spring 2015. Declaration related to writing the End of life care section of that handbook. There was no payment involved.	Personal non-pecuniary interest	Declare and participate
	Palliative Care Pharmacist Network – committee member. This has taken on pharmaceutical sponsorship since 2013 from Napp. Committee makes shared decisions over where funding is used for the website development or annual conference but GK is not solely responsible for decisions.	Non-Personal pecuniary interest	Declare and participate
	My work as a specialist palliative care pharmacist for Oxford University Hospitals NHS Trust involves the development of guidance and protocols for symptom management of palliative and end of life care patients.	n/a	-
	Chair of the Palliative Care Medicines Management Group for Oxford University Hospital (OUH) comprising healthcare professionals from Sobell and Katharine House Hospices. Will not actively get involved in similar activities for the next 12 months unless directly involved with personal employment with OUH.	Personal non-pecuniary interest	Declare and participate
Guideline Committee meeting 2 31 October 2014	No change to declaration	-	-
Guideline Committee	No change to declaration	-	-

Guideline Committee meeting	Declaration of interest	Classification	Action taken
meeting 3 5 December 2014			
Guideline Committee meeting 4 16 January 2015	No change to declaration	-	-
Guideline Committee meeting 5 23 February 2015	Declaration made relating to leading teaching sessions, one to acute general medicine registrars on prescribing end of life and one to heart failure nurses on heart failure end of life. No funding was received for these engagements.	Personal non-pecuniary interest	Declare and participate
Guideline Committee meeting 6 24 February 2015	No change to declaration.	-	-
Guideline Committee meeting 7 26 March 2015	No change to declaration.	-	-
Guideline Committee meeting 8 27 March 2015	No change to declaration.	-	-
Guideline Committee meeting 9 5 May 2015	No change to declaration.	-	-
Guideline Committee meeting 10 6 May 2015	No change to declaration.	-	-
Guideline Committee meeting 11 17 June 2015	Community pharmacist: palliative care pharmacist & EOCC symptom management. Received an honorarium of £150 – Thames Valley. Local pharmaceutical committee.	Non-personal pecuniary interest	Declare and participate

Guideline Committee meeting	Declaration of interest	Classification	Action taken
	24/04/15: Clinical Pharmacy Congress. Meds optimisation workshop on palliative care.	Non-personal pecuniary interest	Declare and participate
Guideline Committee meeting 12 7 October 2015	No change in declarations		

B.10 Diana Robinson – Lay Member

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Initial declaration (application)	Has a small shareholding in Reckitt Benckiser (yields less than £1,000 pa) with no control over allocations of funds. PPI work - the following may pay expenses and/or honoraria for meetings, workshops or conference attendance; and for reviewing research proposals. National Institute for Health Research. PGfAR funding panel from June 14. Occasional lay peer reviews. National Cancer Research Institute. National Cancer Intelligence Network, NICE UK DUETs Steering Group. Health Research Authority, University of Leeds (IMPACCT study); Leeds Clinical Research Facility Executive (from Feb 14); CQC; NHS England; Healthcare Quality Improvement Partnership - Service User Network; NICOR at UCL; Cancer Research UK (Research Coach from June 2014); Royal College of Radiologists Academic Committee and Lay Network (from September 2014)	Personal pecuniary non-specific interest	Declare and participate
	Sister-in-law works for UCL in Credit Control Section	Personal family interest	Declare and participate
Guideline Committee meeting 1 and 2 30 October 2014 31 October 2014	No change to declaration	-	-
Guideline Committee meeting 3 5 December 2014	Will join the SCIE Co-production Network to act as a stakeholder to support user, carer and equality groups' involvement in SCIE's strategic decision making and to help to co-produce SCIE projects and programmes	Personal pecuniary non-specific interest	Declare and participate

Guideline Committee meeting	Declaration of interest	Classification	Action taken
	(from December '14). Attendance fees and expenses are received for this work."		
Guideline Committee meeting 4 16 January 2015	No change to declaration	-	-
Guideline Committee meeting 5 23 February 2015	Declaration made in relation to work with the British heart foundation reviewing their research.	Personal non-pecuniary interest	Declare and participate
Guideline Committee meeting 6 24 February 2015	Declaration was made related to appointment to the position of lay member of the low back pain guideline.	Personal non-pecuniary interest	Declare and participate
Guideline Committee meeting 7 26 March 2015	No change to declaration	-	-
Guideline Committee meeting 8 27 March 2015	No change to declaration	-	-
Guideline Committee meeting 9 5 May 2015	No change to declaration	Personal pecuniary interest	Declare and participate
Guideline Committee meeting 10 6 May 2015	No change to declaration	-	-
Guideline Committee meeting 11 17 June 2015	NHS England New Care Models Team: public participation (June 2015). Expenses paid for by NHS England.	Personal pecuniary non-specific interest	Declare and participate
Guideline Committee meeting 12	No change in declarations		

Guideline Committee meeting	Declaration of interest	Classification	Action taken
7 October 2015			

B.11 Joy Ross – Palliative Care Physician

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Initial declaration (application)	None	-	-
Guideline Committee meeting 1 and 2 30 October 2014 31 October 2014	No change to declaration	-	-
Guideline Committee meeting 3 5 December 2014	No change to declaration	-	-
Guideline Committee meeting 4 16 January 2015	No change to declaration	-	-
Guideline Committee meeting 5 23 February 2015	No change to declaration	-	-
Guideline Committee meeting 6 24 February 2015	No change to declaration	-	-
Guideline Committee meeting 7 26 March 2015	No change to declaration	-	-
Guideline Committee meeting 8 27 March 2015	No change to declaration	-	-
Guideline Committee meeting 9	No change to declaration	-	-

Guideline Committee meeting	Declaration of interest	Classification	Action taken
5 May 2015			
Guideline Committee meeting 10 6 May 2015	No change to declaration	-	-
Guideline Committee meeting 11 17 June 2015	No change to declaration	-	-
Guideline Committee meeting 12 7 October 2015	No change in declarations		

B.12 Cheryl Young – Care Home Representative

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Initial declaration (application)	None	-	-
Guideline Committee meeting 1 and 2 30 October 2014 31 October 2014	No change to declaration	-	-
Guideline Committee meeting 3 5 December 2014	No change to declaration	-	-
Guideline Committee meeting 4 16 January 2015	No change to declaration	-	-
Guideline Committee meeting 5 23 February 2015	No change to declaration	-	-
Guideline Committee meeting 6 24 February 2015	No change to declaration	-	-
Guideline Committee meeting 7 26 March 2015	No change to declaration	-	-
Guideline Committee meeting 8 27 March 2015	No change to declaration	-	-
Guideline Committee meeting 9	No change to declaration	-	-

Guideline Committee meeting	Declaration of interest	Classification	Action taken
5 May 2015			
Guideline Committee meeting 10 6 May 2015	No change to declaration	-	-
Guideline Committee meeting11 17 June 2015	No change to declaration	-	-
Guideline Committee meeting 12 7 October 2015	No change in declarations		

Cooptee Guideline Development Group Members

B.13 Abdallah Al-Mohammad

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Initial declaration (application)	I am PI for SILHF, PARAGON, LIVE:LIFE and RELAX HF Europe I had accepted hospitality from Servier in May 2014 to attend the European Heart Failure Conference in Athens where I presented 5 personal papers (this was pre-authorised by NCGC).	Personal non-pecuniary interest	Declare and participate
Guideline Committee meeting 1 and 2 30 October 2014 31 October 2014	*	-	-
Guideline Committee meeting 3 5 December 2014	*	-	-
Guideline Committee meeting 4 16 January 2015	*	-	-
Guideline Committee meeting 5 23 February 2015	*	-	-
Guideline Committee meeting 6 24 February 2015	*	-	-

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Guideline Committee meeting 7 26 March 2015	*	-	-
Guideline Committee meeting 8 27 March 2015	No change to declaration	-	-
Guideline Committee meeting 9 5 May 2015	*	-	-
Guideline Committee meeting 10 6 May 2015	*	-	-
Guideline Committee meeting 11 17 June 2015	*	-	-
Guideline Committee meeting 12 7 October 2015	*		

*Cooptee was not required to attend these meetings.

B.14 Lynn Bassett

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Initial declaration (application)	None	None	No action required
Guideline Committee meeting 1 and 2 30 October 2014 31 October 2014	*	-	-
Guideline Committee meeting 3 5 December 2014	*	-	-
Guideline Committee meeting 4 16 January 2015	*	-	-
Guideline Committee meeting 5 23 February 2015	*	-	-
Guideline Committee meeting 6 24 February 2015	*	-	-
Guideline Committee meeting 7 26 March 2015	*	-	-
Guideline Committee meeting 8 27 March 2015	*	-	-
Guideline Committee meeting 9	*	-	-

Guideline Committee meeting	Declaration of interest	Classification	Action taken
5 May 2015			
Guideline Committee meeting 10 6 May 2015	No change to declaration	-	-
Guideline Committee meeting 11 17 June 2015	*	-	-
Guideline Committee meeting 12 7 October 2015	*		

*Cooptee was not required to attend these meetings.

B.15 Arun Bhasker

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Initial declaration (application)	None	None	No action required
Guideline Committee meeting 1 and 2 30 October 2014 31 October 2014	*	-	-
Guideline Committee meeting 3 5 December 2014	*	-	-
Guideline Committee meeting 4 16 January 2015	*	-	-
Guideline Committee meeting 5 23 February 2015	*	-	-
Guideline Committee meeting 6 24 February 2015	*	-	-
Guideline Committee meeting 7 26 March 2015	*	-	-
Guideline Committee meeting 8 27 March 2015	No change to declaration	-	-
Guideline Committee meeting 9	*	-	-

Guideline Committee meeting	Declaration of interest	Classification	Action taken
5 May 2015			
Guideline Committee meeting 10 6 May 2015	*	-	-
Guideline Committee meeting 11 17 June 2015	*	-	-
Guideline Committee meeting 12 7 October 2015	*		

*Cooptee was not required to attend these meetings.

B.16 Julie Hendry

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Initial declaration (application)	None	None	No action required
Guideline Committee meeting 1 and 2 30 October 2014 31 October 2014	*	-	-
Guideline Committee meeting 3 5 December 2014	*	-	-
Guideline Committee meeting 4 16 January 2015	*	-	-
Guideline Committee meeting 5 23 February 2015	*	-	-
Guideline Committee meeting 6 24 February 2015	*	-	-
Guideline Committee meeting 7 26 March 2015	*	-	-
Guideline Committee meeting 8 27 March 2015	No change to declaration	-	-
Guideline Committee meeting 9	*	-	-

Guideline Committee meeting	Declaration of interest	Classification	Action taken
5 May 2015			
Guideline Committee meeting 10 6 May 2015	*	-	-
Guideline Committee meeting 11 17 June 2015	*	-	-
Guideline Committee meeting 12 7 October 2015	*		

*Cooptee was not required to attend these meetings.

B.17 Julian Hughes

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Initial declaration (application)	I am opposed to all forms of physician-assisted suicide and euthanasia and have both spoken in debates to this effect, I have written about it and have given financial support to 'Care Not Killing'.	Personal non-pecuniary interest	-
Guideline Committee meeting 1 and 2 30 October 2014 31 October 2014	*	-	-
Guideline Committee meeting 3 5 December 2014	*	-	-
Guideline Committee meeting 4 16 January 2015	*	-	-
Guideline Committee meeting 5 23 February 2015	*	-	-
Guideline Committee meeting 6 24 February 2015	*	-	-
Guideline Committee meeting 7 26 March 2015	*	-	-
Guideline Committee meeting 8 27 March 2015	*	-	-

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Guideline Committee meeting 9 5 May 2015	Interest declared for paid medico-legal work.	Personal pecuniary non-specific interest	Declare and participate
Guideline Committee meeting 10 6 May 2015	*	-	-
Guideline Committee meeting 11 17 June 2015	*	-	-
Guideline Committee meeting 12 7 October 2015	*		

*Cooptee was not required to attend these meetings.

B.18 Ian Mursell

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Initial declaration (application)	None	None	No action required
Guideline Committee meeting 1 and 2 30 October 2014 31 October 2014	*	-	-
Guideline Committee meeting 3 5 December 2014	*	-	-

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Guideline Committee meeting 4 16 January 2015	*	-	-
Guideline Committee meeting 5 23 February 2015	*	-	-
Guideline Committee meeting 6 24 February 2015	*	-	-
Guideline Committee meeting 7 26 March 2015	*	-	-
Guideline Committee meeting 8 27 March 2015	*	-	-
Guideline Committee meeting 9 5 May 2015	*	-	-
Guideline Committee meeting 10 6 May 2015	I am a member of the guideline development group for the National Ambulance Guidelines (JRCALC). I am contributing to a section upon recognition of dying phases. The areas discussed as potential content prior to NICE meeting reflect NICE areas. The JRCALC guidance will not be a systematic review of evidence and will be informed by NICE as they are due to be drafted early 2016. The information from NICE is not shared with this group as the work is due to be commenced fully after the draft guidance from NICE is published for	Personal non-pecuniary interest	Declare and participate.

Guideline Committee meeting	Declaration of interest	Classification	Action taken
	consultation.		
Guideline Committee meeting 11 17 June 2015	*	-	-
Guideline Committee meeting 12 7 October 2015	*		

*Cooptee was not required to attend these meetings.

B.19 Sarah Nightingale

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Initial declaration (application)	No change to declaration	None	No action required
Guideline Committee meeting 1 and 2 30 October 2014 31 October 2014	*	-	-
Guideline Committee meeting 3 5 December 2014	*	-	-
Guideline Committee meeting 4 16 January 2015	*	-	-
Guideline Committee meeting 5 23 February 2015	*	-	-
Guideline Committee meeting 6 24 February 2015	*	-	-
Guideline Committee meeting 7 26 March 2015	*	-	-
Guideline Committee meeting 8 27 March 2015	*	-	-
Guideline Committee meeting 9	*	-	-

Guideline Committee meeting	Declaration of interest	Classification	Action taken
5 May 2015			
Guideline Committee meeting 10 6 May 2015	No change to declaration	-	-
Guideline Committee meeting 11 17 June 2015	*	-	-
Guideline Committee meeting 12 7 October 2015	*		

*Cooptee was not required to attend these meetings.

B.20 Mark Thomas

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Initial declaration (application)	No change to declaration	None	No action required
Guideline Committee meeting 1 and 2 30 October 2014 31 October 2014	*	-	-
Guideline Committee meeting 3 5 December 2014	*	-	-
Guideline Committee meeting 4 16 January 2015	*	-	-
Guideline Committee meeting 5 23 February 2015	*	-	-
Guideline Committee meeting 6 24 February 2015	*	-	-
Guideline Committee meeting 7 26 March 2015	*	-	-
Guideline Committee meeting 8 27 March 2015	No change to declaration	-	-
Guideline Committee meeting 9	*	-	-

Guideline Committee meeting	Declaration of interest	Classification	Action taken
5 May 2015			
Guideline Committee meeting 10 6 May 2015	*	-	-
Guideline Committee meeting 11 17 June 2015	*	-	-
Guideline Committee meeting 12 7 October 2015	*		

*Cooptee was not required to attend these meetings.

B.21 Elizabeth Toy

Guideline Committee meeting	Declaration of interest	Classification	Action taken
Initial declaration (application)	Talk at BTOG on 29th November 2015 - Educational Satellite Symposia sponsored by Pierre Fabra – "NHS England national chemotherapy algorithms support quality and consistency and equality in care" (will not accept honorarium).	Personal non-pecuniary interest	Declare and participate
	Attended an "Optimising Chemotherapy" round table meeting on 4th December 2014; no honorarium received but train fare paid by Roche Products Ltd. (non-promotional meeting).	Personal non-pecuniary interest	Declare and participate
	Attended ASCO 2014 – Conference registration and travel grant which covered two-thirds of the cost of travel provided by Boehringer Ingelheim.	Personal non-pecuniary interest	Declare and participate
	Received an honorarium on 4th April 2014 for a review on slide deck and educational resource, regarding AFATANIB from Boehringer Ingelheim which focused on trial data and management of toxicity.	Personal pecuniary non-specific interest	Declare and participate
	Attended an advisory board on 11th June 2014 for Boehringer Ingelheim where I received an honorarium. The subjects covered included: Management of the toxicity associated with Afatinib Review of data regarding, Nintedanib in the LUME 1&3 studies	Personal pecuniary non-specific interest	Declare and participate
	Attended an advisory board for Roche where an honorarium was received. The topic covered the use of		

Guideline Committee meeting	Declaration of interest	Classification	Action taken
	Tarceva in the first- and second-line setting. This event took place on 28th Jan 2014 Will not perform any advisory board work or speech at any promotional meetings whilst being involved in the NICE review. Clinical lead for oncology – some trials we run are commercial (although most NCIN badged). Money goes to trust R&I department who employ staff who conduct trials in the department. I am not a direct line manager of this group of staff, although we do use them to conduct clinical studies. None within scope of the guideline, however, I have a publically known opposition to assisted suicide and have previously published a letter in support of the principles of the LCP in the Catholic Press.	Personal pecuniary non-specific interest Non-personal pecuniary interest Personal non-pecuniary interest	Declare and participate Declare and participate Declare and participate
Guideline Committee meeting 1 and 2	*	-	-

Guideline Committee meeting	Declaration of interest	Classification	Action taken
30 October 2014 31 October 2014			
Guideline Committee meeting 3 5 December 2014	*	-	-
Guideline Committee meeting 4 16 January 2015	*	-	-
Guideline Committee meeting 5 23 February 2015	*	-	-
Guideline Committee meeting 6 24 February 2015	*	-	-
Guideline Committee meeting 7 26 March 2015	*	-	-
Guideline Committee meeting 8 27 March 2015	None	-	-
Guideline Committee meeting 9 5 May 2015	*	-	-
Guideline Committee meeting 10 6 May 2015	*	-	-
Guideline Committee	*	-	-

Guideline Committee meeting	Declaration of interest	Classification	Action taken
meeting 11 17 June 2015			
Guideline Committee meeting 12 7 October 2015	*		

*Cooptee was not required to attend these meetings.

Appendix C: Clinical review protocols

C.1 Recognising Dying

Table 1: Review protocol: Recognising dying

Review question	What signs and symptoms indicate that adults are likely to be entering their final days of life; or that they may be recovering? How are uncertainties about either situation dealt with?
Objectives	To determine signs and symptoms of imminent death (that is, in the final days of life), signs and symptoms showing if the patient is recovering, and the uncertainty of the signs and symptoms for predicting imminent death in order to: • communicate this to the person and the family • communicate this with multi-professional team • inform discussions about individual care planning (note link to other qualitative reviews). Recovery objective (to check), or uncertainty of dying as separate objective.
Population	Adults (aged 18 years and over). Exclusions: • Children and young people (aged less than 18 years).
Signs/symptoms (for quantitative/prognostic component of the review)	Signs and symptoms including in at least one of the following categories (symptom categories as described in Domeisen et al., 2013[135]): • Breathing (including rattle and irregular breathing) • General deterioration (including extreme weakness) • Consciousness/cognition (including reduced cognition) • Related to condition of skin (including discolouration) • Intake of fluid, food • Urine output • Emotional state (including anxiety) • Social withdrawal • Acute – bleeding, renal failure.
Outcomes/themes	Quantitative/prognostic review component: Death (within a few days/hours) (time to event data, if available). Qualitative review component: thematic analysis and presentation of a theoretical framework/conceptual map. Trajectory Patient perspective (if they think they are near death) Resolution with family/relationships).
Study design	Quantitative/prognostic review component: Prospective or retrospective cohorts Qualitative review component: Qualitative review such as large scale or Delphi consensus surveys, interviews Systematic reviews of the above Exclusions: • Editorials/commentaries/opinion pieces (other than large consensus surveys).
Exclusions	Non-English language studies Abstracts

	Papers that focus on transition to palliative care as this is not specific to the final days and hours of life.
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL, PsychINFO Studies will be restricted to English language only.
Key confounders	Treatments that may suppress conscious level Artificial organ support, such as ventilation
Review strategy	Integrative literature review methods, as used in in Kennedy et al, 2014,[257] will be explored. This type of review allows for the inclusion of different study designs (experimental, observational and qualitative) in order to fully understand an area of concern. The review involves both quantitative (prognostic for this review) and qualitative elements. **For the quantitative review component:** Pooling of individual patient data, if available from the published literature. Pooling of data, if deemed appropriate. Data on the following groups will be presented separately, if the evidence allows: • Dementia or other cognitive impairment • Learning disabilities • Organ system failure (such as heart failure). Subgroups of people: • People already diagnosed with a terminal condition • Persons with a sudden deterioration of a condition • Persons in acute setting without a long-term terminal condition. **For the qualitative review component:** Thematic analysis and presentation of a theoretical framework/conceptual map.

C.2 Communication

Table 2: Review protocol: Communication

Review question	**What are the barriers and facilitators to good communication between the dying person, those important to them and the healthcare professional surrounding the likelihood of entering the last days of life?**
Objective	• To explore the experiences, opinions and attitudes of the dying person and those important to them on the factors that encourage and prevent good communication between them and the healthcare professional when conveying the likelihood they are entering the last days of life. • To explore the experiences, opinions and attitudes of the healthcare professional on the factors that encourage and prevent good communication between them and the dying person and those important to them when conveying the likelihood they are entering the last days of life.
Population and setting	Adults who have been recognised as likely to be entering the last days of life, those important to them and healthcare professionals in all settings where NHS funded care is provided.
Context	**Context**: Communication about the likelihood of entering the last days of life or recovering.

	Outcomes: Themes will be identified from the literature found. For example: • Healthcare professionals level of skills or training. • Use of empathy and rapport • Time and resource (seniority of staff) • Degree of uncertainty • Language differences • Cultural differences • People with cognitive disability • People with learning disability • Terminology used • Timing and place of communication.
Exclusions	None
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL, PsychINFO Studies will be restricted to English language only.
Review strategy	**Study designs to be considered:** • Qualitative studies (for example, interviews, focus groups, observations) • Surveys **Review strategy:** • Population size and directness: o No sample size specification (for surveys). o Studies with indirect populations will not be considered for example, people who are not entering the last days of life **Setting:** • Any setting where people receive intervention relevant to the NHS. **Appraisal of methodological quality** The methodological quality of each study will be assessed using NCGC modified NICE checklists and the quality of the evidence will be assessed by a modified GRADE approach for each outcome. **Data synthesis** Thematic analysis of the data will be conducted and findings presented. If any studies include informationon advance directives we will extract this information for discussion with the Committee. Data on the following groups will be presented separately, if the evidence allows: • Dementia or other cognitive impairment • Learning disabilities. The recommendations made in CG138 (NICE guideline on 'Patient experience in adult NHS services' [341] will be taken into consideration where appropriate.

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C.3 Shared Decision Making

Table 3: Review protocol: Shared decision making

Review question	What are the facilitators and barriers to the multi-professional team, dying person and those important to them in being involved in shared decision making to inform the development of personalised care plans for the last days of life?
Objective	• To consider which positive and negative experiences and opinions of the dying person and those important to them to facilitate or hinder the formulation of personalised care plans for the last days of life and how they can be used to improve current practice. • To consider which positive and negative experiences and opinions of healthcare professionals could be used to facilitate the active involvement of dying people and those important to them in formulating personalised care plans.
Population and setting	Adults who have been recognised as likely to be entering the last days of life, those important to them and healthcare professionals in all settings where NHS funded care is provide.
Context	**Context:** Care planning in the last days of life **Outcomes:** Themes will be identified from the literature. For example: • Professional reticence to include dying people in development of personalised care plans. • Shared decision making in response to sudden changes • Reviewing situation regularly • People with cognitive disabilities • People with learning difficulties • People with communication disorders.
Exclusions	None
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL, PsychINFO Studies will be restricted to English language only.
Review strategy	**Study designs to be considered:** • Qualitative studies (for example, interviews, focus groups, observations) • Surveys. **Review strategy:** • Population size and directness: ○ No sample size specification (for surveys). ○ Studies with indirect populations will not be considered for example, personalised care plans for people who are not in their last days of life. **Setting:** • Any setting where people receive care relevant to NHS care. **Appraisal of methodological quality** The methodological quality of each study will be assessed using NCGC modified NICE checklists and the quality of the evidence will be assessed by a modified GRADE approach for each outcome. **Data synthesis** Thematic analysis of the data will be conducted and findings presented. Data on the following groups will be presented separately, if the evidence allows: • Dementia or other cognitive impairment • Learning disabilities.

	The recommendations made in CG138 (NICE guideline on 'Patient experience in adult NHS services' [341] will be taken into consideration where appropriate.

C.4 Maintaining Hydration

Table 4: Review protocol: Clinically assisted hydration

Component	Description
Review question	In patients in their last days of life, is clinically assisted hydration effective in improving symptoms and general comfort?
Objectives	To identify whether clinically assisted hydration is effective in the clinical management of a patient in their last days of life.
Population	Adult people in the last days of life who are not maintaining sufficient oral hydration.
Interventions	Clinically assisted hydration • Enteral hydration (via nasogastric tube, gastrostomy or jejunostomy) • Parenteral hydration (intravenously or subcutaneously).
Comparator	• Placebo, for example, clinically insignificant amounts • No intervention • Oral hydration only.
Outcomes	Critical: • Quality of life (either patient-rated, clinician-rated, carer-rated) • Symptom improvement on rating scales pre and post intervention. Important: • Hydration status using both objective and subjective measures (for example, hydration of oral mucosa, measuring vital signs and skin turgor). • Adverse events both procedural (phlebitis, or line infections, for example) and from positive fluid balance (for example, pleural effusions). • Subjective ratings from informal carers on quality of care received. • Biochemistry results including urea, creatinine and sodium.
Study design	• RCT • Prospective cohort study • Systematic Review Exclusions: • Cohort • Case series • Case reports • Narrative summaries (including literature reviews).
Population size and directness	No restrictions.
Setting	All settings.
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL, PsychINFO Studies will be restricted to English language only.
Review strategy	Appraisal of methodological quality. The methodological quality of each study will be assessed using NICE checklists and the

	quality of the evidence will be assessed by GRADE for each outcome. Synthesis of data. Meta-analysis will be conducted where appropriate. Data on the following groups will be presented separately, if the evidence allows: • Dementia or other cognitive impairment • Learning disabilities.

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C.5 Pharmacological Interventions

Table 5: Review protocol: Pharmacological management of pain, breathlessness, anxiety, agitation and delirium

Component	Description
Review question 6b	For people in the last days of life, which pharmacological agents are most effective in relieving pain, breathlessness, anxiety, agitation and delirium and what degree of sedation do they cause?
Objectives	To identify the most effective pharmacological treatment for pain, breathlessness, anxiety, agitation and delirium in the last days of life.
Population	Adult people in the last days of life.
Interventions	**Benzodiazepines** • lorazepam • midazolam • diazepam • clonazepam **Opioids** • morphine • oxycodone • fentanyl • alfentanil • buprenorphine • diamorphine **Antipsychotics** • haloperidol • levomepromazine • olanzapine • chlorpromazine **Corticosteroids** • Dexamethasone • Prednisolone **Diuretics** • Furosemide **Non-steroidal anti-inflammatories** • ketorolac • diclofenac **Oxygen** • Heliox Note: the use of these interventions for palliative sedation is not being considered in this review
Comparison(s)	• Any of the above • Placebo • Usual care
Outcomes	CRITICAL • Quality of life or patient wellbeing (as rated by doctor, the dying person or

	those important to them) • Control of specific symptoms (for pain, breathlessness , nausea, vomiting, anxiety, agitation and delirium) <u>IMPORTANT</u> • Carer satisfaction • Duration of symptom control • Length of survival • Level of sedation • Adverse effects of treatment, including: o For antihistamines this may include urinary retention or dizziness. o For antipsychotics it may include extrapyramidal side effects, akathisia (restlessness) neuroleptic malignant syndrome, urinary retention and constipation. o For Benzodiazepines this may include hypotension respiratory depression or increased restlessness, confusion, ataxia and falls. o For opiates it may include respiratory depression, nausea and vomiting, drowsiness, itching dry mouth and constipation. o For steroids it may include a change in mental state or gastritis.
Strata	For people with pain with: • Drug dependence (illicit or prescribed) • Organ failure
	• For people with anxiety with: • Dementia • Mood disorders
	• For people with breathlessness with: • Heart failure • Lung disease
	• For people with agitation and/or delirium with: • Brain tumour or brain metastases • Dementia • Metabolic cause of delirium (for example hypercalcaemia, hyponatraemia) • Pharmacological causes of delirium including general anaesthesia and sedation on critical care
	People with nausea and vomiting: • Bowel obstruction • Increased intracranial pressure • Metabolic causes • Opioid therapy
Subgroups	<u>Drug class</u> <u>Routes of administration</u> • Enteral (includes oral and enteral tubes) • Intramuscular • Intravenous • Subcutaneous • Transdermal • Transmucosal (includes sublingual, buccal, nasal)

	Delivery system • 'Melt' tablet • Bolus SC injection or continuous SC delivery by syringe driver • Continuous IV delivery by pump or Intermittent IV delivery by PCA • IM injection • Nasogastric tube • PEG tube • Skin patch • Sublingual, buccal, dissolving tablet • Tablet, liquid for enteral access
Study design	• Systematic reviews of RCTs • RCTs • Non randomised comparative studies **Exclusions**: • Cohort • Case series • Case reports • Narrative summaries (including literature reviews) • Animal studies
Population size and directness	No restrictions.
Setting	All settings.
Search Strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL, PsychINFO Studies will be restricted to English language only.
Review Strategy	**Appraisal of methodological quality:** • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. **Synthesis of data:** • Meta-analysis will be conducted where appropriate. A stepwise approach is suggested: • If sufficient randomised evidence is identified, observational studies will not be added • If observational studies are considered then studies accounting for confounding factors (multivariable analysis or matching) will be considered next. • Only if insufficient randomised or multivariable data is identified will other non-randomised comparative evidence be considered. Data on the following groups will be presented separately, if the evidence allows: • Dementia or other cognitive impairment • Learning disabilities

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Table 6: Review protocol: pharmacological management of nausea and vomiting

Component	Description
Review question	For people in the last days of life, which pharmacological agents are most effective in providing relief for nausea and vomiting and what degree of sedation do they cause?
Objectives	To identify the most effective pharmacological treatment for nausea in the last days of life.
Population	Adult people in the last days of life who are nauseous
Comparator	**Corticosteroids** • Dexamethasone **Somatostatin analogue antisecretory** • Octreotide **Dopamine receptor blocker** • Metoclopramide • Domperidone • Haloperidol • Levomepromazine **5-HT3 antagonists** • Palonosetron • Ondansetron • Granisetron **NK1 antagonists** • Aprepitant • Fosaprepitant **Atypical antipsychotics** • Olanzapine • Prochlorperazine • Chlorpromazine **Antimuscarinic** • Cyclizine • Glycopyrronium • Hyoscine butylbromide • Hyoscine hydrobromide
Outcomes	Critical: • Nausea control (patient-rated, clinician-rated, carer-rated) • Number of vomiting episodes • Sedation either subjective (patient-rated, clinician-rated, carer-rated) or objective (Glasgow Coma Scale or equivalent scale of responsiveness) • Quality of life. Important: • Adverse events/withdrawal of the medication due to adverse events • Length of survival.
Subgroups	Patients with: • Increased intracranial pressure • Bowel obstruction • Opioid therapy • Metabolic causes

Component	Description
	Routes of administration • Enteral (includes oral and enteral tubes) • Transmucosal (includes sublingual, buccal, nasal) • Subcutaneous • Intramuscular • Intravenous • Transdermal **Delivery system** • Tablet, liquid for enteral access • Sublingual, buccal, dissolving tablet • 'Melt' tablet • Nasogastric tube • PEG tube • Bolus SC injection or continuous SC delivery by syringe driver • Continuous IV delivery by pump or intermittent IV delivery by PCA • IM injection • Skin patch
Study design	• Systematic reviews of RCTs • RCTs • Non-randomised comparative studies Exclusions: • Cohort • Case series • Case reports • Narrative summaries (including literature reviews) • Animal studies
Population size and directness	No restrictions.
Setting	All settings.
Search Strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL, PsychINFO Studies will be restricted to English language only.
Review Strategy	Appraisal of methodological quality. The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Synthesis of data. Meta-analysis will be conducted where appropriate. A stepwise approach is suggested in the following circumstances: If sufficient randomised evidence is identified; observational studies will not be added. If observational studies are considered then studies accounting for confounding factors (multivariable analysis or matching) will be considered next. Only if insufficient randomised or multivariable data are identified will other non-randomised comparative evidence be considered. Data on the following groups will be presented separately, if the evidence allows:

Component	Description
	• Dementia or other cognitive impairment Learning disabilities

1 **Table 7: Review protocol: pharmacological management of respiratory secretions**

Component	Description
Review question 6b	For people in the last days of life, which pharmacological agents are most effective in providing relief for troublesome respiratory secretions and what degree of sedation do they cause?
Objectives	To identify the most effective pharmacological treatment for respiratory secretions in the last days of life.
Population	Adults in the last days of life **Exclusions:** • Noisy breathing related to trauma or congenital abnormalities involving the respiratory tract were excluded
Intervention	• Anticholinergics • Muscarinic acetylcholine receptor antagonist • Somatostatin analogue
Comparison(s(	• Any of the above • Placebo • Usual care
Outcomes	CRITICAL • Quality of life (either patient-rated, clinician-rated, carer-rated) • Sedation (either patient-rated, clinician-rated, carer-rated) • Subjective or objective improvement in respiratory secretions (patient-rated, clinician-rated, carer-rated). IMPORTANT • Frequency of adverse events - for example Paradoxical agitation, Failure to expectorate, Dry mouth • Subjective ratings from informal carers' on distress relating to noisy breathing/respiratory secretions. • Subjective ratings from patients' on distress related to noisy breathing/respiratory secretions.
Subgroups	<u>Drug class</u> <u>Routes of administration</u> • Enteral (includes oral and enteral tubes) • Intramuscular • Intravenous • Subcutaneous • Transdermal • Transmucosal (includes sublingual, buccal, nasal). <u>Delivery system</u> • 'Melt' tablet • Bolus SC injection or continuous SC delivery by syringe driver • Continuous IV delivery by pump or Intermittent IV delivery by PCA • IM injection • Nasogastric tube

Component	Description
	• PEG tube • Skin patch • Sublingual, buccal, dissolving tablet • Tablet, liquid for enteral access.
Study design	• Systematic reviews of RCTs • RCTs • Non randomised comparative studies **Exclusions**: • Cohort • Case series • Case reports • Narrative summaries (including literature reviews) Animal studies
Population size and directness	No restrictions.
Setting	All settings.
Search Strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL, PsychINFO Studies will be restricted to English language only.
Review Strategy	**Appraisal of methodological quality:** • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. **Synthesis of data:** • Meta-analysis will be conducted where appropriate. A stepwise approach is suggested: • If sufficient randomised evidence is identified, observational studies will not be added • If observational studies are considered then studies accounting for confounding factors (multivariable analysis or matching) will be considered next. Only if insufficient randomised or multivariable data are identified will other non-randomised comparative evidence be considered Data on the following groups will be presented separately, if the evidence allows: • Dementia or other cognitive impairment • Learning disabilities.

C.6 Anticipatory prescribing

Table 8: Quantitative review protocol: Anticipatory prescribing

Review question	How effective is anticipatory prescribing at improving comfort in adults in the last days of life compared with prescribing at the bed side?
Population and setting	Adults likely to be entering the last days of life, those important to them and healthcare professionals in all settings where NHS funded care is provided.
Intervention	Anticipatory prescribing of all necessary medications for symptom relief of breathlessness, pain, nausea and vomiting, respiratory secretions, anxiety and agitation available in the home, with sufficient for use over a weekend (plus bank

	holidays).
Comparison	Usual care (for example prescribing at the bedside).
Exclusions	• Drugs outside of end of life symptom management • Non-pharmacological treatments • Oxygen • Studies published prior to 2000.
Outcome	**Critical outcomes:** • Quality of life (as rated by the dying person or those important to them or healthcare professional) • Control of specific symptoms (agitation, terminal restlessness, breathlessness, pain, nausea and vomiting, respiratory secretions and anxiety) **Important outcomes:** • Subjective ratings from informal carers on quality of care received. • The amount of medication prescribed that is administered. • Incidence of prescribed medication misused. • Admissions to hospitals for symptom management.
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL. Studies will be restricted to English language only.
Study design	• Systematic reviews of RCTs • RCTs • Non-randomised comparative studies **Exclusions**: • Cohort • Case series • Case reports • Narrative summaries (including literature reviews)
Population size and directness	No restrictions.
Review Strategy	Appraisal of methodological quality: • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Synthesis of data: • Meta-analysis will be conducted where appropriate. Data on the following groups will be presented separately, if the evidence allows: • Dementia or other cognitive impairment • Learning disabilities.

1 **Table 9: Qualitative review protocol: Anticipatory prescribing**

Review question	**What are the experiences, opinions and attitudes of healthcare professionals, the dying person and those important to them regarding access to anticipatory prescribing?**
Objective	• To explore the experiences, opinions and attitudes of healthcare professionals with regards to who should be responsible for anticipatory prescribing. • To explore the experiences, opinions and attitudes of healthcare professionals with regards to when it should be initiated.

	• To explore the experiences, opinions and attitudes of the dying person and those important to them with regards to when it should be initiated.
Population and setting	Adults likely to be entering the last days of life, those important to them and healthcare professionals in all settings where NHS funded care is provided.
Context	Anticipatory prescribing for the last days of life
Exclusions	• Drugs outside of end of life symptom management • Non-pharmacological interventions • Oxygen • Studies published prior to 2000
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL. Studies will be restricted to English language only.
The review strategy	**Study designs to be considered:** • Qualitative studies (for example, interviews, focus groups, observations) • Surveys **Review strategy:** • Population size and directness: o Sample size specification (for surveys) o Studies with indirect populations will not be considered for example., Anticipatory prescribing outside of the last days of life **Setting:** Any setting where people receive intervention relevant to the NHS **Data synthesis** Thematic analysis of the data will be conducted and findings presented. Data on the following groups will be presented separately, if the evidence allows: • Dementia or other cognitive impairment • Learning disabilities.

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Appendix D: Economic review protocol

Table 10: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify economic evaluations relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the individual review protocol above. • Studies must be of a relevant economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix G [in the Full guideline].
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 1999, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix G of the NICE guidelines manual (2012).[342] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. An economic evidence table will be completed and it will be included in the economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then an economic evidence table will not be completed and it will not be included in the economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the Committee if required. The ultimate aim is to include studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the Committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded economic studies in Appendix M. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France,

	Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will have been excluded before being assessed for applicability and methodological limitations. *Economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will have been excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 1999 or later but that depend on unit costs and resource data entirely or predominantly from before 1999 will be rated as 'Not applicable'. • Studies published before 1999 will have been excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the economic analysis:* • The more closely the effectiveness data used in the economic analysis matches with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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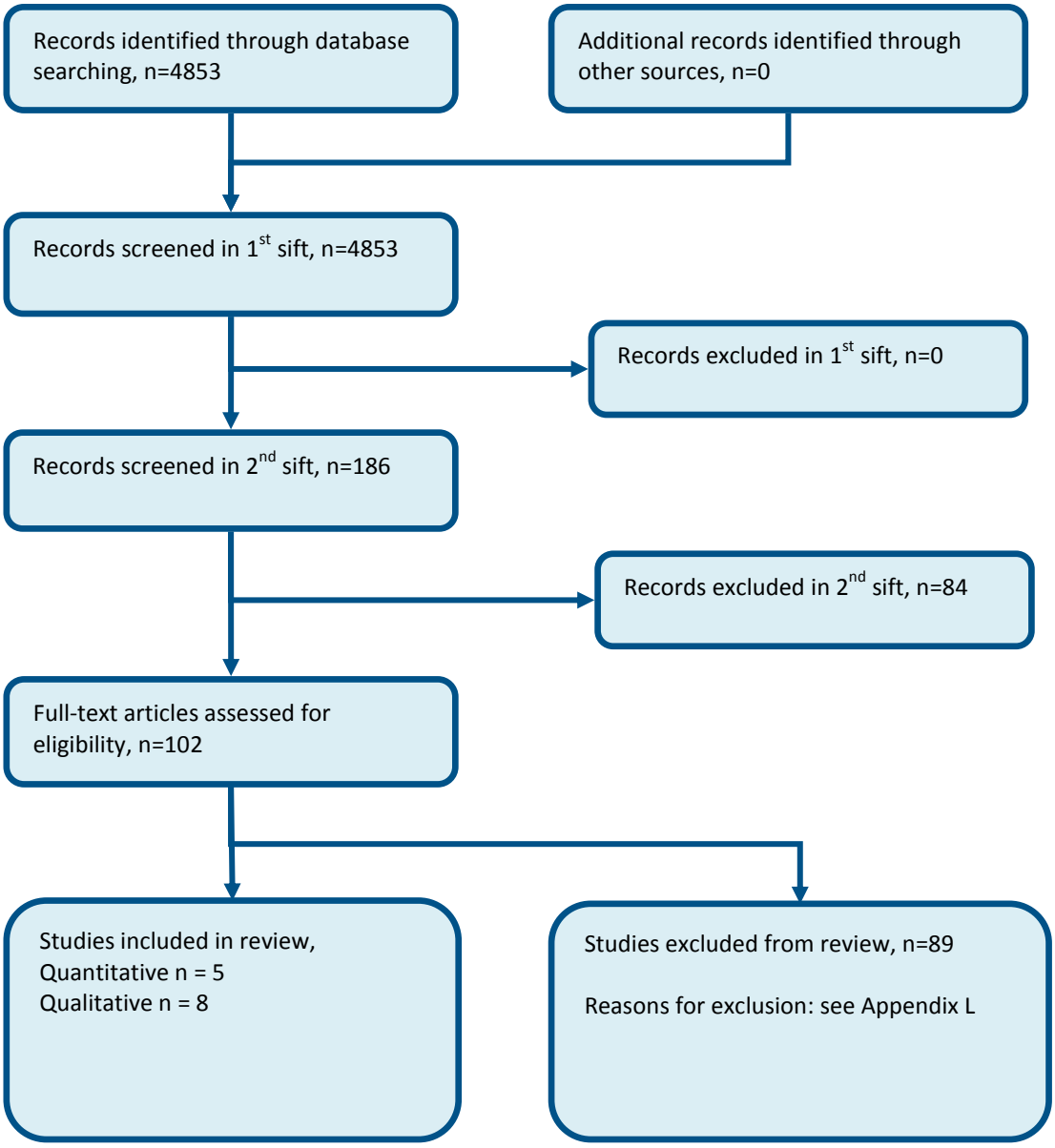
Appendix E: Clinical article selection

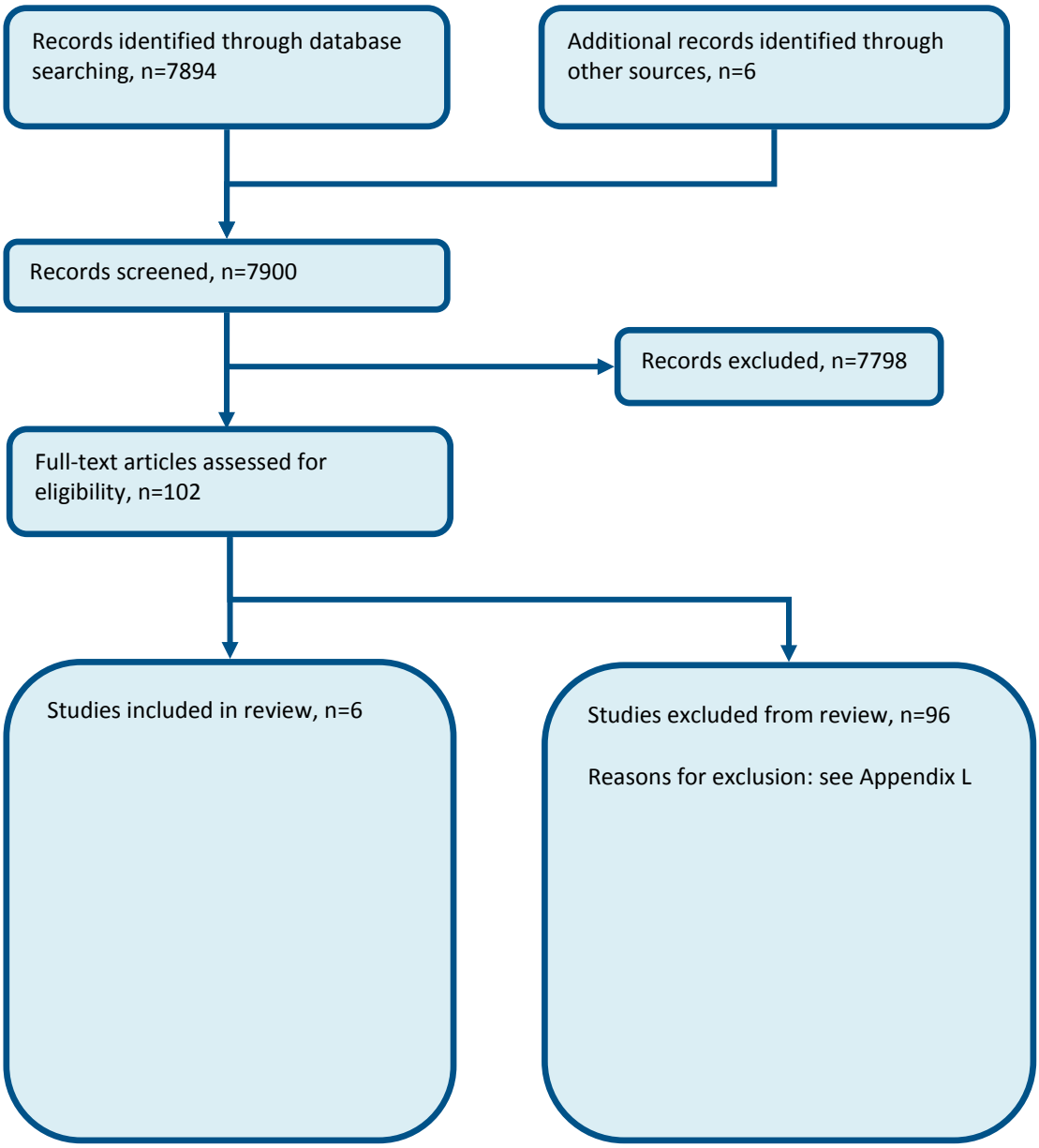
E.1 Recognising Dying

Figure 1: Flow chart of clinical article selection for the review of recognising dying



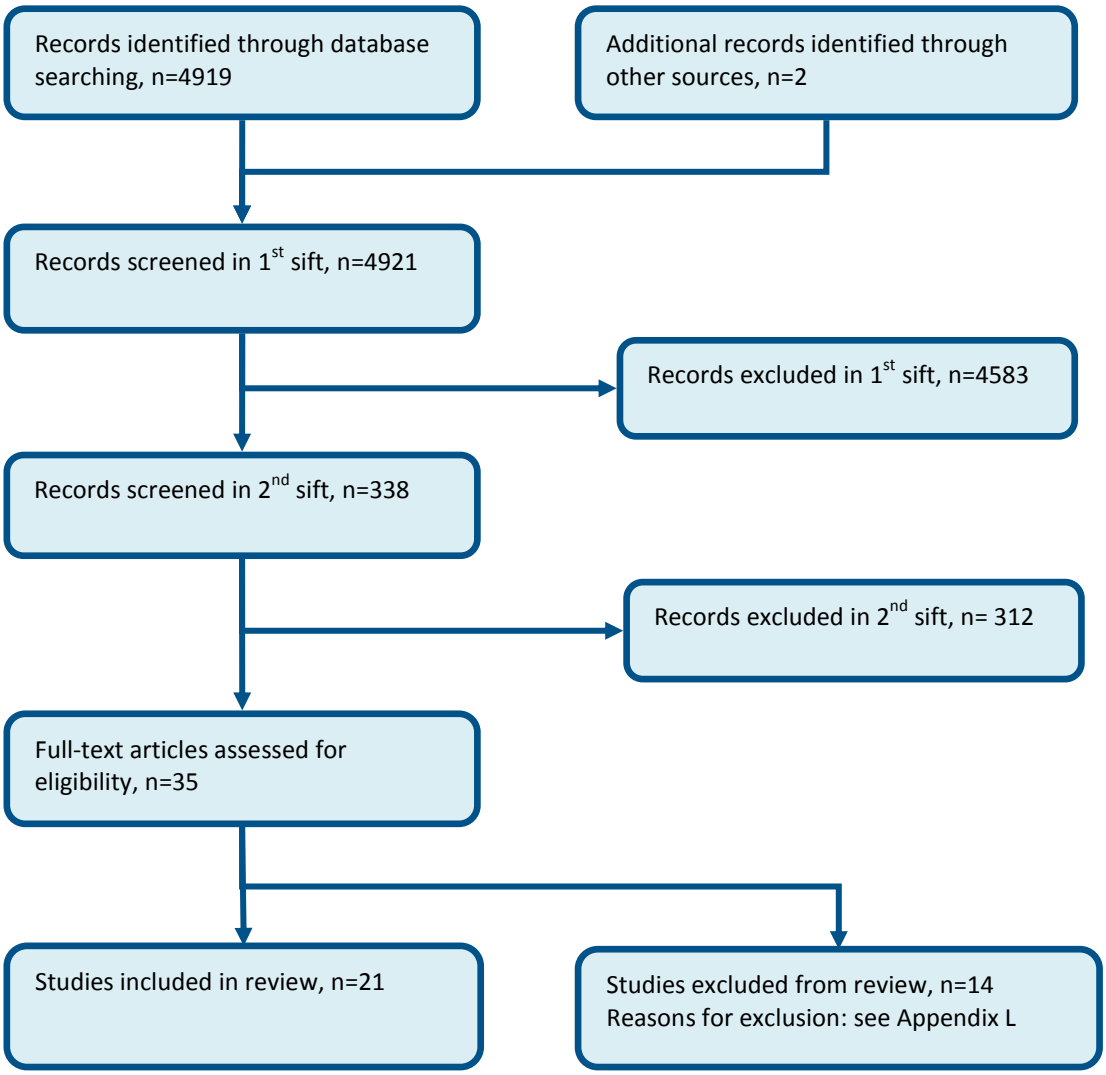
E.2 Communication

Figure 2: Flow chart of clinical article selection for the review of communication



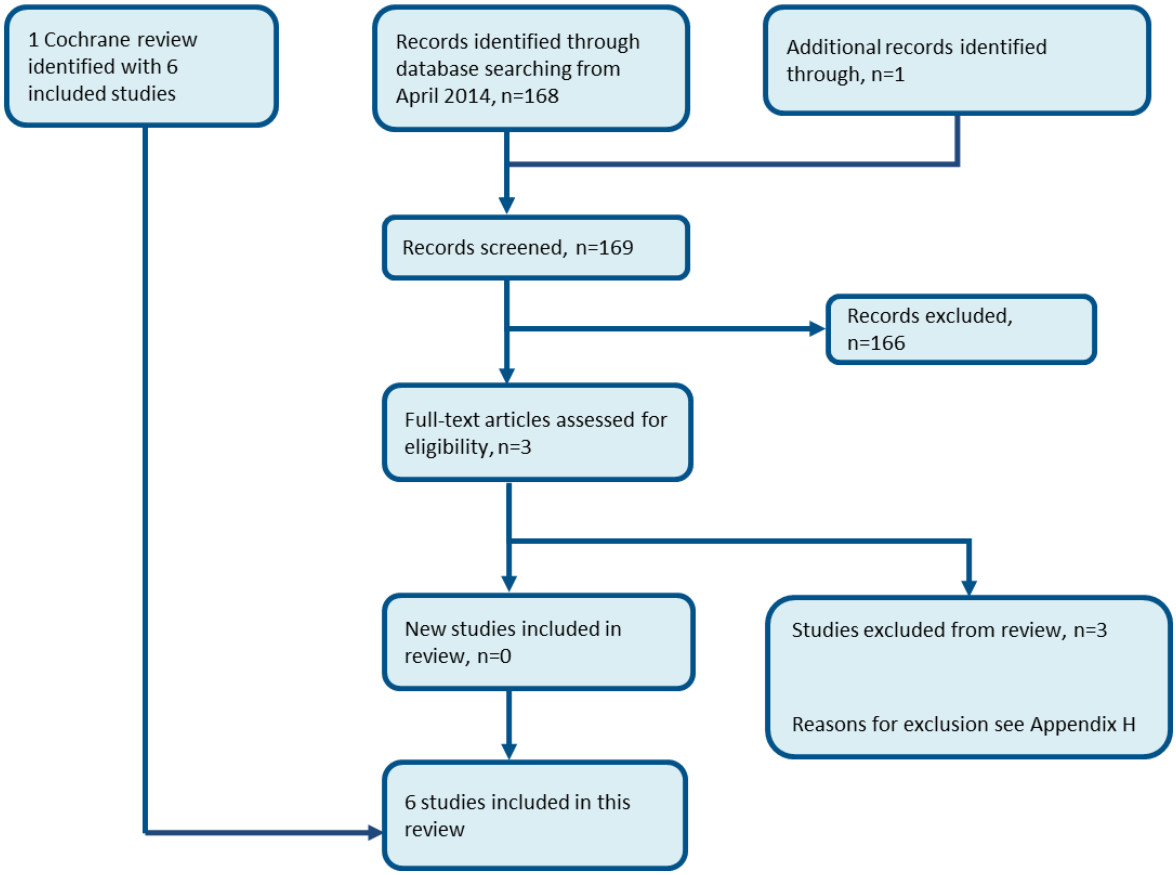
E.3 Shared Decision Making

Figure 3: Flow chart of clinical article selection for the review of shared decision making



E.4 Assisted Hydration

Figure 4: Flow chart of clinical article selection for the update of the Cochrane review of assisted hydration (in the recently updated Cochrane search, 1,632 studies were identified from between 2008-2014 from which 1 study was included and 5 were brought forward from an older version).



E.5 Pharmacological Intervention

Three searches were run for the pharmacological review. One search for agitation, anxiety, breathlessness, delirium and pain, 1 for nausea and vomiting and 1 for noisy respiratory secretions. The flow charts for article selection are shown in Figure 5 to Figure 7.

Figure 5: Flow chart of clinical article selection for the review of agitation, anxiety, breathlessness, delirium and pain

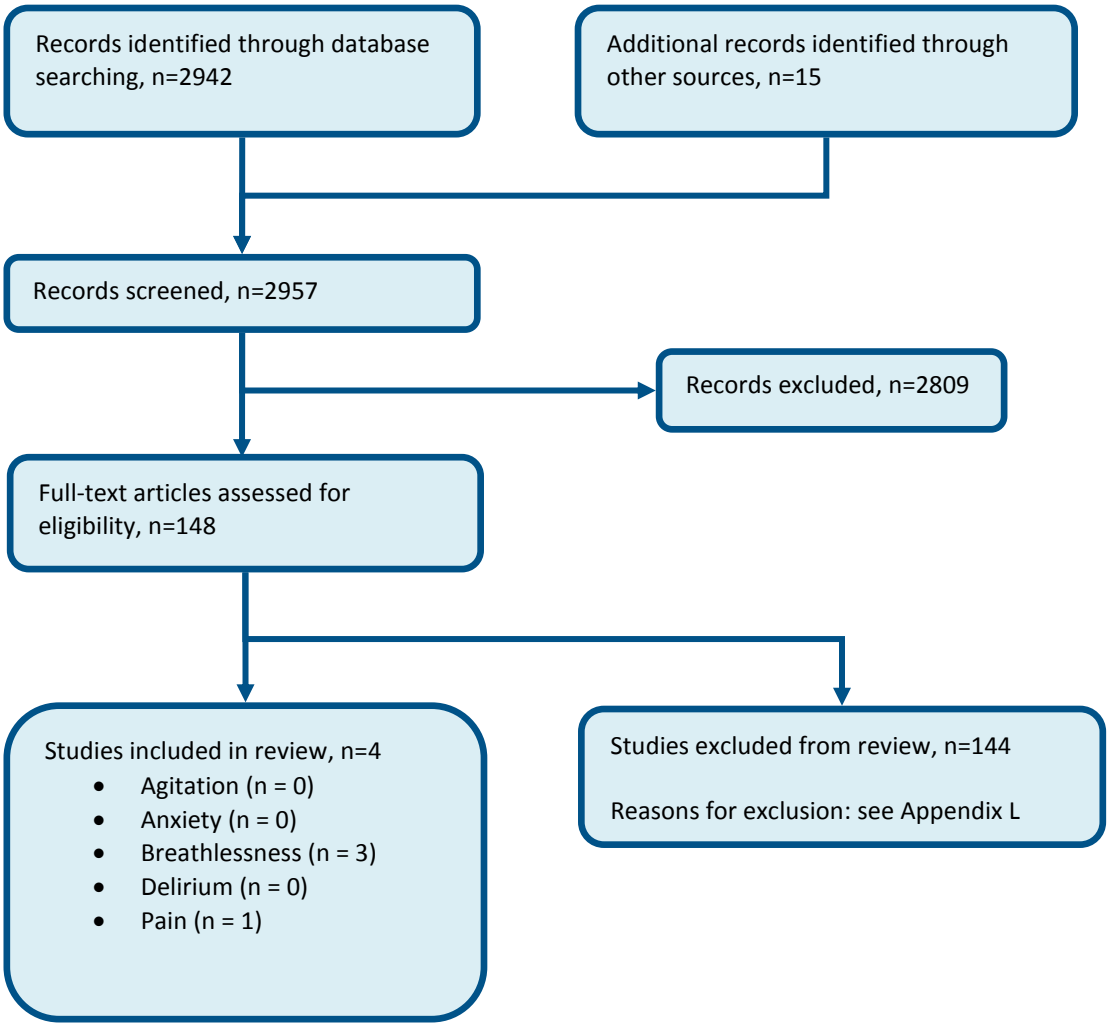


Figure 6: Flow chart of clinical article selection for the review of nausea and vomiting

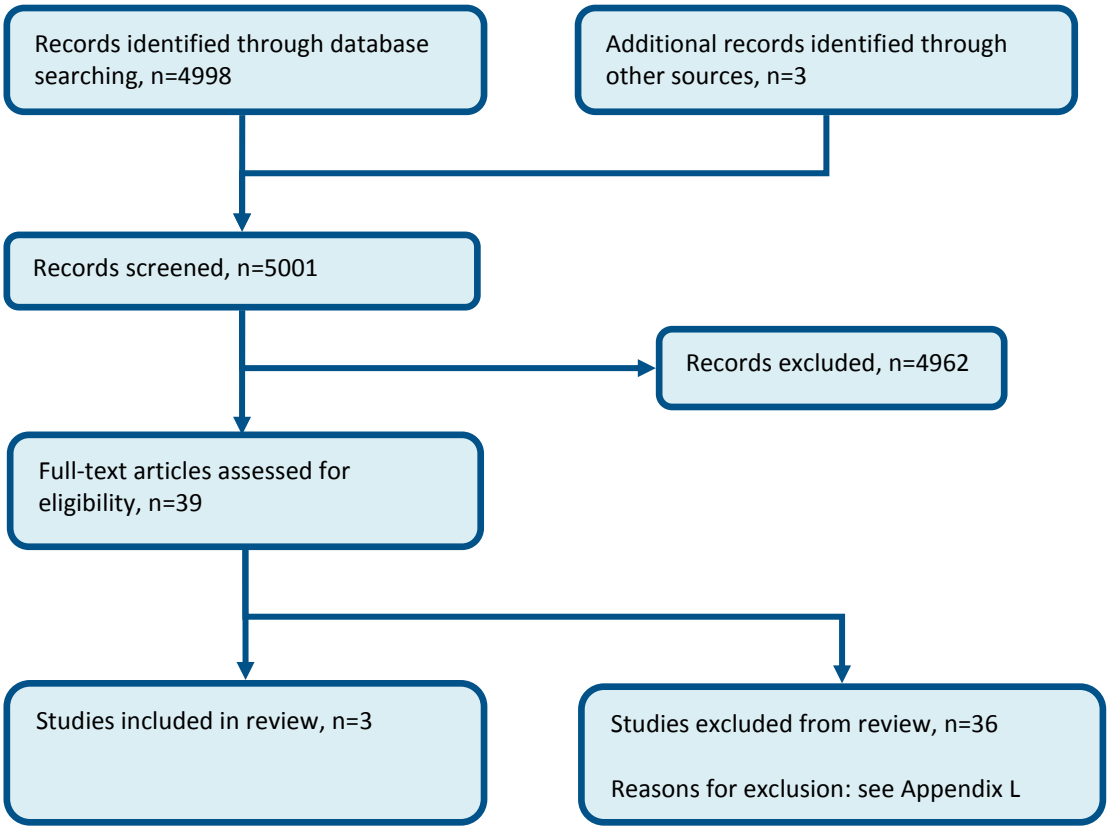
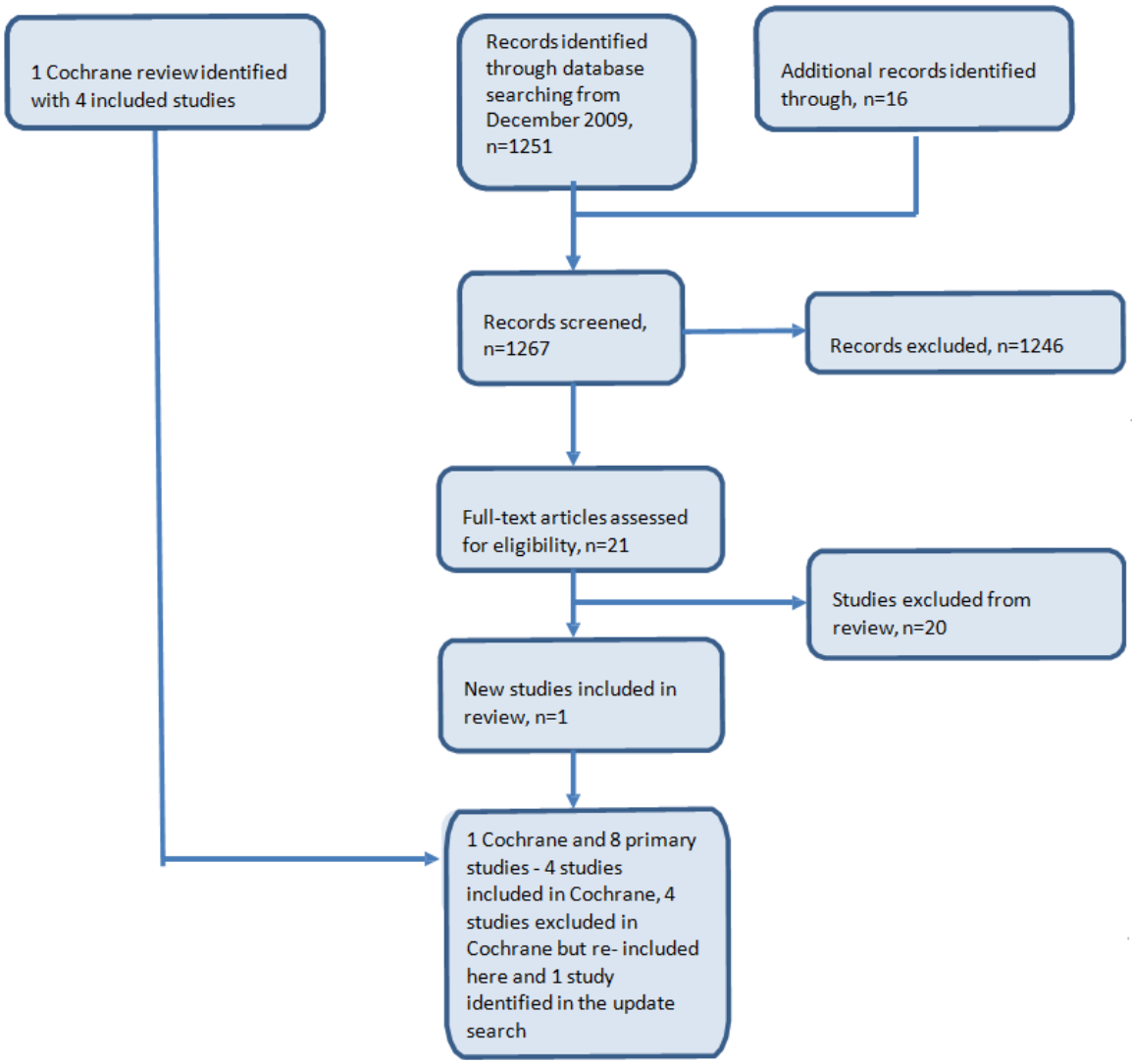


Figure 7: Flow chart of clinical article selection for the review of noisy respiratory secretions



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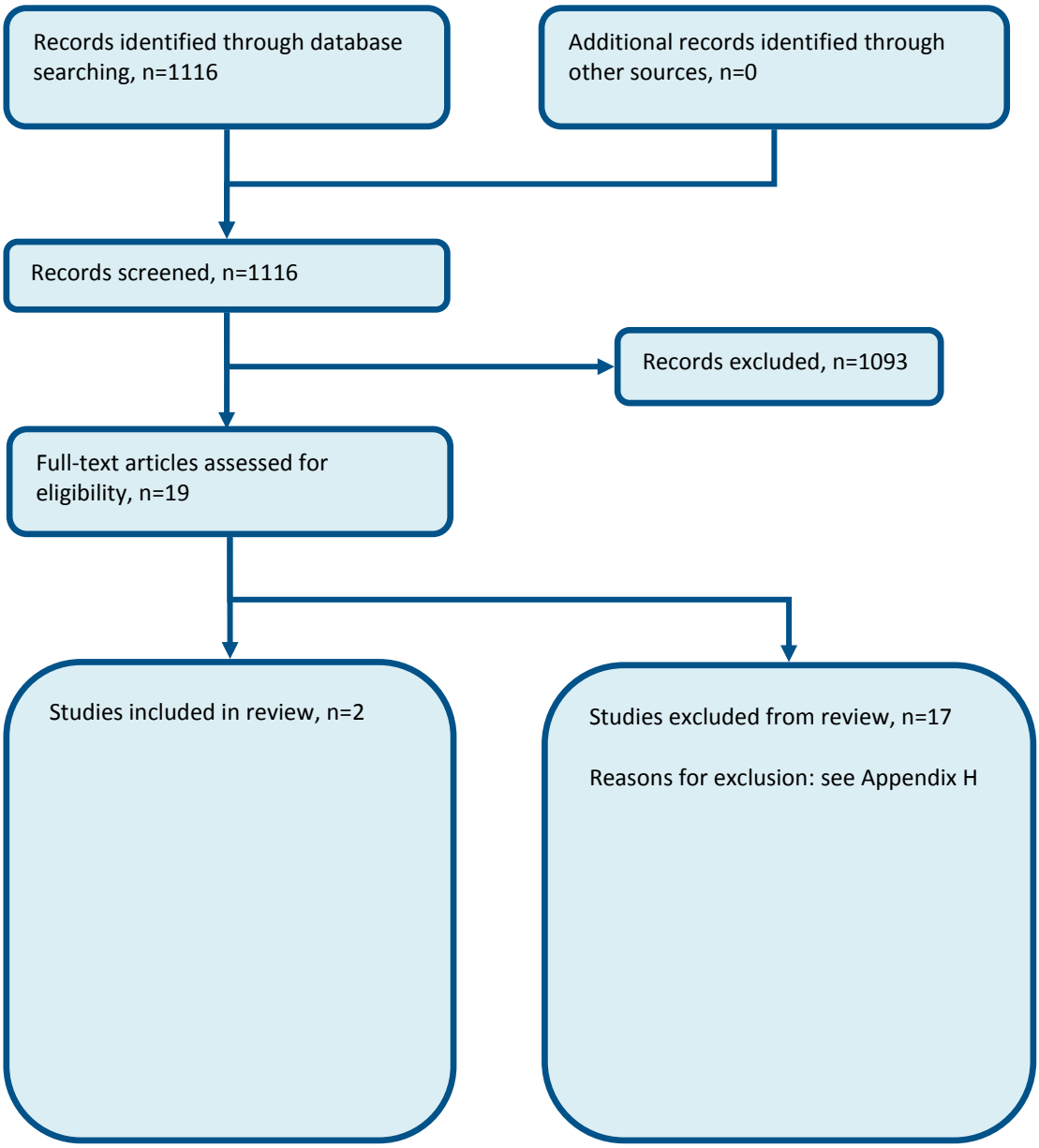
E.6 Anticipatory Prescribing

Figure 8: Flow chart of clinical article selection for the review of anticipatory prescribing



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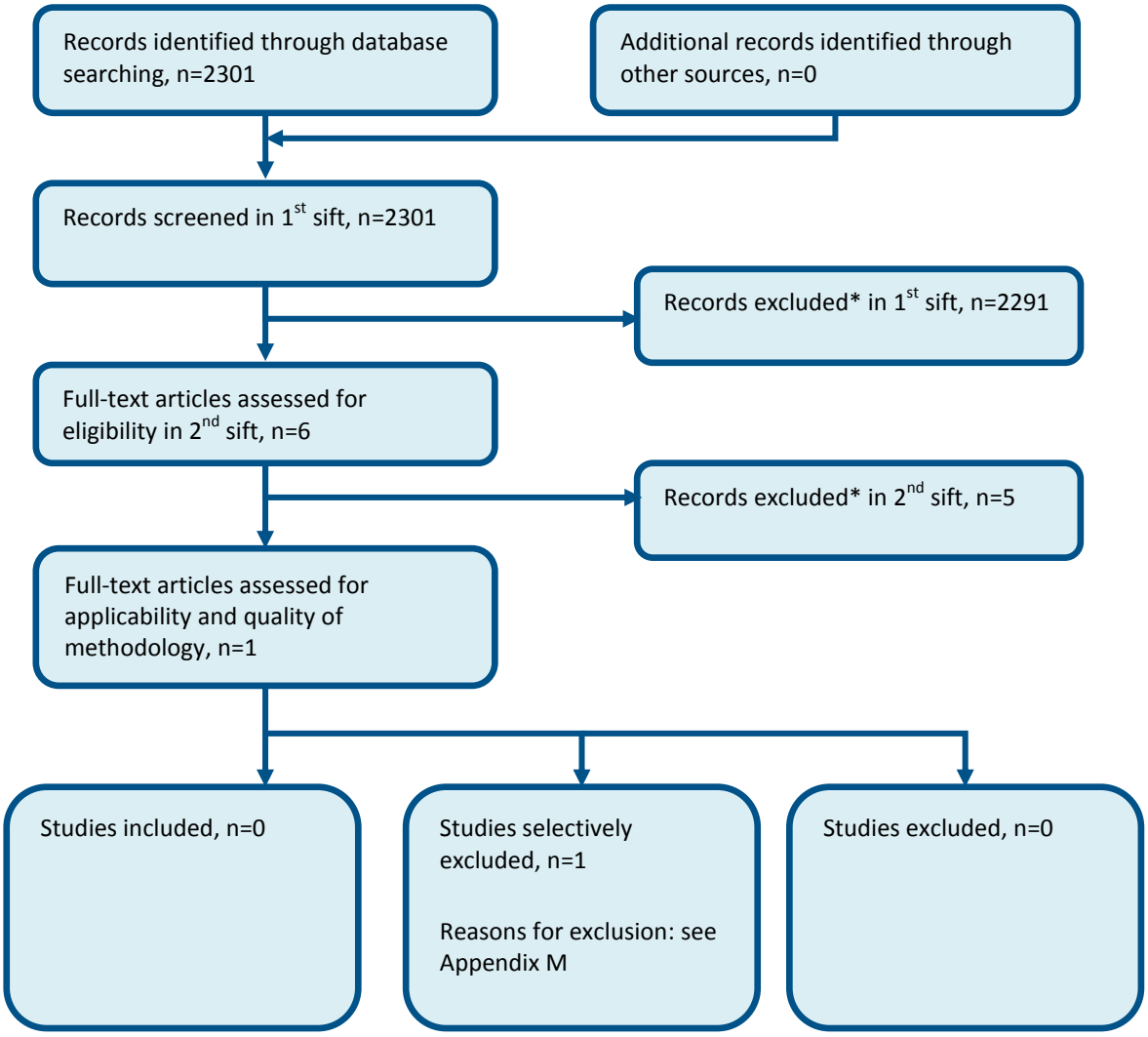
Appendix F: Economic article selection

Figure 9: Flow chart of economic article selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

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Appendix G: Literature search strategies

G.1 Contents

Search strategies used for the care of the dying adult guideline are outlined below and were run in accordance with the methodology in the NICE guidelines manual 2012.[342] All searches were run up to **as indicated in table 2 below**. Any studies added to the databases after this date (even those published prior to this date) were not included unless specifically stated in the text. We do not routinely search for electronic, ahead of print or 'online early' publications. Where possible searches were limited to retrieve material published in English.

Table 11: Database date parameters

Database	Date search from
Medline	1946
Embase	1974
The Cochrane Library	Cochrane Reviews up to Issue 01/2015 CENTRAL up to 01/2015 DARE, HTA and NHSEED up to 01/15
CINAHL	1960
PsycINFO (OVID)	1967

Searches for the **clinical reviews** were run in Medline (OVID) and Embase (OVID). Additional searches were run in the Cochrane Library, CINAHL (EBSCO) and PsycInfo (OVID) for some questions. See Table 2.

Table 12: Databases searched by question

Question	Question number	Databases	Date search run (specific parameters are outlined in question summary)
Recognising dying	A.2.1	Medline, Embase, Cochrane	29/10/14
Communication	A.2.2	Medline, Embase, Cochrane, CINAHL, PsycINFO	16/12/15
Shared decision making	A.2.3	Medline, Embase, Cochrane, CINAHL, PsycINFO	17/12/15
Maintaining hydration	A.2.4	Medline, Embase, Cochrane, CINAHL	29/09/14
Respiratory secretions	A.2.5	Medline, Embase, Cochrane, CINAHL	04/11/14
Pharmacological agents: pain, anxiety, breathlessness, agitation and delirium	A.2.6	Medline, Embase, Cochrane,	09/01/15
Pharmacological agents: nausea and vomiting	A.2.7	Medline, Embase, Cochrane,	11/11/14
Anticipatory prescribing	A.2.8	Medline, Embase, Cochrane, CINAHL	07/01/15
Health economics	A.3.1	Medline, Embase, HTA & NHS EED on CRD, HEED	10/10/14
Minimally Important differences	A.4	Medline, Embase	20/04/15

Searches for **intervention and diagnostic studies** were usually constructed using a PICO format where population (P) terms were combined with Intervention (I) and sometimes Comparison (C) terms. An intervention can be a drug, a procedure or a diagnostic test. Outcomes (O) are rarely used in search strategies for interventions. Search filters were also added to the search where appropriate.

Searches for **prognostic studies** were usually constructed combining population terms with prognostic variable terms and sometimes outcomes. Search filters were added to the search where appropriate.

Searches for the **health economic reviews** were run in Medline (OVID), Embase (OVID), the NHS Economic Evaluations Database (NHS EED), the Health Technology Assessment (HTA) database and the Health Economic Evaluation Database (HEED). Searches in NHS EED and HEED were constructed using population terms only. For Medline and Embase an economic filter (instead of a study type filter) was added to the same clinical search strategy.

Searches for **minimally important differences** were run in Medline (OVID) and Embase (OVID)

G.1 Study filter search terms

G.1.1 Systematic review (SR) search terms

Medline search terms

1.	meta-analysis/
2.	meta-analysis as topic/

3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.
10.	or/1-9

Embase search terms

1.	systematic review/
2.	meta-analysis/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
5.	(reference list* or bibliography* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	((pool* or combined) adj2 (data or trials or studies or results)).ab.
10.	cochrane.jw.
11.	or/1-10

G.1.2 Randomised controlled trials (RCTs) search terms

Medline search terms

1.	randomized controlled trial.pt.
2.	controlled clinical trial.pt.
3.	randomized.ab.
4.	placebo.ab.
5.	randomly.ab.
6.	clinical trials as topic.sh.
7.	trial.ti.
8.	or/1-7

Embase search terms

1.	random*.ti,ab.
2.	factorial*.ti,ab.
3.	(crossover* or cross over*).ti,ab.
4.	((doubl* or singl*) adj blind*).ti,ab.
5.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
6.	crossover procedure/
7.	double blind procedure/
8.	single blind procedure/
9.	randomized controlled trial/
10.	or/1-9

G.1.3 Health economics (HE) search terms

Medline search terms

1.	economics/
2.	value of life/
3.	exp "costs and cost analysis"/
4.	exp economics, hospital/
5.	exp economics, medical/
6.	economics, nursing/
7.	economics, pharmaceutical/
8.	exp "fees and charges"/
9.	exp budgets/
10.	budget*.ti,ab.
11.	cost*.ti.
12.	(economic* or pharmaco?economic*).ti.
13.	(price* or pricing*).ti,ab.
14.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
15.	(financ* or fee or fees).ti,ab.
16.	(value adj2 (money or monetary)).ti,ab.
17.	or/1-16

Embase search terms

1.	health economics/
2.	exp economic evaluation/
3.	exp health care cost/
4.	exp fee/
5.	budget/
6.	funding/
7.	budget*.ti,ab.
8.	cost*.ti.
9.	(economic* or pharmaco?economic*).ti.
10.	(price* or pricing*).ti,ab.
11.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
12.	(financ* or fee or fees).ti,ab.
13.	(value adj2 (money or monetary)).ti,ab.
14.	or/1-13

G.1.4 Excluded study designs and publication types

The following study designs and publication types were removed from retrieved results using the NOT operator.

Medline search terms

1.	letter/
2.	editorial/
3.	news/
4.	exp historical article/

5.	anecdotes as topic/
6.	comment/
7.	case report/
8.	(letter or comment*).ti.
9.	or/1-8
10.	randomized controlled trial/ or random*.ti,ab.
11.	9 not 10
12.	animals/ not humans/
13.	exp animals, laboratory/
14.	exp animal experimentation/
15.	exp models, animal/
16.	exp rodentia/
17.	(rat or rats or mouse or mice).ti.
18.	or/11-17

Embase search terms

1.	letter.pt. or letter/
2.	note.pt.
3.	editorial.pt.
4.	case report/ or case study/
5.	(letter or comment*).ti.
6.	or/1-5
7.	randomized controlled trial/ or random*.ti,ab.
8.	6 not 7
9.	animal/ not human/
10.	nonhuman/
11.	exp animal experiment/
12.	exp experimental animal/
13.	animal model/
14.	exp rodent/
15.	(rat or rats or mouse or mice).ti.
16.	or/8-15

PsycInfo search terms

1.	animals/ not humans/
2.	exp rodents/ or exp mice/
3.	(rat or rats or mouse or mice).ti.
4.	or/1-3

G.2 Searches for specific questions

G.2.1 Recognising dying

1. What signs and symptoms indicate that adults are likely to be entering their final days of life; or that they may be recovering? How are uncertainties about either situation dealt with?

Medline search terms

1.	Death/

2.	(dying or die* or death).ti,kf.	
3.	Terminally ill/ or Terminal care/ or Palliative care/	
4.	((terminal or palliati*) adj1 care).ti,kf.	
5.	"terminally ill".ti,kf.	
6.	"terminal illness".ti,kf.	
7.	(palliati* adj1 stage*).ti,ab.	
8.	("end of life" adj2 (stage or stages)).ti,ab.	
9.	or/1-9	
10.	"end of life".ti,ab.	
11.	((last or final) adj1 (hour* or days* or minute* or stage* or week* or month*)).ti,ab.	
12.	((dying or terminal) adj1 phase*).ti,ab.	
13.	((dying or terminal or end) adj1 stage*).ti,ab.	
14.	(dying adj2 (actively or begin* or begun)).ti,ab.	
15.	(death adj2 (imminent* or impending or near or throes)).ti,ab.	
16.	((dying or death) adj2 (patient* or person* or people)).ti,ab.	
17.	(Body adj2 (shut down or shutting down or deteriorat*)).ti,ab.	
18.	deathbed.ti,ab.	
19.	or/10-18	
20.	9 and 19	***Population***
21.	symptom assessment/	
22.	diagnosis/ or prognosis/	
23.	(diagnos* or prognos* or assess* or criteria* or predict*).ti,kf.	
24.	(sign or signs or symptom* or recogni* or identif*).ti,ab.	
25.	agonal.ti,ab.	
26.	multiple organ failure/	
27.	(organ* adj2 fail*).ti,ab.	
28.	(organ* adj2 dysfunction*).ti,ab.	
29.	or/21-28	***Intervention***
30.	20 and 29	
31.	Excluded study designs and publication types limit A.1.4	
32.	30 not 31	
33.	Limit 32 to English language	

1

2 **Embase search terms**

1.	Death/
2.	(dying or die* or death).ti,kw.
3.	Terminally ill patient/ or Terminal care/ or Palliative therapy/
4.	((terminal or palliati*) adj1 care).ti,kw.
5.	"terminally ill".ti,kw.
6.	"terminal illness".ti,kw.
7.	(palliati* adj1 stage*).ti,ab.
8.	("end of life" adj2 (stage or stages)).ti,ab.
9.	or/1-8
10	"end of life".ti,ab.

11.	((last or final) adj1 (hour* or days* or minute* or stage* or week* or month*)).ti,ab.	
12.	((dying or terminal) adj1 phase*).ti,ab.	
13.	((dying or terminal or end) adj1 stage*).ti,ab.	
14.	(dying adj2 (actively or begin* or begun)).ti,ab.	
15.	(death adj2 (imminent* or impending or near or throes)).ti,ab.	
16.	((dying or death) adj2 (patient* or person* or people)).ti,ab.	
17.	(Body adj2 (shut down or shutting down or deteriorat*)).ti,ab.	
18.	deathbed.ti,ab.	
19.	or/10-18	
20.	9 and 19	***Population***
21.	symptom assessment/	
22.	diagnosis/ or prognosis/	
23.	(diagnos* or prognos* or assess* or criteria* or predict*).ti,kw.	
24.	(sign or signs or symptom* or recogni* or identif*).ti,ab.	
25.	*multiple organ failure/	
26.	(organ* adj2 fail*).ti,ab.	
27.	(organ* adj2 dysfunction*).ti,ab.	
28	or/21-27	***Intervention***
29.	20 and 28	
30.	Excluded study designs and publication types limit A.1.4	
31.	29 not 30	
32.	Limit 31 to English language	

1 **Cochrane search terms**

#1.	MeSH descriptor: [Death] this term only
#2.	(dying or die* or death):ti,kw
#3.	MeSH descriptor: [Terminally Ill] this term only
#4.	MeSH descriptor: [Terminal Care] this term only
#5.	MeSH descriptor: [Palliative Care] this term only
#6.	(terminal or palliati*) near/1 care:ti,kw
#7.	terminally ill:ti,kw
#8.	terminal illness:ti,kw
#9.	palliati* near/1 stage*:ti,ab
#10.	("end of life" near/2 (stage or stages)):ti,kw
#11.	{or #1-#10}
#12.	end of life:ti,ab
#13.	((last or final) near/1 (hour* or days* or minute* or stage* or week* or month*)):ti,ab
#14.	(dying or terminal) near/1 phase*:ti,ab
#15.	(dying or terminal or end) near/1 stage*:ti,ab
#16.	dying near/2 (actively or begin* or begun):ti,ab
#17.	(death near/2 (imminent* or impending or "near" or throes)):ti,ab
#18.	((dying or death) near/2 (patient* or person* or people)):ti,ab
#19.	body near/2 (shut down or shutting down or deteriorat*):ti,ab
#20.	deathbed:ti,ab
#21.	{or #12-#20}

#22.	#11 and #21	***Population***
#23.	MeSH descriptor: [symptom assessment] this term only	
#24.	MeSH descriptor: [diagnosis] this term only	
#25.	MeSH descriptor: [prognosis] this term only	
#26.	(diagnos* or prognos* or assess* or criteria* or predict*):ti,kw	
#27.	(sign or signs or symptom* or recogni* or identif*):ti,ab	
#28.	agonal:ti,ab	
#29.	MeSH descriptor: [multiple organ failure] explode all trees	
#30.	(organ* near/2 fail*):ti,ab	
#31.	(organ* near/2 dysfunction*):ti,ab	
#32.	{or #23-#31}	***Intervention***
#33.	#22 and #32	

G.2.2 Communication

2. What are the barriers and facilitators to good communication between the dying person, those important to them and the healthcare professional surrounding the likelihood of entering the last days of life?

We undertook separate searches for shared decision making and communication with the understanding that due to common terminology the separate searches may retrieve papers relevant for either question.

Medline search terms

1.	death/	
2.	(dying or death).ti,ab.	
3.	terminally ill/ or terminal care/ or palliative care/	
4.	((terminal or palliati*) adj1 care).ti,kf.	
5.	"terminally ill".ti,kf.	
6.	"terminal illness".ti,kf.	
7.	((palliati* or terminal or end) adj1 stage*).ti,ab.	
8.	(terminal adj1 phase*).ti,ab.	
9.	"end of life".ti,ab.	
10.	((last or final) adj1 (hour* or day* or minute* or week* or month* or moment*)).ti,ab.	
11.	(body adj2 (shutdown or shut* down or deteriorat*)).ti,ab.	
12.	deathbed.ti,ab.	
13.	or/1-12	***Population***
14.	((communicat* or discuss* or speak* or talk* or convers*) adj3 (prognosis or life expectanc* or death* or dying or end of life or terminal* or palliat* or recover* or (get* adj2 better*) or improve* or improving or improvement or return* or conscious*)).ti,ab.	***Narrow Population1 and narrow Intervention1***
15.	(communicat* or discuss* or speak* or talk* or convers*).ti,ab.	***Narrow intervention2***
16.	((last or final) adj1 (hour* or day* or minute* or week* or month* or moment*)).ti,ab.	
17.	(body adj2 (shutdown or shut* down or deteriorat*)).ti,ab.	
18.	deathbed.ti,ab.	
19.	or/16-18	***Narrow population2***

20.	15 and 19	***Narrow intervention2 and narrow population2***
21.	14 or 20	***Final intervention***
22.	13 and 21	
23.	Excluded study designs and publication types limit A.1.4	
24.	22 not 23	
25.	Limit 24 to English language	

1 **Embase search terms**

1.	death/	
2.	(dying or death).ti,ab.	
3.	terminally ill patient/ or terminal care/ or palliative therapy/	
4.	((terminal or palliati*) adj1 care).ti,kw.	
5.	"terminally ill".ti,kw.	
6.	"terminal illness".ti,kw.	
7.	((palliati* or terminal or end) adj1 stage*).ti,ab.	
8.	(terminal adj1 phase*).ti,ab.	
9.	"end of life".ti,ab.	
10.	((last or final) adj1 (hour* or day* or minute* or stage* or week* or month* or moment*)).ti,ab.	
11.	(body adj2 (shut* down or shutdown or deteriorat*)).ti,ab.	
12.	deathbed.ti,ab.	
13.	or/1-12	***Population***
14.	((communicat* or discuss* or speak* or talk* or convers*) adj3 (prognosis or life expectanc* or death* or dying or end of life or terminal* or palliat* or recover* or (get* adj2 better*) or improve* or improving or improvement or return* or conscious*)).ti,ab.	***Narrow Population1 and narrow intervention1***
15.	(communicat* or discuss* or speak* or talk* or convers*).ti,ab.	***Narrow intervention2***
16.	((last or final) adj1 (hour* or day* or minute* or week* or month* or moment*)).ti,ab.	
17.	(body adj2 (shutdown or shut* down or deteriorat*)).ti,ab.	
18.	deathbed.ti,ab.	
19.	or/16-18	***Narrow population2***
20.	15 and 19	***Narrow Intervention2 and narrow population2***
21.	14 or 20	***Final intervention***
22.	13 and 21	
23.	Excluded study designs and publication types limit A.1.4	
24.	22 not 23	
25.	Limit 24 to English language	

2 **Cochrane search terms**

#1.	MeSH descriptor: [terminally ill] explode all trees
#2.	MeSH descriptor: [terminal care] explode all trees
#3.	MeSH descriptor: [palliative care] explode all trees
#4.	MeSH descriptor: [death] explode all trees

#5.	((palliati* or terminal or end) near/1 stage*):ti,ab,kw	
#6.	((terminal or palliati*) near/1 care):ti,ab,kw	
#7.	(dying or death):ti,ab,kw	
#8.	terminally ill:ti,ab,kw	
#9.	terminal illness:ti,ab,kw	
#10.	(terminal near/1 phase*):ti,ab,kw	
#11.	end of life:ti,ab,kw	
#12.	((last or final) near/1 (hour* or day* or minute* or stage* or week* or month* or moment*)):ti,ab,kw	
#13.	(body near/2 (shutdown or shut* down or deteriorat*)):ti,ab,kw	
#14.	deathbed:ti,ab,kw	
#15.	{or #1-#14}	***Population***
#16.	((communicat* or discuss* or speak* or talk* or convers*) near/3 (prognosis or life expectanc* or death* or dying or end of life or terminal* or palliat* or recover* or (get* near/2 better*) or improve* or improving or improvement or return* or conscious*)):ti,ab	***Narrow population1 and intervention1***
#17.	(communicat* or discuss* or speak* or talk* or convers*):ti,ab	***Narrow intervention2***
#18.	((last or final) near/1 (hour* or day* or minute* or week* or month* or moment*)):ti,ab	
#19.	(Body near/2 (shutdown or shut* down or deteriorat*)):ti,ab	
#20.	deathbed.ti,ab.	
#21.	#18 or #19 or #20	***Narrow population2***
#22.	#17 and #21	***Narrow population2 and intervention2***
#23.	#16 or #22	***Final Intervention***
#24.	#15 and #23	

1 **Cinahl search terms**

S1.	(MH "death"# or #MH "terminally ill patients"# or #MH "terminal care"# or #MH "palliative care"#	
S2.	(dying or death)	
S3.	((terminal or palliati*) n1 care)	
S4.	terminally ill or terminal illness	
S5.	((palliati* or terminal or end) n1 stage*)	
S6.	(terminal n1 phase*)	
S7.	end of life	
S8.	((last or final) n1 (hour* or day* or minute* or week* or month* or moment*))	
S9.	(body n2 (shutdown or shut* down or deteriorat*))	
S10.	deathbed	
S11.	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10	***Population***
S12.	((communicat* or discuss* or speak* or talk* or convers*) n3 (prognosis or life expectanc* or death* or dying or end of life or terminal* or palliat* or recover* or (get* n2 better*) or improve* or improving or improvement or return* or conscious*))	***Narrow population1 and intervention1***
S13.	(communicat* or discuss* or speak* or talk*	***Narrow Intervention2***

	or convers*)	
S14.	((last or final) n1 (hour* or day* or minute* or week* or month* or moment*))	
S15.	(body n2 (shutdown or shut* down or deteriorat*))	
S16.	deathbed	
S17.	S14 OR S15 OR S16	***Narrow Population2***
S18.	S13 AND S17	***Narrow population2 and intervention2***
S19.	S12 OR S18	***Final intervention***
S20.	S11 and S19	*Limits: Exclude Medline, Humans*

PsycInfo search terms

1.	(dying or death).ti,ab.	
2.	terminally ill/ or terminal care/ or palliative care/	
3.	((terminal or palliati*) adj1 care).ti,ab.	
4.	"terminally ill".ti,ab.	
5.	"terminal illness".ti,ab.	
6.	((palliati* or terminal or end) adj1 stage*).ti,ab.	
7.	(terminal adj1 phase*).ti,ab.	
8.	"end of life".ti,ab.	
9.	((last or final) adj1 (hour* or day* or minute* or week* or month* or moment*)).ti,ab.	
10.	(body adj2 (shutdown or shut* down or deteriorat*)).ti,ab.	
11.	deathbed.ti,ab.	
12.	exp "death and dying"/	
13.	or/1-12	***Population***
14.	((communicat* or discuss* or speak* or talk* or convers*) adj3 (prognosis or life expectanc* or death* or dying or end of life or terminal* or palliat* or recover* or (get* adj2 better*) or improve* or improving or improvement or return* or conscious*)).ti,ab.	***Narrow population1 and intervention1***
15.	(communicat* or discuss* or speak* or talk* or convers*).ti,ab.	***Narrow Intervention2***
16.	((last or final) adj1 (hour* or day* or minute* or week* or month* or moment*)).ti,ab.	
17.	(body adj2 (shutdown or shut* down or deteriorat*)).ti,ab.	
18.	deathbed.ti,ab.	
19.	or/16-18	***Narrow Population2***
20.	15 and 19	***Narrow Intervention2 and population2***
21.	14 or 20	***Final intervention***
22.	13 and 21	
23.	Excluded study designs and publication types limit A.1.4	
24.	22 not 23	
25.	Limit 24 to English language	

G.2.3 Shared decision making

3. What are the facilitators and barriers to the multi-professional team, dying person and those important to them in being involved in shared decision making to inform the development of personalised care plans for the last days of life?

We undertook separate searches for shared decision making and communication with the understanding that due to common terminology the separate searches may retrieve papers relevant for either question.

Medline search terms

1.	death/	
2.	(dying or death).ti,ab.	
3.	terminally ill/ or terminal care/ or palliative care/	
4.	((terminal or palliati*) adj1 care).ti,kf.	
5.	"terminally ill".ti,kf.	
6.	"terminal illness".ti,kf.	
7.	((palliati* or terminal or end) adj1 stage*).ti,ab.	
8.	(terminal adj1 phase*).ti,ab.	
9.	"end of life".ti,ab.	
10.	((last or final) adj1 (hour* or day* or minute* or week* or month* or moment*)).ti,ab.	
11.	(body adj2 (shutdown or shut* down or deteriorat*)).ti,ab.	
12.	deathbed.ti,ab.	
13.	or/1-12	***Population***
14.	*decision making/	
15.	((share* or sharing or making or made or agree* or participat* or support* or collaborat* or joint) adj1 decision*).ti,ab.	
16.	exp consumer participation/	
17.	patient care planning/	
18.	exp advance care planning/	
19.	((care or treatment or admission* or personal* or individual*) adj2 plan*).ti,ab.	
20.	or/14-19	***Intervention1***
21.	attitude of health personnel/	
22.	attitude to death/	
23.	((health professional or health personnel or physician* or consultant* or nurse* or doctor* or health care assistant* or healthcare assistant*) adj4 (preference* or satisfaction or satisfied or satisfaction or satisfy or experience* or need* or facilitator or facilitation or facilitate or barrier* or relation* or attitude* or reticence*)).ti,ab.	
24.	((consumer* or client* or resident* or patient* or people or person or spouse* or wife or wives or husband* or carer* or caregiver* or care giver* or significant other* or family or families or individual*) adj4 (preference* or satisfaction or satisfied or satisfaction or satisfy or experience* or need* or facilitator or facilitation or facilitate or barrier* or relation* or attitude* or reticence* or wish* or choice*)).ti,ab.	
25.	((interdisciplinary or multidisciplinary or combin* or inter disciplinary or multi disciplinary or interprofessional or multiprofessional or inter professional or multi professional) adj2 (work* or team* or care or ward#)).ti,ab.	
26.	or/21-25	***Intervention2***
27.	13 and 20 and 26	
28.	Excluded study designs and publication types limit A.1.4	
29.	27 not 28	
30.	Limit 29 to English language	

Embase search terms

1.	death/
2.	(dying or death).ti,ab.

3.	terminally ill patient/ or terminal care/ or palliative therapy/	
4.	((terminal or palliati*) adj1 care).ti,kw.	
5.	"terminally ill".ti,kw.	
6.	"terminal illness".ti,kw.	
7.	((palliati* or terminal or end) adj1 stage*).ti,ab.	
8.	(terminal adj1 phase*).ti,ab.	
9.	"end of life".ti,ab.	
10.	((last or final) adj1 (hour* or day* or minute* or stage* or week* or month* or moment*)).ti,ab.	
11.	(body adj2 (shut* down or shutdown or deteriorat*)).ti,ab.	
12.	deathbed.ti,ab.	
13.	or/1-12	***Population***
14.	*decision making/	
15.	((share* or sharing or making or made or agree* or participat* or support* or collaborat* or joint) adj1 decision*).ti,ab.	
16.	*patient care planning/	
17.	((care or treatment or admission* or personal* or individual*) adj2 plan*).ti,ab.	
18.	or/14-17	***Intervention1***
19.	*health personnel attitude/	
20.	*attitude to death/	
21.	((health professional or health personnel or physician* or consultant* or nurse* or doctor* or health care assistant* or healthcare assistant*) adj4 (preference* or satisfaction or satisfied or satisfaction or satisfy or experience* or need* or facilitator or facilitation or facilitate or barrier* or relation* or attitude* or reticence*)).ti,ab.	
22.	((consumer* or client* or resident* or patient* or people or person or spouse* or wife or wives or husband* or carer* or caregiver* or care giver* or significant other* or family or families or individual*) adj4 (preference* or satisfaction or satisfied or satisfaction or satisfy or experience* or need* or facilitator or facilitation or facilitate or barrier* or relation* or attitude* or reticence* or wish* or choice*)).ti,ab.	
23.	((interdisciplinary or multidisciplinary or combin* or inter disciplinary or multi disciplinary or interprofessional or multiprofessional or inter professional or multi professional) adj2 (work* or team* or care or ward#)).ti,ab.	
24.	or/19-23	***Intervention2***
25.	13 and 18 and 24	
26.	Excluded study designs and publication types limit A.1.4	
27.	25 not 26	
28.	Limit 27 to English language	

1 **Cochrane search terms**

#1.	MeSH descriptor: [terminally ill] explode all trees
#2.	MeSH descriptor: [terminal care] explode all trees
#3.	MeSH descriptor: [palliative care] explode all trees
#4.	MeSH descriptor: [death] explode all trees
#5.	((palliati* or terminal or end) near/1 stage*):ti,ab,kw
#6.	((terminal or palliati*) near/1 care):ti,ab,kw
#7.	(dying or death):ti,ab,kw
#8.	terminally ill:ti,ab,kw
#9.	terminal illness:ti,ab,kw

#10.	(terminal near/1 phase*):ti,ab,kw	
#11.	end of life:ti,ab,kw	
#12.	((last or final) near/1 (hour* or day* or minute* or stage* or week* or month* or moment*)):ti,ab,kw	
#13.	(body near/2 (shutdown or shut* down or deteriorat*)):ti,ab,kw	
#14.	deathbed:ti,ab,kw	
#15.	{or #1-#14}	***Population***
#16.	MeSH descriptor: [decision making] this term only	
#17.	((share* or sharing or making or made or agree* or participat* or support* or collaborat* or joint) near/1 decision*):ti,ab	
#18.	MeSH descriptor: [consumer participation] explode all trees	
#19.	MeSH descriptor: [patient care planning] explode all trees	
#20.	MeSH descriptor: [advance care planning] explode all trees	
#21.	((care or treatment or admission* or personal* or individual*) near/2 plan*):ti,ab	
#22.	{or #16-#21	***Intervention1***
#23.	MeSH descriptor: [attitude of health personnel] this term only	
#24.	MeSH descriptor: [attitude to death] this term only	
#25.	((health professional or health personnel or physician* or consultant* or nurse* or doctor* or health care assistant* or healthcare assistant*) near/4 (preference* or satisfaction or satisfied or satisfaction or satisfy or experience* or need* or facilitator or facilitation or facilitate or barrier* or relation* or attitude* or reticence*)):ti,ab	
#26.	((consumer* or client* or resident* or patient* or people or person or spouse* or wife or wives or husband* or carer* or caregiver* or care giver* or significant other* or family or families or individual*) near/4 (preference* or satisfaction or satisfied or satisfaction or satisfy or experience* or need* or facilitator or facilitation or facilitate or barrier* or relation* or attitude* or reticence* or wish* or choice*)):ti,ab	
#27.	((interdisciplinary or multidisciplinary or combin* or inter disciplinary or multi disciplinary or interprofessional or multiprofessional or inter professional or multi professional) near/2 (work* or team* or care or ward*)):ti,ab	
#28.	{or #23-#27}	***Intervention2***
#29.	#15 and #22 and #28	

1 **Cinahl search terms**

S1.	1. (MH "death"# or #MH "terminally ill patients"# or #MH "terminal care"# or #MH "palliative care"#	
S2.	2. (dying or death)	
S3.	3. ((terminal or palliati*) n1 care)	
S4.	4. terminally ill or terminal illness	
S5.	5. ((palliati* or terminal or end) n1 stage*)	
S6.	6. (terminal n1 phase*)	
S7.	7. end of life	
S8.	8. ((last or final) n1 (hour* or day* or minute* or week* or month* or moment*))	
S9.	9. (body n2 (shutdown or shut* down or deteriorat*))	
S10.	10. deathbed	
S11.	*11.* S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10	*12.* ***Population***
S12.	13. (MM "decision making") or (MM "decision making, patient") or (MM "decision making, family")	
S13.	14. (share* or sharing or making or made or agree* or participat* or support* or collaborat*	

	or joint) and decision*	
S14.	15. (MM "consumer participation")	
S15.	16. (MM "patient care plans")	
S16.	17. (MM "advance care planning")	
S17.	18. (care or treatment or admission* or personal* or individual*) and plan*	
S18.	*19.* S12 or S13 or S14 or S15 or S16 or S17	*20.* ***Intervention1***
S19.	21. (MM "attitude of health personnel")	
S20.	22. (MM "attitude to death")	
S21.	23. (health professional or health personnel or physician* or consultant* or nurse* or doctor* or health care assistant* or healthcare assistant*) and (preference* or satisfaction or satisfied or satisfaction or satisfy or experience* or need* or facilitator or facilitation or facilitate or barrier* or relation* or attitude* or reticence*)	
S22.	24. (consumer* or client* or resident* or patient* or people or person or spouse* or wife or wives or husband* or carer* or caregiver* or care giver* or significant other* or family or families or individual*) and (preference* or satisfaction or satisfied or satisfaction or satisfy or experience* or need* or facilitator or facilitation or facilitate or barrier* or relation* or attitude* or reticence* or wish* or choice*)	
S23.	25. (interdisciplinary or multidisciplinary or combin* or inter disciplinary or multi disciplinary or interprofessional or multiprofessional or inter professional or multi professional) and (work* or team* or care or ward*)	
S24.	*26.* S19 or S20 or S21 or S22 or S23	*27.* ***Intervention2***
S25.	*28.* S11 and S18 and S24	29. Limits: exclude Medline, Humans

1 **PsycInfo search terms**

1.	(dying or death).ti,ab.	
2.	terminally ill/ or terminal care/ or palliative care/	
3.	((terminal or palliati*) adj1 care).ti,ab.	
4.	"terminally ill".ti,ab.	
5.	"terminal illness".ti,ab.	
6.	((palliati* or terminal or end) adj1 stage*).ti,ab.	
7.	(terminal adj1 phase*).ti,ab.	
8.	"end of life".ti,ab.	
9.	((last or final) adj1 (hour* or day* or minute* or week* or month* or moment*)).ti,ab.	
10.	(body adj2 (shutdown or shut* down or deteriorat*)).ti,ab.	
11.	deathbed.ti,ab.	
12.	exp "death and dying"/	
13.	or/1-12	***Population***
14.	*decision making/	
15.	((share* or sharing or making or made or agree* or participat* or support* or collaborat* or joint) adj1 decision*).ti,ab.	
16.	*consumer behavior/	
17.	exp treatment planning/	
18.	*group decision making/	
19.	((care or treatment or admission* or personal* or individual*) adj2 plan*).ti,ab.	
20.	or/14-19	***Intervention1***
21.	health personnel attitudes/	
22.	death attitudes/	

23.	*advance directives/	
24.	((health professional or health personnel or physician* or consultant* or nurse* or doctor* or health care assistant* or healthcare assistant*) adj4 (preference* or satisfaction or satisfied or satisfaction or satisfy or experience* or need* or facilitator or facilitation or facilitate or barrier* or relation* or attitude* or reticence*)).ti,ab.	
25.	((consumer* or client* or resident* or patient* or people or person or spouse* or wife or wives or husband* or carer* or caregiver* or care giver* or significant other* or family or families or individual*) adj4 (preference* or satisfaction or satisfied or satisfaction or satisfy or experience* or need* or facilitator or facilitation or facilitate or barrier* or relation* or attitude* or reticence* or wish* or choice*)).ti,ab.	
26.	((interdisciplinary or multidisciplinary or combin* or inter disciplinary or multi disciplinary or interprofessional or multiprofessional or inter professional or multi professional) adj2 (work* or team* or care or ward#)).ti,ab.	
27.	or/21-26	***Intervention2***
28.	13 and 20 and 27	
29.	Excluded study designs and publication types limit A.1.4	
30.	28 not 29	
31.	Limit 30 to English language	

G.2.4 Maintaining hydration

4. For people in the last days of life is clinically assisted hydration effective compared to oral hydration or placebo?

We updated the Cochrane search strategy from the review: Good P, Richard R, Syrmis W, Jenkins-Marsh S, Stephens J. Medically assisted hydration for adult palliative care patients. Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD006273. DOI: 10.1002/14651858.CD006273.pub3.

The search was conducted in Cochrane Central Register of Controlled Trials (CENTRAL) only; we expanded this by searching the Cochrane Database of Systematic Reviews (CDSR) and the Database of Reviews and Abstracts (DARE). We did not search the science citation index as we did not have access.

Medline search terms

1.	exp palliative care/	
2.	palliat*.tw.	
3.	terminally ill/	
4.	terminal care/	
5.	(terminal* adj6 care*).tw.	
6.	((terminal* adj6 ill*) or terminal-stage* or dying or (close adj6 death)).tw.	
7.	(terminal* adj6 disease*).tw.	
8.	(end adj6 life).tw.	
9.	hospice*.tw.	
10.	("end-stage disease*" or "end stage disease*" or "end-stage illnessor end stage").tw.	
11.	"advanced disease*".tw.	
12.	("incurable illness*" or "incurable disease*").tw.	
13.	("advanced directive*" or "living will*" or "do-not-resuscitate order*").tw.	
14.	or/1-13	***Population***

15.	fluid therapy/	
16.	dehydration/	
17.	(hydrat* or dehydrat* or rehydrat* or (fluid* adj6 therap*) or (fluid* adj6 balance*) or (fluid* adj6 manag*) or hypodermoclysis).tw.	
18.	or/15-17	***Intervention***
19.	14 and 18	

1 **Embase search terms**

1.	exp palliative care/	
2.	palliat*.tw.	
3.	terminally ill/	
4.	terminal care/	
5.	(terminal* adj6 care*).tw.	
6.	((terminal* adj6 ill*) or terminal-stage* or dying or (close adj6 death)).tw.	
7.	(terminal* adj6 disease*).tw.	
8.	(end adj6 life).tw.	
9.	hospice*.tw.	
10.	("end-stage disease*" or "end stage disease*" or "end-stage illnessor end stage").tw.	
11.	"advanced disease*".tw.	
12.	("incurable illness*" or "incurable disease*").tw.	
13.	("advanced directive*" or "living will*" or "do-not-resuscitate order*").tw.	
14.	or/1-13	***Population***
15.	fluid therapy/	
16.	dehydration/	
17.	(hydrat* or dehydrat* or rehydrat* or (fluid* adj6 therap*) or (fluid* adj6 balance*) or (fluid* adj6 manag*) or hypodermoclysis).tw.	
18.	or/15-17	***Intervention***
19.	14 and 18	

2 **Cochrane search terms**

#1.	MeSH descriptor: [palliative care] explode all trees	
#2.	palliat*:ti,ab,kw	
#3.	MeSH descriptor: [terminally ill] this term only	
#4.	MeSH descriptor: [terminal care] explode all trees	
#5.	(terminal* near/6 care*):ti,ab,kw	
#6.	((terminal* near/6 ill*) or terminal-stage* or dying or (close near/6 death)):ti,ab,kw	
#7.	(terminal* near/6 disease*):ti,ab,kw	
#8.	(end near/6 life):ti,ab,kw	
#9.	hospice*:ti,ab,kw	
#10.	("end-stage disease*" or "end stage disease* or end-stage illness" or "end stage"):ti,ab,kw	
#11.	advanced disease*:ti,ab,kw	
#12.	("incurable illness*" or "incurable disease*"):ti,ab,kw	
#13.	("advanced directive*" or "living will*" or "do-not-resuscitate order*"):ti,ab,kw	
#14.	{or #1- #13}	***Population***
#15.	MeSH descriptor: [fluid therapy] this term only	
#16.	MeSH descriptor: [dehydration] this term only	

#17.	(hydrat* or dehydrat* or rehydrat* or (fluid* near/6 therap*) or (fluid* near/6 balance*) or (fluid* near/6 manag*) or hypodermoclysis):ti,ab,kw	
#18.	{or #15-#17}	***Intervention***
#19.	#14 AND #18	

Cinahl search terms

S1.	(MH "palliative care")	
S2.	palliat*	
S3.	(MH "terminally ill patients+")	
S4.	(MH "terminal care+")	
S5.	(terminal* n6 care*)	
S6.	(terminal* n6 ill*)	
S7.	(terminal* n6 disease*)	
S8.	(end n3 life)	
S9.	hospice*	
S10.	("end-stage disease*" or "end stage disease* or end-stage illness" or "end stage")	
S11.	"advanced disease*"	
S12.	("incurable illness*" or "incurable disease*")	
S13.	("advanced directive*" or "living will*" or "do-not-resuscitate order*")	
S14.	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13	***Population***
S15.	(MH "fluid therapy")	
S16.	(MH "dehydration")	
S17.	(hydrat* or dehydrat* or rehydrat*)	
S18.	hypodermoclysis	
S19.	(fluid* n6 therap*)	
S20.	(fluid* n6 balance*)	
S21.	(fluid* n6 manag*)	
S22.	S15 or S16 or S17 or S18 or S19 or S20 or S21	***Intervention***
S23.	S14 and S22	

G.2.5 Respiratory secretions

5. For people in the last days of life which pharmacological agents are most effective in treating troublesome respiratory secretions, and what degree of sedation do they cause?

We updated the Cochrane search strategy from the review: Wee B, Hillier R. Interventions for noisy breathing in patients near to death. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD005177. DOI: 10.1002/14651858.CD005177.pub2.

The search was conducted in Cochrane Central Register of Controlled Trials (CENTRAL) only; we expanded this by searching the Cochrane Database of Systematic Reviews (CDSR) and the Database of Reviews and Abstracts (DARE). We did not search the Cochrane Pain, Palliative & Supportive Care Trials Register as we did not have access. Where possible we added an exclusions filter and English language limit.

Medline search terms

1.	respiratory sounds/

2.	bronchi/se [secretion]	
3.	lung/se [secretion]	
4.	(non-expectorated adj2 secretion*).tw.	
5.	(respiratory adj sound*).tw.	
6.	(respiration adj sound*).tw.	
7.	(respiration adj2 secretion*).tw.	
8.	(respiratory adj2 secretion*).tw.	
9.	(bronchial adj2 secretion*).tw.	
10.	(retained adj2 secretion*).tw.	
11.	(noisy adj2 respirat*).tw.	
12.	(noisy adj2 breath*).tw.	
13.	(death adj rattle*).tw.	
14.	(terminal adj2 breath*).tw.	
15.	((rattling adj2 breath*) or gasping breath*).tw.	
16.	(pulmonary adj secretion).tw.	
17.	((airway adj secretion) or airway receptor*).tw.	
18.	(glycopyrronium or hyoscine).tw.	
19.	(anticholinergic* adj drug*).tw.	
20.	(antimuscarinic* adj drug*).tw.	
21.	(anti-cholinergic* adj drug*).tw.	
22.	(anti-muscarinic* adj drug*).tw.	
23.	narcolep*.tw.	
24.	(sleep adj apnoea).tw.	
25.	(sleep adj apnea).tw.	
26.	sleep apnea, obstructive/	
27.	narcolepsy/	
28.	or/1-27	***Intervention***
29.	terminal care/	
30.	exp terminally ill/	
31.	palliative care/	
32.	hospice care/	
33.	(terminal* adj2 care).tw.	
34.	(terminal* adj2 ill*).tw.	
35.	palliat*.tw.	
36.	hospice*.tw.	
37.	((end adj stage adj ill*) or (end adj stage adj care) or (end adj stage adj life) or (end adj life)).tw.	
38.	(close adj2 death).tw.	
39.	(dying or death or (end adj2 life)).tw.	
40.	or/29-39	***Population***
41.	28 and 40	
42.	Excluded study designs and publication types limit A.1.4	
43.	41 not 42	
44.	Limit 43 to English language	

1 **Embase search terms**

1.	*bronchus/	
2.	*lung/	
3.	*abnormal respiratory sound/	
4.	(non-expectorated adj2 secretion*).tw.	
5.	(respiratory adj sound*).tw.	
6.	(respiration adj sound*).tw.	
7.	(respiration adj2 secretion*).tw.	
8.	(respiratory adj2 secretion*).tw.	
9.	(bronchial adj2 secretion*).tw.	
10.	(retained adj2 secretion*).tw.	
11.	(noisy adj2 respirat*).tw.	
12.	(noisy adj2 breath*).tw.	
13.	(death adj rattle*).tw.	
14.	(terminal adj2 breath*).tw.	
15.	((rattling adj2 breath*) or gasping breath*).tw.	
16.	(pulmonary adj secretion).tw.	
17.	((airway adj secretion) or airway receptor*).tw.	
18.	(glycopyrronium or hyoscine).tw.	
19.	(anticholinergic* adj drug*).tw.	
20.	(antimuscarinic* adj drug*).tw.	
21.	(anti-cholinergic* adj drug*).tw.	
22.	(anti-muscarinic* adj drug*).tw.	
23.	narcolep*.tw.	
24.	(sleep adj apnoea).tw.	
25.	(sleep adj apnea).tw.	
26.	*sleep disordered breathing/	
27.	*narcolepsy/	
28.	or/1-27	***Intervention***
29.	*terminal care/	
30.	*terminally ill patient/	
31.	*palliative therapy/	
32.	*hospice care/	
33.	(terminal* adj2 care).tw.	
34.	(terminal* adj2 ill*).tw.	
35.	palliat*.tw.	
36.	hospice*.tw.	
37.	((end adj stage adj ill*) or (end adj stage adj care) or (end adj stage adj life) or (end adj life)).tw.	
38.	(close adj2 death).tw.	
39.	(dying or death or (end adj2 life)).tw.	
40.	or/29-39	***Population***
41.	28 and 40	
42.	*Excluded study designs and publication types limit A.1.4*	
43.	41 not 42	
44.	Limit 43 to English language	

1 **Cochrane search terms**

#1.	MeSH descriptor: [respiratory sounds] explode all trees	
#2.	MeSH descriptor: [bronchi] explode all trees	
#3.	MeSH descriptor: [lung] explode all trees	
#4.	(non-expectorated near/2 secretion*):ti,ab,kw	
#5.	(respiratory next sound*):ti,ab,kw	
#6.	(respiration next sound*):ti,ab,kw	
#7.	(respiration near/2 secretion*):ti,ab,kw	
#8.	(respiratory near/2 secretion*):ti,ab,kw	
#9.	(bronchial near/2 secretion*):ti,ab,kw	
#10.	(retained near/2 secretion*):ti,ab,kw	
#11.	(noisy near/2 respirat*):ti,ab,kw	
#12.	(noisy near/2 breath*):ti,ab,kw	
#13.	(death next rattle*):ti,ab,kw	
#14.	(terminal near/2 breath*):ti,ab,kw	
#15.	((rattling near/2 breath*) or gasping breath*):ti,ab,kw	
#16.	(pulmonary next secretion):ti,ab,kw	
#17.	((airway next secretion) or airway receptor*):ti,ab,kw	
#18.	(glycopyrronium or hyoscine):ti,ab,kw	
#19.	(anticholinergic* next drug*):ti,ab,kw	
#20.	(antimuscarinic* next drug*):ti,ab,kw	
#21.	(anti-cholinergic* next drug*):ti,ab,kw	
#22.	(anti-muscarinic* next drug*):ti,ab,kw	
#23.	narcolep*:ti,ab,kw	
#24.	(sleep next apnoea):ti,ab,kw	
#25.	(sleep next apnea):ti,ab,kw	
#26.	MeSH descriptor: [sleep apnea, obstructive] explode all trees	
#27.	MeSH descriptor: [narcolepsy] explode all trees	
#28.	{or #1- #27}	***Intervention***
#29.	MeSH descriptor: [terminal care] explode all trees	
#30.	MeSH descriptor: [terminally ill] explode all trees	
#31.	MeSH descriptor: [palliative care] explode all trees	
#32.	MeSH descriptor: [hospice care] explode all trees	
#33.	(terminal* near/2 care):ti,ab,kw	
#34.	(terminal* near/2 ill*):ti,ab,kw	
#35.	palliat*:ti,ab,kw	
#36.	hospice*:ti,ab,kw	
#37.	((end next stage next ill*) or (end next stage next care) or (end next stage next life) or (end next life)):ti,ab,kw	
#38.	(close near/2 death):ti,ab,kw	
#39.	(dying or death or (end near/2 life)):ti,ab,kw	
#40.	{or #29- #39}	***Population***
#41.	#28 AND #39	

2 **Cinahl search terms**

S1.	(MH "respiratory sounds")

S2.	(MH "bronchi")	
S3.	(MH "lung")	
S4.	(non-expectorated n2 secretion*)	
S5.	(respiratory n1 sound*)	
S6.	(respiration n1 sound*)	
S7.	(respiration n2 secretion*)	
S8.	(respiratory n2 secretion*)	
S9.	(bronchial n2 secretion*)	
S10.	(retained n2 secretion*)	
S11.	(noisy n2 respirat*)	
S12.	(noisy n2 breath*)	
S13.	(death n1 rattle*)	
S14.	(terminal n2 breath*)	
S15.	(rattling n2 breath*) or gasping breath*	
S16.	(pulmonary n1 secretion)	
S17.	airway n1 secretion or airway receptor*	
S18.	glycopyrronium or hyoscine	
S19.	(anticholinergic* n1 drug*)	
S20.	(antimuscarinic* n1 drug*)	
S21.	(anti-cholinergic* n1 drug*)	
S22.	(anti-muscarinic* n1 drug*)	
S23.	narcolep*	
S24.	sleep n1 apnoea	
S25.	sleep n1 apnea	
S26.	(MH "sleep apnea, obstructive")	
S27.	(MH "narcolepsy")	
S28.	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27	***Intervention***
S29.	(MH "terminal care")	
S30.	(MH "terminally ill patients")	
S31.	(MH "palliative care")	
S32.	(MH "hospice care")	
S33.	(terminal* n2 care)	
S34.	(terminal* n2 ill*)	
S35.	palliat*	
S36.	hospice*	
S37.	end n1 stage n1 ill* or end n1 stage n1 care	
S38.	end n1 stage n1 life or end n1 life	
S39.	dying or death or end n2 life	
S40.	(close n2 death)	
S41.	S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40	***Population***
S42.	S28 AND S41	Limits: exclude Medline, Humans, English Language

G.2.6 Pharmacological management: Pain, anxiety, breathlessness and agitation

6. For people in the last days of life, which pharmacological agents are most effective in relieving pain, breathlessness, anxiety, agitation and delirium and what degree of sedation do they cause?

Medline search terms

1.	death/	
2.	(dying or death).ti,ab.	
3.	terminally ill/ or terminal care/ or palliative care/	
4.	((terminal or palliati*) adj1 care).ti,kf.	
5.	"terminally ill".ti,kf.	
6.	"terminal illness".ti,kf.	
7.	((palliati* or terminal or end) adj1 stage*).ti,ab.	
8.	(terminal adj1 phase*).ti,ab.	
9.	"end of life".ti,ab.	
10.	((last or final) adj1 (hour* or day* or minute* or week* or month* or moment*)).ti,ab.	
11.	(body adj2 (shutdown or shut* down or deteriorat*)).ti,ab.	
12.	deathbed.ti,ab.	
13.	or/1-12	***Population***
14.	benzodiazepines/ or clonazepam/ or diazepam/ or lorazepam/ or midazolam/	
15.	(benzodiazepine* or lorazepam or ativan or orfidal or midazolam or hypnovel or dormicum or versed or diazepam or rimapam or tensium or dialar or diastat or desitin or valium or valrelease or diazemuls or stesolid or clonazepam or rivotril or ravotril or rivatril or iktorivil or clonex or paxam or petril or naze or kriadex or linotril or clonotril or klonopin).ti,ab.	
16.	analgesics, opioid/	
17.	buprenorphine/ or fentanyl/ or oxycodone/ or opium/ or alfentanil/ or heroin/ or morphine/	
18.	(morphine or oramorph or sevredol or morphgesic or "mst continus" or zomorph or "mxl" or minijet or cyclimorph or filnarine or astramorph or duramorph or infumorph or "ms contin" or roxanol or "rms suppository").ti,ab.	
19.	(oxycodone or oxynorm or oxycontin or dolocodon or longtec or targinact or endocone or oxydose or oxyfast or oxylr or percolone or dazidox or roxicodone or oxecta or endone or percocet).ti,ab.	
20.	(fentanyl or sublimaze or abstral or effentora or recivit or actiq or instanyl or pecfent or fencino or fentalis or matrifen or mexolar or opiodur or osmanil or tilofyl or victanyl or durogesic or duragesic or onsolis or haldid or fentora or dtrans or lazanda or alfentanil or alfenta or rapifen or buprenorphine or temgesic or butrans or transtec or buprenex or norspan or hapoctasin or transtec or subutex or diamorphine).ti,ab.	
21.	antipsychotic agents/	
22.	haloperidol/ or levomepromazine/ or chlorpromazine/	
23.	(haloperidol or haloperidon or dozic or haldol or serenace).ti,ab.	
24.	(levomepromazine or nozinan or nosinan or levoprome).ti,ab.	
25.	(olanzapine or zyprexa or zalasta or zypadhera or velotab or lanzek or oleanz).ti,ab.	
26.	(chlorpromazine or chloractil or largactil or thorazine or megaphen or promapar).ti,ab.	
27.	exp histamine antagonists/	
28.	(antihistamine* or anti-histamine* or (histimine* adj antagonist*)).ti,ab.	
29.	prednisolone/ or dexamethasone/	
30.	(prednisolone or methylprednisolone or prednisone or dexamethasone or depo-medrone or solu-medrone or medrone or dexsol or martapan or deltacortril or decadron or organon or hospira or predfoam or predsol or predemena).ti,ab.	

31.	furosemide/	
32.	(furosemide or frusemide or rusyde or frusol or lasix).ti,ab.	
33.	exp oxygen/	
34.	(oxygen or heliox).ti,ab.	
35.	or/14-34	***Intervention***
36.	13 and 35	
37.	Randomised controlled trials search studies filter A.1.2	
38.	Systematic reviews search filter A.1.1	
39.	37 or 38	
40.	36 and 39	
41.	Excluded study designs and publication types limit A.1.4	
42.	40 not 41	
43.	Limit 42 to English language	

1 **Embase search terms**

1.	death/	
2.	(dying or death).ti,ab.	
3.	terminally ill patient/ or terminal care/ or palliative therapy/	
4.	((terminal or palliati*) adj1 care).ti,kw.	
5.	"terminally ill".ti,kw.	
6.	"terminal illness".ti,kw.	
7.	((palliati* or terminal or end) adj1 stage*).ti,ab.	
8.	(terminal adj1 phase*).ti,ab.	
9.	"end of life".ti,ab.	
10.	((last or final) adj1 (hour* or day* or minute* or stage* or week* or month* or moment*)).ti,ab.	
11.	(body adj2 (shut* down or shutdown or deteriorat*)).ti,ab.	
12.	deathbed.ti,ab.	
13.	or/1-12	***Population***
14.	*clonazepam/ or *diazepam/ or *lorazepam/ or *midazolam/	
15.	*benzodiazepine/	
16.	(benzodiazepine* or lorazepam or ativan or orfidal or midazolam or hypnovel or dormicum or versed or diazepam or rimapam or tensium or dialar or diastat or desitin or valium or valrelease or diazemuls or stesolid or clonazepam or rivotril or ravotril or rivatril or iktorivil or clonex or paxam or petril or naze or kriadex or linotril or clonotril or klonopin).ti,ab.	
17.	*opiate/ or *narcotic analgesic agent/	
18.	*buprenorphine/ or *fentanyl/ or *oxycodone/ or *alfentanil/ or *diamorphine/ or *morphine/	
19.	(morphine or oramorph or sevredol or morphgesic or "mst continus" or zomorph or "mxl" or minijet or cyclimorph or filnarine or astramorph or duramorph or infumorph or "ms contin" or roxanol or "rms suppository").ti,ab.	
20.	(oxycodone or oxynorm or oxycontin or dolocodon or longtec or targinact or endocone or oxydose or oxyfast or oxylr or percolone or dazidox or roxicodone or oxecta or endone or percocet).ti,ab.	
21.	(fentanyl or sublimaze or abstral or effentora or recivit or actiq or instanyl or pecfent or fencino or fentalis or matrifen or mexolar or opiodur or osmanil or tilofyl or victanyl or durogesic or duragesic or onsolis or haldid or fentora or dtrans or lazanda or alfentanil or alfenta or rapifen or buprenorphine or temgesic or butrans or transtec or buprenex or norspan	

	or hapoctasin or transtec or subutex or diamorphine).ti,ab.	
22.	*neuroleptic agent/	
23.	*haloperidol/ or *levomepromazine/ or *chlorpromazine/	
24.	(haloperidol or haloperidon or dozic or haldol or serenace).ti,ab.	
25.	(levomepromazine or nozinan or nosinan or levoprome).ti,ab.	
26.	(olanzapine or zyprexa or zalasta or zypadhera or velotab or lanzek or oleanz).ti,ab.	
27.	(chlorpromazine or chloractil or largactil or thorazine or megaphen or promapar).ti,ab.	
28.	exp *antihistaminic agent/	
29.	(antihistamine* or anti-histamine* or (histimine* adj antagonist*)).ti,ab.	
30.	*prednisolone/ or *dexamethasone/	
31.	(prednisolone or methylprednisolone or prednisone or dexamethasone or depo-medrone or solu-medrone or medrone or dexsol or martapan or deltacortril or decadron or organon or hospira or predfoam or predsol or predemena).ti,ab.	
32.	*furosemide/	
33.	(furosemide or frusemide or rusyde or frusol or lasix).ti,ab.	
34.	exp *oxygen/	
35.	(oxygen or heliox).ti,ab.	
36.	or/14-35	***Population***
37.	13 and 36	
38.	Randomised controlled trials search studies filter A.1.2	
39.	Systematic reviews search filter A.1.1	
40.	38 or 39	
41.	37 and 40	
42.	Excluded study designs and publication types limit A.1.4	
43.	41 not 42	
44.	Limit 43 to English language	

1 **Cochrane search terms**

#1.	MeSH descriptor: [terminally ill] explode all trees	
#2.	MeSH descriptor: [terminal care] explode all trees	
#3.	MeSH descriptor: [palliative care] explode all trees	
#4.	MeSH descriptor: [death] explode all trees	
#5.	((palliati* or terminal or end) near/1 stage*):ti,ab,kw	
#6.	((terminal or palliati*) near/1 care):ti,ab,kw	
#7.	(dying or death):ti,ab,kw	
#8.	terminally ill:ti,ab,kw	
#9.	terminal illness:ti,ab,kw	
#10.	(terminal near/1 phase*):ti,ab,kw	
#11.	end of life:ti,ab,kw	
#12.	((last or final) near/1 (hour* or day* or minute* or stage* or week* or month* or moment*)):ti,ab,kw	
#13.	(body near/2 (shutdown or shut* down or deteriorat*)):ti,ab,kw	
#14.	deathbed:ti,ab,kw	
#15.	{or #1-#14}	***Population***
#16.	MeSH descriptor: [benzodiazepines] explode all trees	
#17.	MeSH descriptor: [diazepam] explode all trees	

#18.	MeSH descriptor: [clonazepam] explode all trees	
#19.	MeSH descriptor: [lorazepam] explode all trees	
#20.	MeSH descriptor: [midazolam] explode all trees	
#21.	(benzodiazepine* or lorazepam or ativan or orfidal or midazolam or hypnovel or dormicum or versed or diazepam or rimapam or tensium or dialar or diastat or desitin or valium or valrelease or diazemuls or stesolid or clonazepam or rivotril or ravotril or rivatril or iktorivil or clonex or paxam or petril or naze or kriadex or linotril or clonotril or klonopin):ti,ab	
#22.	MeSH descriptor: [analgesics, opioid] explode all trees	
#23.	MeSH descriptor: [buprenorphine] explode all trees	
#24.	MeSH descriptor: [fentanyl] explode all trees	
#25.	MeSH descriptor: [oxycodone] explode all trees	
#26.	MeSH descriptor: [opium] explode all trees	
#27.	MeSH descriptor: [alfentanil] explode all trees	
#28.	MeSH descriptor: [heroin] explode all trees	
#29.	MeSH descriptor: [morphine derivatives] explode all trees	
#30.	(morphine or oramorph or sevredol or morphgesic or "mst continus" or zomorph or "mxl" or minijet or cyclimorph or filnarine or astramorph or duramorph or infumorph or "ms contin" or roxanol or "rms suppository"):ti,ab	
#31.	(oxycodone or oxynorm or oxycontin or dolocodon or longtec or targinact or endocone or oxydose or oxyfast or oxylr or percolone or dazidox or roxicodone or oxecta or endone or percocet):ti,ab	
#32.	(fentanyl or sublimaze or abstral or effentora or recivit or actiq or instanyl or pecfent or fencino or fentalis or matrifen or mexolar or opiodur or osmanil or tilofyl or victanyl or durogesic or duragesic or onsolis or haldid or fentora or dtrans or lazanda or alfentanil or alfenta or rapifen or buprenorphine or temgesic or butrans or transtec or buprenex or norspan or hapoctasin or transtec or subutex or diamorphine):ti,ab	
#33.	MeSH descriptor: [antipsychotic agents] explode all trees	
#34.	MeSH descriptor: [haloperidol] explode all trees	
#35.	MeSH descriptor: [methotrimeprazine] explode all trees	
#36.	MeSH descriptor: [chlorpromazine] explode all trees	
#37.	(haloperidol or haloperidon or dozic or haldol or serenace):ti,ab	
#38.	(levomepromazine or nozinan or nosinan or levoprome):ti,ab	
#39.	(olanzapine or zyprexa or zalasta or zypadhera or velotab or lanzek or oleanz):ti,ab	
#40.	(chlorpromazine or chloractil or largactil or thorazine or megaphen or promapar):ti,ab	
#41.	MeSH descriptor: [histamine antagonists] explode all trees	
#42.	(antihistamine* or anti-histamine* or (histimine* next antagonist*)):ti,ab	
#43.	MeSH descriptor: [prednisolone] explode all trees	
#44.	MeSH descriptor: [dexamethasone] explode all trees	
#45.	(prednisolone or methylprednisolone or prednisone or dexamethasone or depo-medrone or solu-medrone or medrone or dexsol or martapan or deltacortril or decadron or organon or hospira or predfoam or predsol or predemena):ti,ab	
#46.	MeSH descriptor: [furosemide] explode all trees	
#47.	(furosemide or frusemide or rusyde or frusol or lasix) .ti,ab.	
#48.	MeSH descriptor: [oxygen] explode all trees	
#49.	(oxygen or heliox):ti,ab	
#50.	{or #16-49}	***Intervention***
#51.	#15 and #50	

G.2.7 Pharmacological management: Nausea and vomiting

7. For people in the last days of life, which pharmacological agents are most effective in relieving nausea and vomiting and what degree of sedation do they cause?

Medline search terms

1.	death/	
2.	(dying or death).ti,ab.	
3.	terminally ill/ or terminal care/ or palliative care/	
4.	((terminal or palliati*) adj1 care).ti,kf.	
5.	"terminally ill".ti,kf.	
6.	"terminal illness".ti,kf.	
7.	((palliati* or terminal or end) adj1 stage*).ti,ab.	
8.	(terminal adj1 phase*).ti,ab.	
9.	"end of life".ti,ab.	
10.	((last or final) adj1 (hour* or day* or minute* or week* or month* or moment*)).ti,ab.	
11.	(body adj2 (shutdown or shut* down or deteriorat*)).ti,ab.	
12.	deathbed.ti,ab.	
13.	or/1-12	***Population***
14.	cyclizine/	
15.	histamine h1 antagonists/	
16.	(cyclizine or valoid or marezine).ti,ab.	
17.	exp antiemetics/	
18.	(antiemetic* or anti emetic*).ti,ab.	
19.	dexamethasone/	
20.	dexamethasone.ti,ab.	
21.	octreotide/	
22.	octreotide.ti,ab.	
23.	metoclopramide/	
24.	(metoclopramide or maxolon).ti,ab.	
25.	domperidone/	
26.	(domperidone or motilium).ti,ab.	
27.	haloperidol/	
28.	(haloperidon or dozic or haldol or serenace).ti,ab.	
29.	methotrimeprazine/	
30.	(levomepromazine or nozinan).ti,ab.	
31.	(palonosetron or aloxi).ti,ab.	
32.	ondansetron/	
33.	(ondansetron or zofran).ti,ab.	
34.	granisetron/	
35.	(granisetron or kytril or sancruso).ti,ab.	
36.	(aprepitant or emend).ti,ab.	
37.	neurokinin-1 receptor antagonists/	
38.	(fosaprepitant or ivemend).ti,ab.	
39.	(olanzapine or zyprexa).ti,ab.	
40.	prochlorperazine/	
41.	(prochlorperazine or stemetil or buccastem).ti,ab.	

42.	glycopyrrolate/	
43.	((hyoscine adj1 butylbromide) or hyrdobromide).ti,ab.	
44.	muscarinic antagonists/	
45.	(glycopyrrolate or glycopyrronium).ti,ab.	
46.	haloperidol.ti,ab.	
47.	methotrimeprazine.ti,ab.	
48.	or/14-47	***Intervention***
49.	13 and 48	
50.	Randomised controlled trials search studies filter A.1.2	
51.	Systematic reviews search filter A.1.1	
52.	50 or 51	
53.	49 and 52	
54.	Excluded study designs and publication types limit A.1.4	
55.	53 not 54	
56.	Limit 55 to English language	

1 **Embase search terms**

1.	death/	
2.	(dying or death).ti,ab.	
3.	terminally ill patient/ or terminal care/ or palliative therapy/	
4.	((terminal or palliati*) adj1 care).ti,kw.	
5.	"terminally ill".ti,kw.	
6.	"terminal illness".ti,kw.	
7.	((palliati* or terminal or end) adj1 stage*).ti,ab.	
8.	(terminal adj1 phase*).ti,ab.	
9.	"end of life".ti,ab.	
10.	((last or final) adj1 (hour* or day* or minute* or stage* or week* or month* or moment*)).ti,ab.	
11.	(body adj2 (shut* down or shutdown or deteriorat*)).ti,ab.	
12.	deathbed.ti,ab.	
13.	or/1-12	***Population***
14.	*cyclizine/	
15.	*histamine h1 receptor antagonist/	
16.	(cyclizine or valoid or marezine).ti,ab.	
17.	exp *antiemetic agent/	
18.	(antiemetic* or anti emetic*).ti,ab.	
19.	*dexamethasone/	
20.	dexamethasone.ti,ab.	
21.	*octreotide/	
22.	octreotide.ti,ab.	
23.	octreotide.ti,ab.	
24.	*metoclopramide/	
25.	(metoclopramide or maxolon).ti,ab.	
26.	*domperidone/	
27.	(domperidone or motilium).ti,ab.	
28.	*haloperidol/	

29.	(haloperidon or dozic or haldol or serenace).ti,ab.	
30.	*methotrimeprazine/	
31.	(levomepromazine or nozinan).ti,ab.	
32.	(palonosetron or aloxi).ti,ab.	
33.	*ondansetron/	
34.	(ondansetron or zofran).ti,ab.	
35.	*granisetron/	
36.	(granisetron or kytril or sancruso).ti,ab.	
37.	*aprepitant/	
38.	(aprepitant or emend).ti,ab.	
39.	*fosaprepitant/	
40.	(fosaprepitant or ivemend).ti,ab.	
41.	*olanzapine/	
42.	(olanzapine or zyprexa).ti,ab.	
43.	*prochlorperazine/	
44.	(prochlorperazine or stemetil or buccastem).ti,ab.	
45.	glycopyrrolate/	
46.	((hyoscine adj1 butylbromide) or hyrdobromide).ti,ab.	
47.	muscarinic antagonists/	
48.	(glycopyrrolate or glycopyrronium).ti,ab.	
49.	haloperidol.ti,ab.	
50.	methotrimeprazine.ti,ab.	
51.	or/14-50	***Intervention***
52.	13 and 51	
53.	Randomised controlled trials search studies filter A.1.2	
54.	Systematic reviews search filter A.1.1	
55.	53 or 54	
56.	52 and 55	
57.	Excluded study designs and publication types limit A.1.4	
58.	56 not 57	
59.	Limit 58 to English language	

1 **Cochrane search terms**

#1.	MeSH descriptor: [terminally ill] explode all trees
#2.	MeSH descriptor: [terminal care] explode all trees
#3.	MeSH descriptor: [palliative care] explode all trees
#4.	MeSH descriptor: [death] explode all trees
#5.	((palliati* or terminal or end) near/1 stage*):ti,ab,kw
#6.	((terminal or palliati*) near/1 care):ti,ab,kw
#7.	(dying or death):ti,ab,kw
#8.	terminally ill:ti,ab,kw
#9.	terminal illness:ti,ab,kw
#10.	(terminal near/1 phase*):ti,ab,kw
#11.	end of life:ti,ab,kw
#12.	((last or final) near/1 (hour* or day* or minute* or stage* or week* or month* or moment*)):ti,ab,kw

#13.	(body near/2 (shutdown or shut* down or deteriorat*)):ti,ab,kw	
#14.	deathbed:ti,ab,kw	
#15.	{or #1-#14}	***Population***
#16.	MeSH descriptor: [cyclizine] explode all trees	
#17.	MeSH descriptor: [histamine h1 antagonists] explode all trees	
#18.	(cyclizine or valoid or marezine):ti,ab	
#19.	MeSH descriptor: [antiemetics] explode all trees	
#20.	(antiemetic* or anti emetic*):ti,ab	
#21.	MeSH descriptor: [dexamethasone] explode all trees	
#22.	dexamethasone:ti,ab	
#23.	MeSH descriptor: [octreotide] explode all trees	
#24.	octreotide:ti,ab	
#25.	MeSH descriptor: [metoclopramide] explode all trees	
#26.	(metoclopramide or maxolon):ti,ab	
#27.	MeSH descriptor: [domperidone] explode all trees	
#28.	(domperidone or motilium):ti,ab	
#29.	MeSH descriptor: [haloperidol] explode all trees	
#30.	(haloperidon or dozic or haldol or serenace):ti,ab	
#31.	MeSH descriptor: [methotrimeprazine] explode all trees	
#32.	(levomepromazine or nozinan):ti,ab	
#33.	(palonosetron or aloxi):ti,ab	
#34.	MeSH descriptor: [ondansetron] explode all trees	
#35.	(ondansetron or zofran):ti,ab	
#36.	MeSH descriptor: [granisetron] explode all trees	
#37.	(granisetron or kytril or sancruso):ti,ab	
#38.	MeSH descriptor: [neurokinin-1 receptor antagonists] explode all trees	
#39.	(aprepitant or emend):ti,ab	
#40.	(fosaprepitant or ivemend):ti,ab	
#41.	MeSH descriptor: [prochlorperazine] explode all trees	
#42.	(prochlorperazine or stemetil or buccastem) .ti,ab.	
#43.	MeSH descriptor: [glycopyrrolate] this term only	
#44.	((hyoscine near/1 butylbromide) or hyrdobromide):ti,ab	
#45.	MeSH descriptor: [muscarinic antagonists] this term only	
#46.	(glycopyrrolate or glycopyrronium):ti,ab	
#47.	haloperidol:ti,ab	
#48.	methotrimeprazine:ti,ab	
#49.	MeSH descriptor: [cyclizine] explode all trees	
#50.	MeSH descriptor: [histamine h1 antagonists] explode all trees	
#51.	{or #16-#50}	***Intervention***
#52.	#15 and #51	

G.2.8 Anticipatory prescribing

8. What are the experiences, opinions and attitudes of healthcare professionals, the dying person and those important to them regarding o access to anticipatory prescribing?

9. How effective is anticipatory prescribing at improving comfort in adults in the last days of life compared with prescribing at the bed side?

Medline search terms

1.	death/	
2.	(dying or death).ti,ab.	
3.	terminally ill/ or terminal care/ or palliative care/	
4.	((terminal or palliati*) adj1 care).ti,kf.	
5.	"terminally ill".ti,kf.	
6.	"terminal illness".ti,kf.	
7.	((palliati* or terminal or end) adj1 stage*).ti,ab.	
8.	(terminal adj1 phase*).ti,ab.	
9.	"end of life".ti,ab.	
10.	((last or final) adj1 (hour* or day* or minute* or week* or month* or moment*)).ti,ab.	
11.	(body adj2 (shutdown or shut* down or deteriorat*)).ti,ab.	
12.	deathbed.ti,ab.	
13.	or/1-12	***Population***
14.	(prescrib* or prescription* or medicat* or medicine* or drug* or pharma or pharmaceutical* or packet* or pack* or pak* or box* or kit*).ti,ab.	
15.	(crisis* or comfort* or anticipate* or anticipatory or anticipation or preemptive or pre-emptive).ti,ab.	
16.	14 and 15	
17.	just in case.ti,ab.	
18.	16 or 17	***Intervention***
19.	13 and 18	
20.	Excluded study designs and publication types limit A.1.4	
21.	19 not 20	
22.	Limit 21 to English language	

Embase search terms

1.	death/	
2.	(dying or death).ti,ab.	
3.	terminally ill patient/ or terminal care/ or palliative therapy/	
4.	((terminal or palliati*) adj1 care).ti,kw.	
5.	"terminally ill".ti,kw.	
6.	"terminal illness".ti,kw.	
7.	((palliati* or terminal or end) adj1 stage*).ti,ab.	
8.	(terminal adj1 phase*).ti,ab.	
9.	"end of life".ti,ab.	
10.	((last or final) adj1 (hour* or day* or minute* or stage* or week* or month* or moment*)).ti,ab.	
11.	(body adj2 (shut* down or shutdown or deteriorat*)).ti,ab.	
12.	deathbed.ti,ab.	
13.	or/1-12	***Population***
14.	(prescrib* or prescription* or medicat* or medicine* or drug* or pharma or pharmaceutical* or packet* or pack* or pak* or box* or kit*).ti,ab.	

15.	(crisis* or comfort* or anticipate* or anticipatory or anticipation or preemptive or pre-emptive).ti,ab.	
16.	14 and 15	
17.	just in case.ti,ab.	
18.	16 or 17	***Intervention***
19.	13 and 18	
20.	Excluded study designs and publication types limit A.1.4	
21.	19 not 20	
22.	Limit 21 to English language	

1

2 **Cochrane search terms**

#1.	MeSH descriptor: [terminally ill] explode all trees	
#2.	MeSH descriptor: [terminal care] explode all trees	
#3.	MeSH descriptor: [palliative care] explode all trees	
#4.	MeSH descriptor: [death] explode all trees	
#5.	((palliati* or terminal or end) near/1 stage*):ti,ab,kw	
#6.	((terminal or palliati*) near/1 care):ti,ab,kw	
#7.	(dying or death):ti,ab,kw	
#8.	terminally ill:ti,ab,kw	
#9.	terminal illness:ti,ab,kw	
#10.	(terminal near/1 phase*):ti,ab,kw	
#11.	end of life:ti,ab,kw	
#12.	((last or final) near/1 (hour* or day* or minute* or stage* or week* or month* or moment*)):ti,ab,kw	
#13.	(body near/2 (shutdown or shut* down or deteriorat*)):ti,ab,kw	
#14.	deathbed:ti,ab,kw	
#15.	{or #1-#14}	***Population***
#16.	(prescrib* or prescription* or medicat* or medicine* or drug* or pharma or pharmaceutical* or packet* or pack* or pak* or box* or kit*):ti,ab	
#17.	(crisis* or comfort* or anticipate* or anticipatory or anticipation or preemptive or pre-emptive):ti,ab	
#18.	#16 and #17	
#19.	just in case:ti,ab	
#20.	#18 or #19	***Intervention***
#21.	#15 and #20	

3 **Cinahl search terms**

S1.	(MH "death"# or #MH "terminally ill patients"# or #MH "terminal care"# or #MH "palliative care"#
S2.	(dying or death)
S3.	((terminal or palliati*) n1 care)
S4.	terminally ill or terminal illness
S5.	((palliati* or terminal or end) n1 stage*)
S6.	(terminal n1 phase*)
S7.	end of life
S8.	((last or final) n1 (hour* or day* or minute* or week* or month* or moment*))

S9.	(body n2 (shutdown or shut* down or deteriorat*))	
S10.	deathbed	
S11.	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10	***Population***
S12.	prescrib* or prescription* or medicat* or medicine* or drug* or pharma or pharmaceutical* or packet* or pack* or pak* or box* or kit*	
S13.	crisis* or comfort* or anticipate* or anticipatory or anticipation or preemptive or pre-emptive	
S14.	S12 and S13	
S15.	just in case	
S16.	S14 or S15	***Intervention***
S17.	S11 and S16	Limits: exclude Medline, Humans, English Language

G.3 Health economics search

G.3.1 Health economic reviews

Economic searches were conducted in Medline, Embase, HEED and CRD for NHS EED and HTA.

Medline search terms

1.	death/	
2.	(dying or death).ti,ab.	
3.	terminally ill/ or terminal care/ or palliative care/	
4.	((terminal or palliati*) adj1 care).ti,kf.	
5.	"terminally ill".ti,kf.	
6.	"terminal illness".ti,kf.	
7.	((palliati* or terminal or end) adj1 stage*).ti,ab.	
8.	(terminal adj1 phase*).ti,ab.	
9.	"end of life".ti,ab.	
10.	((last or final) adj1 (hour* or day* or minute* or week* or month* or moment*)).ti,ab.	
11.	(body adj2 (shutdown or shut* down or deteriorat*)).ti,ab.	
12.	deathbed.ti,ab.	
13.	or/1-12	***Population***
14.	Health economics study designs filter A.1.3	
15.	13 and 14	
16.	Excluded study designs and publication types limit A.1.4	
17.	15 not 16	
18.	Limit 17 to English language	

Embase search terms

1.	death/
2.	(dying or death).ti,ab.
3.	terminally ill patient/ or terminal care/ or palliative therapy/
4.	((terminal or palliati*) adj1 care).ti,kw.
5.	"terminally ill".ti,kw.
6.	"terminal illness".ti,kw.

7.	((palliati* or terminal or end) adj1 stage*).ti,ab.	
8.	(terminal adj1 phase*).ti,ab.	
9.	"end of life".ti,ab.	
10.	((last or final) adj1 (hour* or day* or minute* or stage* or week* or month* or moment*)).ti,ab.	
11.	(body adj2 (shut* down or shutdown or deteriorat*)).ti,ab.	
12.	deathbed.ti,ab.	
13.	or/1-12	***Population***
14.	Health economics study designs filter A.1.3	
15.	13 and 14	
16.	Excluded study designs and publication types limit A.1.4	
17.	15 not 16	
18.	Limit 17 to English language	

1 **CRD search terms**

#1.	(end of life) IN NHSEED, HTA	
#2.	(((last or final) adj1 (hour* or days* or minute* or stage* or week* or month*))) IN NHSEED, HTA	
#3.	(((dying or terminal) adj1 phase*)) IN NHSEED, HTA	
#4.	(((dying or terminal or end) adj1 stage*)) IN NHSEED, HTA	
#5.	((dying adj2 (actively or begin* or begun))) IN NHSEED, HTA	
#6.	(((death or dying) adj2 (approach* or imminent* or impending or near* or close* or throes))) IN NHSEED, HTA	
#7.	((Body adj2 (shut down or shutting down or deteriorat*))) IN NHSEED, HTA	
#8.	(deathbed) IN NHSEED, HTA	
#9.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 IN NHSEED, HTA	***Population***

2 **HEED search terms**

1.	AX=end AND of AND life	
2.	AX=last or final	
3.	AX=hour* or days* or minute* or stage* or week* or month*	
4.	CS=2 and 3	
5.	AX=dying or terminal AND phase*	
6.	AX=dying or terminal or end AND stage*	
7.	AX=dying AND actively or begin* or begun	
8.	AX=death or dying	
9.	AX=approach* or imminent* or impending or near* or close* or throes	
10.	CS=8 and 9	
11.	AX=shut AND down or shutting AND down or deteriorat*	
12.	AX=body	
13.	CS=13 and 14	
14.	AX=deathbed	
15.	CS=1 or 4 or 5 or 6 or 7 or 10 or 13 or 14	***Population***
16.	JD=1999 or 2000 OR 2001 OR 2002 OR 2003 OR 2004 OR 2005 OR 2006 or 2007 or 2008 or 2009 or 2010 OR 2011 OR 2012 OR 2013 OR 2014	
17.	CS=15 and 16	

G.4 Minimally Important differences

Medline search terms

1.	death/	
2.	(dying or death).ti,ab.	
3.	terminally ill/ or terminal care/ or palliative care/	
4.	((terminal or palliati*) adj1 care).ti,kf.	
5.	"terminally ill".ti,kf.	
6.	"terminal illness".ti,kf.	
7.	((palliati* or terminal or end) adj1 stage*).ti,ab.	
8.	(terminal adj1 phase*).ti,ab.	
9.	"end of life".ti,ab.	
10.	((last or final) adj1 (hour* or day* or minute* or week* or month* or moment*)).ti,ab.	
11.	(body adj2 (shutdown or shut* down or deteriorat*)).ti,ab.	
12.	deathbed.ti,ab.	
13.	or/1-12	***Population***
14.	((minimal* or minimum or clinical*) adj3 (importan* or significan*) adj3 (differen* or change* or effect or finding* or increas* or decreas* or reduction*)).ti,ab.	***MID terms***
15.	13 and 14	
16.	*Excluded study designs and publication types limit A.1.4*	
17.	15 not 16	
18.	Limit 17 to English language	

Embase search terms

1.	death/	
2.	(dying or death).ti,ab.	
3.	terminally ill patient/ or terminal care/ or palliative therapy/	
4.	((terminal or palliati*) adj1 care).ti,kw.	
5.	"terminally ill".ti,kw.	
6.	"terminal illness".ti,kw.	
7.	((palliati* or terminal or end) adj1 stage*).ti,ab.	
8.	(terminal adj1 phase*).ti,ab.	
9.	"end of life".ti,ab.	
10.	((last or final) adj1 (hour* or day* or minute* or stage* or week* or month* or moment*)).ti,ab.	
11.	(body adj2 (shut* down or shutdown or deteriorat*)).ti,ab.	
12.	deathbed.ti,ab.	
13.	or/1-12	***Population***
14.	((minimal* or minimum or clinical*) adj3 (importan* or significan*) adj3 (differen* or change* or effect or finding* or increas* or decreas* or reduction*)).ti,ab.	***MID terms***
15.	13 and 14	
16.	*Excluded study designs and publication types limit A.1.4*	
17.	15 not 16	
18.	Limit 17 to English language	

Appendix H: Clinical evidence tables

H.1 Recognising Dying

H.1.1 Quantitative review

Table 13: Chiang 2009

Reference	Chiang 2009 [95] and Kao 2009 [251]
Study type and analysis	Prospective cohort (derivation and validation of a prognostic tool)
Number of participants and characteristics	n=729 (first 374 were derivation group for prognostic tool, latter 374 patients were the validation group). Inclusion criteria: People with terminal cancer admitted to the palliative care unit referred from other wards of the same hospital, from other hospital or home. Exclusion criteria: Admission during bank holidays/weekends. People referred to other hospitals, as their complete records could not be accessed. Setting: Hospice ward, general hospital Country: Taiwan, China Age, years. Median (range) = derivation 67 (54, 75) validation 67 (58, 75) Male:Female: derivation 228: 146 validation 205: 148 Informed consent of unconscious people was obtained by proxy from relatives. Unconscious people n = 6 (derivation = 3 and validation group = 3). Eighteen signs and symptoms assessed: pain, dyspnoea, tiredness, heart rhythm, poor appetite, medication for insomnia, nausea, vomiting, constipation, edema, ascites, jaundice, cognitive status, performance status score according to Eastern Cooperative Oncology Group scale (ECOG), fever, pressure sores, mean muscle power, naso-gastric tube, intervention tube placement. An additional 12 laboratory items were also examined including blood count and biochemistry examination. Eighteen symptoms and signs were assessed, including pain, dyspnoea, tiredness, heart rhythm (irregular versus regular), poor appetite (<500 cc of

	milk or <2 bowls of porridge by mouth or tube feeding within 24 hours of admission), medication for insomnia, nausea, vomiting, constipation, edema (scored as 0 = no; 1 = less than 1/2 finger breadth; 2 = 1/2 - 1 finger breadth; and 3 = >1 finger breadth), ascites (scored as 0 = no; 1 = only by ultrasound; 2 = shifting dullness by physical examination; 3 = umbilical protrusion), jaundice (scored as 0 = no; 1 = slightly yellowish; 2 = remarkably yellow; and 3 = deeply yellow or greenish), cognitive status (scored as 0 = clear; 1 = lethargy; 2 = confusion; 3 = comatose), performance status score according to the ECOG (range: 1-4), fever (core temperature ≥ 37.5°C), pressure sores, mean muscle power (sum of muscle power of each extremity divided by 4, muscle powers graded using the Medical Research Council (MRC) scale of 0-5: 5 = normal power, 4 = moderate movement against resistance, 3 = movement against gravity but not against resistance, 2 = movement with gravity eliminated, 1 = flicker of movement, 0 = no movement), naso-gastric tube, and intervention tube placement (for example, percutaneous nephrostomy (PCN), percutaneous transhepatic cholangio drainage (PTCD), pig tail for pleural effusion or ascites drainage, jejunostomy tube and percutaneous endoscopic gastrostomy tube). An additional 12 laboratory items were examined: complete blood count (for example, white blood cell (WBC) count (normal range: male: 3.8-9.8*103/microlitres, female: 3.6-9.6*103/microlitres) and differential percentages, haemoglobin (normal range: male: 13-18 g/dL, female: 12-16 g/dL), and platelet (normal range: 120-320*103/microlitres); and biochemistry examination: blood urea nitrogen (BUN) (normal range: ≤20 mg/dL), creatinine (normal range: ≤1.2 mg/dL), serum glutamic oxaloacetic transaminase (SGOT) (normal range: ≤38 IU/litre), serum glutamic pyruvate transaminase (SGPT) (normal range: ≤41 IU/litre), total bilirubin (normal range: ≤1.0 mg/dL), albumin (normal range: 3.4-4.8 g/dL), corrected calcium (normal range: 2.1-2.55 mmol/litre), and blood sugar (normal range:70-110 mg/dL). Duration of survival days, which was defined as the period (in days) from the date of a hospice ward admitted to the date of death, or the end of follow-up, were also recorded. Extraction of independent prognostic factors from the training model to establish a predictor model to consider factors associated with the person's expectation of dying within 7 days. Univariate logistic regression analysis was performed to analyse the odds ratio of significant factors associated with people who expired within 7 days. Variables having a p value <0.05 in univariate analysis were selected and evaluated by multivariate logistic regression models. Kao et al 2009, reports a subgroup of these patients aged 65 and over (n = 459), of which 112 people died within 1 week. Mean age = 74.25 (±6.12 years)
Prognostic variable(s)	Multivariate analysis indicated that the following factors were significantly associated with the likelihood of people dying within 7 days: Cognitive status, edema, ECOG score, blood urea nitrogen and respiratory rate.
Confounders OR stratification strategy	Multivariate logistic regression model used following variables: Cognitive status, edema, ECOG score, blood urea nitrogen (BUN) and respiratory rate. Predictive model: Log[probability of dying within 7 days/(1 - probability of dying within 7 days)[-5.37 + 0.864*cognitive status (1 if cognitive = 0, 0 if otherwise) + 0.782*edema (1 if edema = 0, 0 otherwise) + 1.208* ECOG (1 if ECOG = 1 and 2, 0 if otherwise) + 0.022* BUN + 0.104* respiratory rate]
Outcomes and effect sizes	ROC curve given for predictor model, based on 5 predictors shown below (multivariate analysis) Area under curve = 0.81 (p <0.001, 95% CI 0.76 to 0.86 **Derivation**

	Sensitivity 80.9% Specificity 65.9% PPV 42.6% NPV 91.7% **Validation** Sensitivity 71.0% Specificity 57.7% PPV 26.8% NPV 90.1% **Multivariate analysis of clinical signs (OR, 95% CI) - in training set n = 374:** Cognitive (1 to 3 vs. 0) 2.29 (1.18, 4.43) Edema (1 to 3 vs. 0) 1.94 (1.04, 3.62) Jaundice (1 to 3 vs. 0) 1 (0.47, 2.15) ECOG score (3, 4 vs. 1, 2) 3.45 (1.65, 7.19) Ascites (1 to 3 vs. 0) 1.01 (0.49, 2.11) Additional laboratory parameters used within prognostic tool: BUN (mg/dl) 1.02 (1.00, 1.03) Respiratory rate 1.12 (1.04, 1.20) **Multivariate analysis of clinical signs (OR, 95% CI) - in subgroup 65 and over n = 459** Systolic blood pressure (per mm Hg) = 0.985 (0.974 - 0.997) Heart rate (per 1 beat/min) = 1.017 (0.001 - 1.032) Haemoglobin (per 1 mg/dL) = 1.216 (1.067 - 1.385) BUN (per 1mg/dL) = 1.028 (1.017 - 1.038) ECOG (per 1 score) = 2.018 (1.397 - 2.9150) Muscle power (per 1 score) = 0.722 (0.542 - 0.961)
Comments	Project supported by grants from Buddhist Dalin Tzu Chi General Hospital.

Table 14: Escalante 2000[149]

Reference	Escalante 2000[149,149]
Study type and analysis	Retrospective cohort (randomised sample stratified by malignancy)
Number of participants and characteristics	n=122 Inclusion criteria: People with cancer presenting to the emergency centre with acute dyspnoea as a primary or secondary complaint. Exclusion criteria: miscoded complaints (no complaints of dyspnoea, direct transfers from other hospitals after treatment elsewhere for their dyspnoea, charts unavailable for review, no available physician note documenting the presence of dyspnoea in the ED, scheduled visits to the ED for thoracentesis, pneumothoraces after central venous catheter placement in the outpatient clinic, developed dyspnoea in the chemotherapy clinic and X-ray unavailable for review (excluded patients = 57). Etiology of dyspnoea was determined and further details given in Escalente 1996, these included primary lung cancer, COPD, pneumonia, pleural effusion, congestive heart failure, lung metastasis and tumour obstruction. Setting: Emergency Centre Country: USA Age, years. Median (range): 58 (29 - 90) Female, n (%):53% 68% had uncontrolled progressive disease. 25 (20%) died within the first 2 weeks 63 (52%) died within the first 3 months. Randomisation stratified by malignancy (divided into thirds: breast cancer, lung cancer and other cancer).
Prognostic variable(s)	Triage blood pressure. Triage respiration, response to treatment, triage pulse, cancer diagnosis, history of metastasis.

Confounders OR stratification strategy	Univariate factors: Imminent death (survival of 2 weeks or less) N (%) Triage blood pressure systolic ≤80mmHg = 8 (41.7) systolic >80mmHg = 19 (17.9) diastolic ≤40mmHg = 1 (100.0) diastolic >40mmHg = 23 (19.8) Triage respiration = Respiratory ≤ 28 breaths/min = 3 (5.2) Respiratory > 28 breaths/min = 22 (34.9) Triage pulse = 60< pulse <110 beats /min = 6 (10.3) Pulse ≥ 110, or ≤ 60 beats/min = 19 (30.2) Response to treatment = Controlled, or stable disease = 1 (2.6) Uncontrolled, progressive disease = 24 (28.9) History of metastasis = None = 3 (7.3) History of metastasis = 22 (27.5) Cancer diagnosis Breast = 7 (19.4) Lung = 14 (31.1) Other = 4. (	Univariate factors: Imminent death (survival great than 2 weeks) N (%) Triage blood pressure systolic ≤80mmHg = 7 (58.3) systolic >80mmHg = 87 (82.1) diastolic ≤40mmHg = 0 (0) diastolic >40mmHg = 93 (80.2) Triage respiration = Respiratory ≤ 28 breaths/min = 55 (94.8) Respiratory > 28 breaths/min = 41 (65.1) Triage pulse = 60< pulse <110 beats /min = 52 (89.7) Pulse ≥ 110, or ≤ 60 beats/min = 44 (69.8) Response to treatment = Controlled, or stable disease = 38 (97.4) Uncontrolled, progressive disease = 59 (71.1) History of metastasis = None = 38 (92.7)) History of metastasis = 58 (72.5)
	Variables that exhibited a relationship with the survival variables (p<0.1), that is, occurred by chance less than 10 times in 100 in univariate analysis were used in a logistic regression to build preliminary models. Multivariate model - logistic regression used to evaluate predictors of imminent death.	

Outcomes and effect sizes	Multivariate predictive model: Imminent death (survival of 2 weeks or less) Triage respiration = RR 12.72 (3.1 - 52.8) p = 0.0000 Response to treatment = RR 21.93 (2.5 - 196.0) p = 0.0010 Triage pulse = RR 4.92 (1.4 - 16.9) p = 0.0025 History of metastasis = RR 3.85 (1.8 - 17.7) p = 0.0367
Comments	ROC curve given in paper. Source of funding not reported.

Table 15: Hui 2014[228]

Reference	**Hui 2014[228]**
Study type and analysis	Prospective longitudinal observational cohort.
Number of participants and characteristics	n=357 (151 USA, 206 Brazil) Inclusion criteria: Consecutive patients with a diagnosis of advanced cancer who were ≥18 years. Exclusion criteria: None reported Setting: Acute palliative care setting Country: USA and Brazil Age, years. Mean (range): 58 (18 - 88) Female, n (%): 195 (55) Baseline demographics were collected at admission. Every 12 hours from admission to discharge or death standardised data forms were completed capturing the 10 variables detailed below.
Diagnostic indicators	**Clinical signs associated with impending death and description (criteria for positive sign):** Apnea periods - prolonged pauses between each breath (<30 seconds; 30-60 seconds; >60 seconds) Cheyne-Stokes breathing - alternating periods of apnoea and hyperpnoea with a crescendo-decrescendo pattern (present)

	Death rattle - Gurgling sounds produced on inspiration and/or expiration related to airway secretions (audible if very close; audible at the end of bed; audible >6 meters from door of room) Dysphagia of liquids - difficulty with fluid intake (present) Decreased level of consciousness - Richmond Agitation Scale (-2 to -5 [sedation]) Decreased performance status - Palliative Performance Scale, validated for assessing function [0% - 100%] (≤20% [bed bound, completely dependent]) Peripheral cyanosis - Bluish discoloration of extremities (toes; feet; up to knees) Pulselessness of radial artery - Inability to palpate radial pulse (left; right; both) Respiration with mandibular movement - Depression of jaw with inspiration (present) Urine output - Measured volume of urine over a 12-hour period (≤100mL)
Outcomes and effect sizes	Mortality - 52/151 - USA, 151/206 Brazil Diagnostic performance of clinical signs

	Missing data, n (%)	Sensitivity (95% CI)	Specificity (95% CI)	Negative LR (95% CI)	Positive LR (95% CI)	Frequency of signs in last 3 days of life
PPS≤20%	120 (2.1)	64 (63.4 - 64.7)	81.3 (80.9 - 81.7)	0.44 (0.43 - 0.45)	3.5 (3.4 - 3.6)	169 (93)
RASS - 2 or lower	90 (1.6)	50.5 (49.9 - 51.1)	89.3 (88.9 - 89.7)	0.6 (0.5 - 0.6)	4.9 (4.7 - 5)	159 (90)
Dysphagia of liquids	652 (11.7)	40.9 (40.1 - 41.7)	78.8 (78.3 - 79.2)	0.75 (0.74 - 0.76)	1.9 (1.9 - 2)	100 (90)
Urine output over last 12 hours <100mL	3262 (58)	24.2 (23.2 - 25.1)	98.2 (98 - 98.5)	0.77 (0.76 - 0.78)	15.2 (13.4 - 17.1)	48 (72)
Death rattle	101 (1.8)	22.4 (21.8 - 22.9)	97.1 (96.9 - 97.3)	0.8 (0.79 - 0.81)	9 (8.1 - 9.8)	110 (66)
Apnea periods	85 (1.5)	17.6 (17.1 - 18)	95.3 (95.1 - 95.6)	0.86 (0.86 - 0.87)	4.5 (3.7 - 5.2)	71 (46)
Respiration with mandibular movement	86 (1.5)	22 (21.5 - 22.4)	97.5 (97.3 - 97.6)	0.8 (0.8 - 0.81)	10 (9.1 - 10.9)	92 (56)
Peripheral cyanosis	90 (1.6)	26.7 (26.1 - 27.3)	94.9 (94.7 - 95.2)	0.77 (0.77 - 0.78)	5.7 (5.4 - 6.1)	99 (59)
Cheyne-Stokes breathing	83 (1.5)	14.1 (13.6 - 14.5)	98.5 (98.4 - 98.7)	0.9 (0.9 - 0.9)	12.4 (10.8 - 13.9)	61 (41)
Pulselessness of radial artery	94 (1.7)	11.3 (10.9 - 11.8)	99.3 (99.2 - 99.5)	0.89 (0.89 - 0.9)	15.6 (13.7 - 17.4)	57 (38)

Comments	Note the high rate of missing data - urine output was not routinely collected at the Brazilian centre (58% missing data). In addition there is 11.7% missing data for dysphagia of liquids, no comment given in text. This research is supported in part by a University of Texas MD Anderson Cancer Center support grant (CA 016672), which provided the funds for data collection at both study sites. E.B. is supported in part by National Institutes of Health Grants R01NR010162-01A1, R01CA122292-01, and R01CA124481-01.

Table 16: Loekito 2013[296]

Reference	**Loekito 2013[296]**				
Study type and analysis	Retrospective observational				
Number of participants and characteristics	n=71453 Inclusion criteria: Emergency department patients Exclusion criteria: None stated Setting: Emergency department Country: Australia Age, years. Mean = 59.99 ±22.1 Male: 50.5%				
Diagnostic indicators	Haemoglobin, haematocrit, total bicarbonate, white cell count, albumin, pH, bilirubin, creatinine, urea.				
Outcomes and effect sizes		**Death**	**#tests(#patients)**	**Survived**	**#tests(#patients)**
	Haemoglobin (g/litre)	122±26.2	910 (805)	133±20.7	132515 (70381)
	Haematocrit (litre/litre)	0.38±0.08	910 (805)	0.40±0.06	132448 (70369)
	Total bicarbonate (mmol/litre)	20.24±7.07	962 (815)	24.68±3.57	129104 (66131)
	White cell count 10^9/litre	12.5 (8.5,16.9)	910 (805)	8.5 (6.7,11.1)	132445 (70372)

Albumin (g/litre)	30.1±7.4	741 (659)	37.1±5.9	85147 (49289)	
pH	7.22±0.16	1013 (566)	7.38±0.09	25290 (12222)	
Bilirubin (micromoles/litre)	14 (9,22)	660 (602)	11 (8,17)	77668 (46539)	
Creatinine (mmol/litre)	0.14 (0.09,0.23)	966 (815)	0.08 (0.07,0.11)	129144 (66147)	
Urea (mmol/litre)	12.4 (7.9,20.1)	964 (814)	6.0 (4.4,8.6)	129120 (66135)	
Haemoglobin (g/litre)	122±26.2	910 (805)	133±20.7	132515 (70381)	

Mortality (people who died on the same or next day), AUC - ROC [95% CI)
Haemoglobin 0.6330 [0.6133 - 0.6532]
Haematocrit 0.5788 [0.5562 - 0.6004]
Total bicarbonate 0.7318 [0.7126 - 0.7515]
White cell count 0.6913 [0.6711 - 0.7099]
Albumin 0.7791 [0.7614 - 0.7966]
pH 0.8069 [0.7913 - 0.8211]
Bilirubin 0.5799 [0.5574 - 0.6020]
Creatinine 0.7645 [0.7494 - 0.7803]
Urea 0.7905 [0.7766 - 0.8059]

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	DOR [95% CI]
U≥8.75	0.703 [0.673 0.732]	0.760 [0.758 0.763]	0.0215 [0.0199 0.0231]	0.997 [0.997 0.997]	7.53 [6.55 8.65]
cr≥0.1145	0.636 [0.604 0.666]	0.796 [0.794 0.798]	0.0228 [0.0210 0.0246]	0.997 [0.996 0.997]	6.81 [5.97 7.77]
WCC≥11.75	0.552 [0.519 0.584]	0.788 [0.786 0.790]	0.0175 [0.0161 0.0191]	0.996 [0.996 0.996]	4.57 [4.01 5.21]
Bili≥17.5	0.362 [0.325 0.400]	0.773 [0.770 0.776]	0.0134 [0.0118 0.0152]	0.993 [0.992 0.994]	1.94 [1.65 2.27]
Hb≤128.5	0.588 [0.555 0.620]	0.640 [0.637 0.642]	0.0111 [0.0102 0.0120]	0.996 [0.995 0.996]	2.53 [2.22 2.89]
Hct≤0.375	0.475 [0.442 0.508]	0.697 [0.695 0.700]	0.0107 [0.00969 0.0117]	0.995 [0.994 0.995]	2.08 [1.83 2.37]
CO2≤21.5	0.569 [0.537 0.600]	0.847 [0.845 0.849]	0.0269 [0.0248	0.996 [0.996 0.997]	7.30 [6.41 8.30]

				0.0293]		
	pH≤7.325	0.704 [0.675 0.732]	0.794 [0.790 0.800]	0.121 [0.112 0.129]	0.985 [0.984 0.987]	9.18 [8.0 10.5]
	ALB≤34.5	0.718 [0.684 0.750]	0.724 [0.721 0.727]	0.0221 [0.0203 0.0241]	0.997 [0.996 0.997]	6.68 [5.69 7.84]
Comments	Additional data reported on different thresholds.					

Table 17: Loekito 2013[296]

Reference	**Loekito 2013[296]**				
Study type and analysis	Retrospective observational				
Number of participants and characteristics	n=71453 Inclusion criteria: Emergency department patients Exclusion criteria: None stated Setting: Emergency department Country: Australia Age, years. Mean = 59.99 ±22.1 Male: 50.5%				
Diagnostic indicators	Haemoglobin, haematocrit, total bicarbonate, white cell count, albumin, pH, bilirubin, creatinine, urea.				
Outcomes and effect sizes		**Death**	**#tests(#patients)**	**Survived**	**#tests(#patients)**
	Haemoglobin (g/litre)	122±26.2	910 (805)	133±20.7	132515 (70381)
	Haematocrit (litre/litre)	0.38±0.08	910 (805)	0.40±0.06	132448 (70369)
	Total bicarbonate (mmol/litre)	20.24±7.07	962 (815)	24.68±3.57	129104 (66131)
	White cell count 10^9/litre	12.5 (8.5,16.9)	910 (805)	8.5 (6.7,11.1)	132445 (70372)

Albumin (g/litre)	30.1±7.4	741 (659)	37.1±5.9	85147 (49289)	
pH	7.22±0.16	1013 (566)	7.38±0.09	25290 (12222)	
Bilirubin (micromoles/litre)	14 (9,22)	660 (602)	11 (8,17)	77668 (46539)	
Creatinine (mmol/litre)	0.14 (0.09,0.23)	966 (815)	0.08 (0.07,0.11)	129144 (66147)	
Urea (mmol/litre)	12.4 (7.9,20.1)	964 (814)	6.0 (4.4,8.6)	129120 (66135)	
Haemoglobin (g/litre)	122±26.2	910 (805)	133±20.7	132515 (70381)	

Mortality (people who died on the same or next day), AUC - ROC [95% CI)
Haemoglobin 0.6330 [0.6133 - 0.6532]
Haematocrit 0.5788 [0.5562 - 0.6004]
Total bicarbonate 0.7318 [0.7126 - 0.7515]
White cell count 0.6913 [0.6711 - 0.7099]
Albumin 0.7791 [0.7614 - 0.7966]
pH 0.8069 [0.7913 - 0.8211]
Bilirubin 0.5799 [0.5574 - 0.6020]
Creatinine 0.7645 [0.7494 - 0.7803]
Urea 0.7905 [0.7766 - 0.8059]

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	DOR [95% CI]
U≥8.75	0.703 [0.673 0.732]	0.760 [0.758 0.763]	0.0215 [0.0199 0.0231]	0.997 [0.997 0.997]	7.53 [6.55 8.65]
cr≥0.1145	0.636 [0.604 0.666]	0.796 [0.794 0.798]	0.0228 [0.0210 0.0246]	0.997 [0.996 0.997]	6.81 [5.97 7.77]
WCC≥11.75	0.552 [0.519 0.584]	0.788 [0.786 0.790]	0.0175 [0.0161 0.0191]	0.996 [0.996 0.996]	4.57 [4.01 5.21]
Bili≥17.5	0.362 [0.325 0.400]	0.773 [0.770 0.776]	0.0134 [0.0118 0.0152]	0.993 [0.992 0.994]	1.94 [1.65 2.27]
Hb≤128.5	0.588 [0.555 0.620]	0.640 [0.637 0.642]	0.0111 [0.0102 0.0120]	0.996 [0.995 0.996]	2.53 [2.22 2.89]
Hct≤0.375	0.475 [0.442 0.508]	0.697 [0.695 0.700]	0.0107 [0.00969 0.0117]	0.995 [0.994 0.995]	2.08 [1.83 2.37]
CO2≤21.5	0.569 [0.537 0.600]	0.847 [0.845 0.849]	0.0269 [0.0248	0.996 [0.996 0.997]	7.30 [6.41 8.30]

				0.0293]		
	pH≤7.325	0.704 [0.675 0.732]	0.794 [0.790 0.800]	0.121 [0.112 0.129]	0.985 [0.984 0.987]	9.18 [8.0 10.5]
	ALB≤34.5	0.718 [0.684 0.750]	0.724 [0.721 0.727]	0.0221 [0.0203 0.0241]	0.997 [0.996 0.997]	6.68 [5.69 7.84]
Comments	Additional data reported on different thresholds.					

Table 18: Loekito 2013A[295]

Reference	**Loekito 2013A[295]**				
Study type and analysis	Retrospective observational				
Number of participants and characteristics	n=42701 (and additional 13137 people in validation set) Inclusion criteria: People admitted for more than 24h Exclusion criteria: None stated Setting: 2 university affiliated hospitals Country: Australia Age, years. Mean = 65.8 ±17.6 Male: 55%				
Diagnostic indicators	Haemoglobin, haematocrit, total bicarbonate, white cell count, albumin, pH, bilirubin, creatinine, urea.				
Outcomes and effect sizes		**Death**	**#tests(#patients)**	**Survived**	**#tests(#patients)**
	Haemoglobin (g/litre)	106.6 (±22.5)	2106 (1434)	110.8 (±20.1)	350103 (41071)
	Haematocrit (litre/litre)	0.33 (±0.07)	2096 (1431)	0.34 (±0.06)	348605 (40959)
	Total bicarbonate (mmol/litre)	22.8 (±7.2)	2283 (1500)	25.7 (±4.3)	368082 (40767)
	White cell count 10^9/litre	12.3 (8.4, 17.6)	2098 (1431)	8.2 (6.1, 10.8)	348315 (40959)
	Albumin (g/litre)	24.4 (±7.2)	1147 (874)	2835 (±6.6)	163896 (28398)

	pH	7.28 (±0.15)	649 (437)	7.39 (±0.10)	17175 (6681)
	Bilirubin (micromole/litres)	18 (11, 40)	853 (685)	13 (98, 23)	127237 (25858)
	Creatinine (mmol/litre)	0.15 (0.09, 0.24)	2286 (1503)	0.09 (0.07, 0.13)	368220 (40777)
	Urea (mmol/litre)	15.8 (9.3, 24.2)	2284 (1502)	6.7 (4.3, 11.2)	368176 (40770)
	Mortality (people who died on the same or next day), AUC - ROC [95% CI] Haemoglobin 0.5582 (0.5456, 0.5706) Haematocrit 0.5303 (0.5181, 0.5427) Total bicarbonate 0.6506 (0.6358, 0.6632) White cell count 0.7063 (0.6932, 0.7189) Albumin 0.6628 (0.6472, 0.6801) pH 0.7254 (0.7035, 0.7490) Bilirubin 0.6131 (0.5945, 0.6317) Creatinine 0.6870 (0.6767, 0.6972) Urea 0.7724 (0.7625, 0.7818)				
Comments	Multivariate model derived and based on these variables - additional information given. Partially supported by Cooperative Research Centres programme for Smart Services funded by the Australian Government.				

Table 19: Matsunuma 2014 [310]

Reference	**Matsunuma 2014**
Study type and analysis	Retrospective cohort (derivation and validation of a prognostic tool)
Number of participants and characteristics	n=93 Inclusion criteria: People with lung cancer (terminal stage) confirmed pathologically or clinically and admission to the palliative care unit from April 2009 to June 2012 (training group) and July 2012 to June 2013 (testing group).

	Exclusion criteria: None reported Setting: Palliative care unit Country: Japan Time to death : 22/69 (training set) and 8/24 (testing set) patients died within 2 weeks Median survival: 30 days Age, years. Mean (±SD): training: 75 ±10, testing: 73 ±7.9 Female (%): training: 31 (45%), testing: 8 (33%)
Prognostic variable(s)	Twenty six candidate predictors were identified in the training group and factors that were significantly related to survival were extracted and multivariate analysis performed, using Cox proportional hazards regression model. Univariate analysis identified 8 factors with prognostic significance for survival. Multivariate analysis was then conducted using these predictors: Palliative prognostic score, desaturation, supplemental oxygen, anorexia, fatigue, dyspnoea, hypoalbuminemia, hyponatremia.
Confounders OR stratification strategy	Multivariate analysis showed 5 factors were independent for predicting short-term prognosis. - training group , n = 69 Patients divided into 2 groups having 0 - 2 of these factors (0 - 2group) or >3 of these factors (3 - 5 group) - survival curve given.
Outcomes and effect sizes	**Hazard ratios (95 CI)** Palliative prognostic score - not reported Desaturation HR 3.3 (1.42 - 7.65) Supplemental oxygen - not reported Anorexia HR 2.57 (1.14 - 5.88) Fatigue HR 5.9 (2.04 - 17.0) Dyspnoea - not reported Hypoalbuminemia HR 2.37 (1.05 - 5.36) Hyponatremia HR 2.17 (1.01 - 4.68) Mean survival (training group) 0 - 2 of these factors = 48±5.1 days >3 of these factors = 9.2 + 2.6 days

	Diagnostic calculations - in testing group n = 24				
	Items	**Sensitivity (%)**	**Specificity (%)**	**Positive predictive value (%)**	**Negative predictive value (%)**
	This study (death within 2 weeks) - 3 or more factors	100	75	67	100
	PaP (palliative prognostic score) - death within 3 weeks	21	100	100	48
	PPI (palliative prognostic index) - death within 4 weeks	66	100	100	83
Comments	Reporting bias - noted that authors state 8 factors significant using univariate analysis, but then go on to only report significant findings for 5/8 factors using multivariate analysis. Data not reported to complete 2x2 tables for diagnostic outcomes.				

H.1.2 Qualitative review

Table 20: Abarshi 2011[5]

Study (ref id)	**Abarshi 2011[5]**
Aim	To explore the factors that allow primary care physicians to recognise that someone is entering the last days of life, and how this relates to care during this period.
Population	All sentinel general practitioners who form an epidemiological surveillance system in the Netherlands were asked to provide data on all deceased patients aged over 1 year in relation to the care they received in the last 3 months of their life. Sudden and totally unexpected deaths were not included. n=252
Study design	Twenty one question registration form consisting of multiple choice and open response questions designed to assess factors including: • Demographics including presence of dementia and coma • Number of admissions to hospital/ITU in the last 3 months of life, last 2-4 weeks of life and last 1 week of life. • Symptom frequency and distress in the last week of life using the Eastern Cooperative Oncology Group performance status • GP-patient communication about diagnosis, prognosis, incurability of illness, and treatment options, Timing of the GP recognising death in the near future.
Methods and	Univariate and multivariate logistic regression analyses were performed to analyse which patient and care characteristics were related to the

Study (ref id)	Abarshi 2011[5]
analysis	recognition of death in the near future. A logistic regression analysis was done to compare care characteristics that took place after recognising dying with recognising death in the near future as the independent variable. Corrected for cancer diagnosis and ambulant functional state.
Themes with findings	Characteristics associated with recognising death in the near future: On multivariate analysis a diagnosis of cancer (OR(95%CI) = 0.18 (0.1-0.4), and low functional states (OR(CI)= 5.21 (2.3-11.7) both increased the chance of recognising death in the near future. Death in the near future was never recognised 3 times as often among people with cardiorespiratory (26%) and other (43%) illnesses compared to cancer (12%).
	Incidence and timing of recognising dying: Across both home and hospital care settings death in the near future was recognised most in the last week of life (recognised as dying before the last month=15%, within the last month=19% and in the last week of life=34%).
Limitations	Self-reported survey retrospective study design introducing elements of bias. Physician rated symptoms Sudden and totally unexpected deaths were excluded from the study but these were not defined, and given a large proportion were not recognised at 1 week before death that were included this was difficult to judge.
Applicability of evidence	The study included an indirect population as all deaths over 1 years were included and were grouped together with younger adults (1-64 years) forming 20% of the study population.

Table 21: Brandt 2005[62]

Study (ref id)	Brandt 2005[62]
Aim	To examine the dying person in nursing home settings, in particular the patient characteristics and signs that lead physicians to recognise entering the last 6 weeks of life. It also aims to look at the relationship between specific underlying disease and these symptoms.
Population	All long term nursing home care patients assessed by physicians to be entering the last 6 weeks of life. Other inclusion criteria included admittance to nursing home for long term care or admitted for rehabilitation but during their stay it became obvious that the person would not leave the nursing home.
Setting	Sixteen nursing homes were included
Study design	Prospective observational study
Methods and analysis	Physicians at the nursing home were asked to include people who they felt were entering the last 6 weeks of life. They were asked on entry to rate the person's dementia using the Global Deterioration Scale. Symptoms were measured on a survey asking whether they were present and if so to rank the 3 most important symptoms in recognising the people entering last 6 weeks of life. The person's actual cause of death and underlying disease was then recorded on death. The majority of people had died by 9 days of being entered into the study (92.3%), the median duration of survival was 3 days, with the 10^{th} and 90^{th} percentile being death within 24 hours.

Study (ref id)	Brandt 2005[62]
Themes with findings	There were 4 symptoms that were rated important in recognising that people were entering the last 6 weeks of life: • Very little/no fluid intake (42.6% of cases) • Generalised weakness (31.8% of cases) • Respiratory problems/dyspnoea (21.,3% of cases) • Very little/no nutritional intake (24.8% of cases) The very little/no fluid intake and generalised weakness were most commonly recognised as most important.
	The doctors rated the following as important for recognising people entering the last 6 weeks of life in specific underlying disease groups. • Diseases of the circulatory system– reduced fluid intake (45.3%) and respiratory problems/dyspnoea (31.1%) • Mental/behavioural disorders (mainly dementia)- reduced fluid (49.4%) or nutritional intake (32.7%) the most important in this group • Malignant neoplasms, including metastases- Generalised weakness (46.7%) and extreme tiredness (26.7%)
Limitations	The person's dementia ratings although mentioned in the methods were not described in the paper. There was little definition of what constituted the categories listed as underlying disease and cause of death.
Applicability of evidence	Indirect population, as although the doctors were asked to rate people in the last 6 weeks of life (even though the majority of the people had died by day 9).

Table 22: Christakis 2000[96]

Study (ref id)	Christakis 2000[96]
Aim	To investigate factors that affect doctors' prognostication of people in outpatient hospice settings.
Population	All people admitted to 5 outpatient hospice programmes in Chicago, USA. Children were excluded. n=504, mean age 69 (SD 17) years, 45% were men, the diagnosis was cancer in 65%, Aids in 12% and other conditions in 23%. The median performance status was 3.
Setting	Outpatient hospice programme
Study design	Prospective telephone survey of doctors on new referral of a person's admission to outpatient hospice services, gathering: • An estimate of how long the person had to live • Eastern Cooperative Oncology Group performance status • Duration of illness, • Doctors experience of dealing with similar people • Doctors self-rated dispositional optimism • Duration recentness and frequency of contact of the person with the doctor. The patient demographics were taken from hospice records, and the person's actual date of death was taken from public archives.

Methods and analysis	A prognosis accuracy was determined by dividing the observed by the predicted survival: • Values between 0.67-1.33 this was deemed accurate • Values less than 0.67 were deemed optimistic • Values greater than 1.33 were deemed pessimistic Analysis of variance and chi squared tests were used to evaluate continuous and categorical variables. Multinomial logistic regression was used to assess the multivariate effect of patient and doctor variables on prognostic accuracy.
Themes with findings	Doctors are prone to error when predicting survival time. • 20 % of predictions regarding when the person would dies were accurate, 63% optimistic and 17% pessimistic. The longer the observed survival (that is the less ill the person), the lower the error, and conversely the longer the predicted survival, the greater the error. • Factors associated with prognostic accuracy (bivariate analysis): • Speciality of the doctor – doctors in non-oncological medical subspecialties were the least likely to give correct estimates. • Pessimistic predictions were associated with the most recent examinations.
Limitations	There was a high non-response rate in the study (12%)
Applicability of evidence	Indirect- the survival time ranged to over a 1000 days and median survival was 24 days. The predicted time of death was also greater than 14 days in the majority of people.

Table 23: Domeisen 2013[135]

Study (ref id)	Domeisen 2013[135]
Aim	To describe the most pertinent phenomena in identifying whether a person is in the last hours or days of life.
Population	n=252 Healthcare professionals and lay care persons/volunteers who were experienced in palliative care and care of those in the last hours and days of life across 9 countries
Setting	Various settings
Study design	Three stage Delphi. Each stage consisted of development of the questionnaire by a synthesis group from the 9 participating countries made up of nurses, physicians, psycho-social-spiritual professionals, volunteers and researchers. This was then distributed among the target population, and the results reviewed and synthesised, and the output brought forward to next stage. Due to lay persons comments in the 2nd round they were not included in the 3rd round (felt required clinical experience). Questions were: • Please list a maximum of 4 phenomena, observations or perceptions which seem important to you while trying to identify that somebody will die within the next hours or days.

	• Do you agree that this phenomenon is important when identifying or recognising the last hours or days of life? • Please rate the following phenomena in terms of clinical relevance to predict that someone will die within the next few hours/days,	
Methods and analysis	The participants were asked to rate the last 2 questions on 4 point Likert scales. These were then dichotomised in the analysis. The results from the survey were analysed by the group of clinical experts, and coded by 3 researchers and categorised. A consensus level of 50% was predefined as significant.	
(52.6)	Category	Phenomena with high relevance to recognising dying (% who chose relevant or highly relevant
	Breathing	Death rattle (82.1%)
		Changes in breathing rhythm (66.7%)
		Changes in breathing (50%)
		Changes in breathing patterns (64.1%)
	Consciousness/cognition	Irreversible deterioration of consciousness (62.8%)
		Comatose (61.5%)
		Semi-comatose (52.2%)
	Emotional state	Restlessness (50.7%)
	General deterioration	Rapid degradation of general condition (60.3%)
		Organ failure (65.4%)
		Irreversible status (56.5%)
	Intake of fluid, food, other	No fluid or food intake (69.9%)
		Cannot drink (52.65)
		Swallowing impossible (55.1%)
	Non-observations/expressed opinions/other	Intuition of professionals, gut feeling (57.7%)
	Skin	Peripheral shut down (58%)
		Cold extremity (53.6%)
		Marble- like skin (52.6%)
		Pale around nose and mouth (59.4%)
Limitations	Although a large Delphi n=252 in the initial stage only n=36 and n=78 participated in the second and third stages of the Delphi. The study reports a 100% response rate for rounds 1 and 2 and 72% response rate in round 3. It is unclear how the subset of the group was formed for round 2 and 3, given not all those who contributed in round 1 were included.	

Applicability of evidence	Direct population, and good involvement of a wide variety of those important to the care in the last days of life.

Table 24: Dendaas 2002 [133]

Study (ref id)	Dendaas 2002[133]	
Aim	To ascertain how experienced oncology nurses described the dying process of people with advanced cancer with relation to its length, recognisability using key signs and symptoms, and whether it is monitored.	
Population	Fifteen nurses experienced in the care of people with advanced cancer who had looked after at least 6 people in the last days of life with advanced cancer during the previous 2 years. Female=93%, Mean Age (SD)= 40.94 (10.80), range of experience from 3 years (33%) to over 15 years (7%)	
Setting	Either caring in hospices (73%) or inpatient oncology units (27%)	
Study design	Interview	
Methods and analysis	A set questionnaire of open and closed questions was devised, trialled and consulted with expert palliative care nurses. It was then given individually to the participants. The questions included: • *"How would you describe the dying process to someone who has never seen it?* • *Are you able to sense when death is imminent?* • *How do you sense when death is imminent?* • *Have there been times when a patient's death has caught you by surprise? Describe those situations.* • *Is dying a short, long or high variable process?* • *Do you think anything influences the dying process? Describe these influences.* • *Are there common clinical signs that appear as death draws near? Describe these signs. "* The range of length of time was 4-20 minutes. Not all questions were asked to all participants. These were then transcribed by an external source, the content of which was analysed by an investigator through grouping into questions, and general themes devised through discussion with a research mentor. This was then analysed by 2 expert level hospice nurses who individually read and coded the responses from the interviews with the themes earlier devised.	
Themes with findings	Dying process	Most nurses said the process of dying was variable in length (93%)
		93% said they recognised dying through the onset and development of clinical indicators. There was no further comment on monitoring of dying despite being a set objective.
		84% noted that patients deaths occasional '"caught them by surprise"'.
	Changes in psychosocial status in	Increased social isolation - ' *you see a … change in behaviour, a kind of separation from the world I guess'*

	recognising dying	The use of symbolic language was also reported - '*Symbolic language is pretty common…. They talk about going on a trip'.*
	Changes in physical status in recognising dying -	Weight loss and anorexia
		Declining interest in daily life
		Increased weakness and somnolence, and a decreased level of consciousness
		Skin mottling
		Chest and upper airway congestion
		A 'glazed' look in the eye
		Changes in vital signs
		Anuria
		Changes in a person's pain status – ' sometimes the pain is increased and sometimes the pain is just gone'
	Habits and routines in recognising dying -	Change in habits and routine *'…[when you know what] their usual pattern of things are, and when that pattern changes, that's the biggest indicator for me'*.
Limitations	Not all participants asked all questions and interviews lasted a wide range of times from 4-20 minutes. The study did not meet all of its set aims.	
Applicability of evidence	Direct related to our population although focusing only on people with cancer.	

Table 25: Johnson 2003[244]

Study (ref id)	**Johnson 2003[244]**
Aim	To explore how junior doctors think about prognosis and approach care decisions when caring for seriously ill hospitalised people.
Population	n=8 Internal medicine residents with limited experience in intensive care settings ranging from no experience to 2 months
Setting	During ethical and discharge planning sessions junior doctors (residents) presented people that they were caring for. If the person had already died or discharged the discussion was excluded from the study. The sessions were facilitated by a senior doctor who had not taken care of the person presented.
Study design	The junior doctors were asked a set of planned questions The first question they were asked was "*would you be surprised if this patient died*?". From this the facilitator asked further set questions to prompt further discussion including "*if you knew the patient might die, would your management be different?"* and "*has this consideration [that the patient might die] changed your management*"
Methods and	The 2 authors reviewed the responses for patterns and used template analysis to organise and segment the data attempting to identify major

analysis	categories of response and common domains across each category. These were then coded into broad themes and the transcripts reassessed by the 2 authors to identify themes. Data saturation was met by the 5th transcript.
Themes with findings	Changes in the management if suspecting death: • 1. Clarifying goals- 'When you're talking about working up-micromanaging- every little thing, you should probably figure out [what] the person and family would really want… I think [that] talks with the family would clarify these things • 2. improving communication with patients and families. 'Yeah I would probably spend more time with the patient and the family- I would listen to their story • 3. Spending more time with patients/ordering fewer tests- 'I'd probably spend more time with the patient- you know, getting to know his wishes. And I'd order less labs- since it wouldn't make much difference'.
Limitations	An indirect population, the people were not necessarily recognised in the last days of life by the junior doctor. No information provided
Applicability of evidence	Unsatisfactory use of analysis with only the core authors (who facilitated the discussions) coding and theming the transcripts.

Table 26: Kumagai 2012[267]

Study (ref id)	Kumagai 2012[267]
Aim	To identify predictors of the last 10 and 3 days of life in people with lung, gastric, or colorectal cancer at home.
Population	n=72 nurses who had worked in a visiting nurse station or hospital for more than 10 years and been involved in the care of people with terminally ill lung, gastric or colorectal cancer up to the time of death at home.
Setting	29 visiting nurses station in Japan
Study design	Three round Delphi analysis.
Methods and analysis	The 30 items for the initial inclusion in the survey were taken from a literature review with methods described, and 2 extra items were added from the author's experience. Nurses were asked to rate each of the initial items on a 4 point Likert scale. Additional items suggested in the first round were added for the further 2 rounds. The nurses were asked to rate each item if they were specific to either lung or gastrointestinal cancer or whether they are present in both. They were asked to rate these for both 10 days and 3 days before death.
Themes with findings	Common items that appear in the last 10 days in both lung and gastrointestinal cancer- • Digestive symptoms- Anorexia and constipation and diarrhoea. • General condition-fatigue, less conversation, remarkable boney, dry mouth fever and worsening pain.
	Common items that appear in the last 3 days of life in both lung and gastrointestinal cancer- • Digestive symptoms- Anorexia and constipation and diarrhoea • General condition-fatigue, less conversation, remarkable boney, dry mouth fever and worsening pain, lack of energy dull eyes, diminished mimetic muscles.

	• Respiratory symptoms- Dyspnoea at rest mandibular breathing, rattle, changes of respiratory rhythm, apnoea, increases of sputum, difficulty coughing, up sputum, decreased breath sounds, low SPO2, forced breathing, • Cardiovascular symptoms- appearance of arrhythmia, strong pulse, reduction of blood pressure, peripheral oedema, oliguria/anuria • Level of consciousness- cannot move limbs independently, cannot open eyes to call, drowsy, confusion/delirium, coma
	Items that are inappropriate predictors of end of life for people with lung or gastrointestinal cancer in the last 10 days: • Respiratory symptoms- mandibular breathing rattle, apnoea, bloody sputum, cough, forced breathing • Cardiovascular symptoms- cardiac murmur • Level of conscious- cannot move limbs independently, cannot open eyes to call, confusion/delirium, coma. • General condition- hiccups.
	Items that are inappropriate predictors of end of life for people with lung or gastrointestinal cancer in the last 3 days: • Respiratory symptoms- bloody sputum, cough • Cardiovascular symptoms- cardiac murmur • General condition- pleural effusion
Limitations	Good use of Delphi. There was poor response rate in later rounds commented.
Applicability of evidence	An indirect sourced of evidence as this is related to 2 specific kinds of cancer only, and only people in home settings.

Table 27: Van Der Werff 2012[445]

Study (ref id)	**Van Der Werff 2012[445]**
Aim	To assess nurses perspectives on the signs and symptoms that suggest people are entering the last days of life
Population	n=18. Nursing staff recruited from 4 wards who had had recent experience (within 2 years) of caring for oncology patients in their last days of life
Setting	General hospital.
Study design	Focus group.
Methods and analysis	There were 3 focus groups, were a central investigator facilitated discussion around this topic through using set prompts to encourage all participants to engage. Questions included: "*what do you think nurses perceive in patients whom they think will die in a few days*?" and *"what can you say about what nurses see in the physical state of a patient that makes them think this patient might die in a few dies?"* and "*what do nurses hear that makes them aware a patient might die in a few days*?*".* The focus groups were audiotaped, and these were transcribed by 2 of the investigators separately to limit bias. The transcriptions were then analysed separately and results triangulated between 3 interpreters to form 9 discrete themes. Consensual validation and data triangulation using

	the literature was also used to increase validity.	
Themes with findings	Changes in respiratory function	Dying people often becoming progressively dyspnoeic, potentially as a relation to increased pulmonary oedema or effusions: '*you often see them (patients) being restless at night: they can hardly sleep due to this feeling of dyspnoea and their anxiety*'. They also mentioned oxygen desaturation, death rattle, and Cheyne-stokes respiration.
	Changes in blood circulation	Tachycardia, hypotension and fever were seen to be the most significant sign that a person is going to die soon, but some mentioned that they were sings of the end of the dying phase, rather than the onset. The significance of a pointed nose (the nose standing out very clearly against the rest of the face was also mentioned: '*It is so clear for us [nurses and colleagues] when we see a pointed nose*'.
	Deterioration of physical condition	lack of energy, energy surges, extreme weakness, somnolence or difficulty sleeping, bed bound, and extreme fatigue. '*Patient have such a blank stare; it looks like they sleep with their eyes open*'.
	Changes in psychological condition	The patients can become anxious and agitated '*Yes, a couple of days before, they [patients] get anxious, especially in the evening and night and they want to have family around then. They also become socially withdrawn, and can make despondent comment things such as '"It is finished for me now"*'.
	Reduced oral intake.	The oral intake greatly decreased along with appetite and sense of taste, and reduced weight and cachexia. Problems with swallowing medication were also mentioned.
	Changes in excretion	Decreased production of urine, urinary incontinence without apparent cause, vomiting and altered dedecation. Laboratory findings also change including uraemia and renal failure.
	Changes in consciousness	Mental confusion, decreasing consciousness and signs of delirium.
	Pain-.	Increasing pain that is less respondent to treatment.
	Changes in spiritual experience	Existential changes such as a lack of hope, and saying goodbye, and for some people a sense of relief or resignation '*Patients often say something like, it is good the way it is now, and they are at peace with it [dying]'.*
	Complexity of recognising dying	Some commented on the uncertainty of diagnosis due to the heterogeneity between different causes of death on end of life symptoms: '*I hardly ever see a transition or something like that, that makes me thing: these are the final days [for that patient]*'. Others commented on the importance of intuition in recognising dying.

Limitations	This was a small review included only nurses from 4 wards of a hospital. It did not specify what the oncological diagnosis of the people the nurses in the group had recently looked after had. Also, although this study related only to oncology patients, the stem questions such as 'What do you think nurses perceive in patients whom they think will die in a few days?' did not specify oncology patients. The results of the data analysis were not returned to the study participants for validation.
Applicability of evidence	Answered question set using reliable methods, although small scale, it comments it had reached data saturation before the last focus group.

H.2 Communications

Table 28: Anselm 2005

Study (RefID)	**Anselm 2005[28]**
Aim	To determine the barriers to communication regarding end-of-life care
Population	n=67 healthcare professionals (10 attending physicians, 24 residents,33 nurses)
Setting	General medical unit at a tertiary referral unit in Canada
Study design	Focus groups
Methods and analysis	Participants were segregated into 11 homogenous (in terms of training, status and experience) focus groups to facilitate open and frank discussions. Each group was led by 1 or 2 interviewers with experience in qualitative research in medical settings. Sessions were approximately 1 hour in duration. Participants were paid a small honorarium. Interview schedule designed to elicit information on 1) who was responsible for initiating end-of-life discussions 2) perceived institutional, patient and family barriers to discussion 3) personal difficulties in initiating and participating in such discussions 4) views on what should happen during such decision making 5) personal and institutional problems encountered 6) how hospital management could help facilitate the resolution of these difficulties 7) suggestions on interventional strategies for educating providers on approaching end-of-life discussions. Qualitative analysis of content. Audiotapes of interviews were transcribed verbatim. Six analysts with qualitative research experience independently reviewed the transcriptions and identified word clusters that corresponded to discrete ideas related to barriers. A list of themes describing these ideas was developed by each analyst, then themes were distilled using the Delphi method.
Themes with	**Recipient barriers**

Study (RefID)	Anselm 2005[28]
findings	• **Exclusion by family of patients or their wishes** "I've had a couple of instances where the patient himself/herself was very calm and could appreciate the discussion and could carry on a reasonable conversation but the family didn't want this discussion with the patient. Quite often we tell them that that's inappropriate because where they can, the patient is still in charge of his or her own decision making. On occasion the family is the biggest barrier" • **Difficulty in designating a decision maker or reaching consensus** Families have difficulty either determining who the decision maker is, or what the family's consensus is regarding the desired level of intervention. **Family tensions** Coping mechanisms of individuals increase family tension and make it difficult to establish communication. These feelings include feelings of intense guilt, relieving stress through confrontation and distancing themselves from the discussions. *"The family wanted us to do everything despite realising that it was futile and that this patient was going to suffer and so we felt that there was some inner guilt in the family members. They just wouldn't let the patient pass on and they would let us use the right to make the decision not to resuscitate".* • **Differences in culture or values** Certain cultures religions or other sources of deeply held values may conflict with those of providers • **Variable capacity to understand and appreciate discussions** Patients or family incapacity to understand or appreciate these discussions limits communication "*Quite often the family is confused and although you have an idea about how you want to manage the patient and what would be appropriate actions, the family doesn't necessarily understand you".* • **Appropriate timing** A poorly timed discussion may raise anxiety in or alienate people who are relatively well, young, insufficiently informed about their condition, afraid of death, unprepared for death or who have not achieved closure in a personal relationship. • **Temporal lability of appropriateness of resuscitation** The appropriateness and desirability of resuscitation might be different at different times for either the patient or provider.
	System barriers
	• **Suboptimal coordination of information exchange** Providers in teaching hospitals do not communicate optimally with each other or with other institutions regarding end-of-life discussions even if these have occurred previously. The system for sharing information is inefficient. The resultant uncertainty regarding optimal management can delay initiation of communication. • **Impersonality of large teaching hospitals** Teaching hospitals are large impersonal institutions care is typically short-term with minimal involvement of community providers.

Study (RefID)	Anselm 2005[28]
	"It's not easy, Decisions for us are different from those made by long term care physicians; our usually short term relationship with patients can pose a barrier… my willingness is reflected by my not really knowing the patient on a long term basis" • **Providers unskilled in discussions as a result of specialization in certain areas** In teaching hospitals care is specialty-based; certain specialties are unskilled at conducting (or recognising the need for) these discussions. • **Scheduling difficulties** Busy work schedules of providers and the physical environment of hospitals make it difficult to arrange for private discussions. • **Lack of external support** External factors work against providers to create barriers to discussion: fear of legal action, lack of effective policy documents, and lack of institutional resources including education programs, better staffing or 24-hour support for ethical decision making by resource people. • **Risk of abandonment for "DNR" patients** "DNR" labels the patient and leads to abandonment or less aggressive care by others *"One of the problems that I've come across is that when you do put a DNR on a patients chart they frequently do not get the sake care that they should get up until the point where they have to be resuscitated, It does brand them…that's the one barrier that I have to the idea of DNR"*
	Provider barriers
	• **Inadequate expertise in prognosticating and leading discussions** A lack of expertise due to inadequate training or inexperience makes providers feel uncomfortable about leading these discussions • **Discomfort with emotion involved** Identification with the person and/or other emotions, makes these discussions difficult *"Some doctors have difficulty…we had 3 physicians recently who, no matter how hard we tried, they never would talk with the patients and family about this… they themselves had difficulty dealing with it… they couldn't come to grips with it"* • **Role ambiguity** Providers' roles and responsibilities in this domain are not well outlined; they fear reprimand due to overstepping the boundaries of their position • **Prognostic uncertainty** Providers prefer not to discuss end-of-life care until they are certain that the patient's prognosis is dismal. *"Often you don't know with 100% certainty that there's no hope… It's awkward but I guess you can say that the chance is unlikely or less likely. However, people often want you to be more specific and that's hard because again, you just don't know"*
	Dialogue barriers
	• **Nature of "DNR" that may be perceived as nonsensical or defeatist** Discussing or ordering "DNR" is either nonsensical (because it specifies things not to do which is unique) or inappropriate because it is seen as being defeatist

Study (RefID)	Anselm 2005[28]
	• **Societal values surrounding death** Society does not generally recognise or appreciate death as a natural and acceptable part of life this is reflected in expectations of unrealistically high survival rates from CPR due to media portrayal. • **Lack of trust in providers commitment or competence** Recipients of care lacked trust in providers. They questioned providers' commitment or competence by charging that issues such as resource allocation were interfering with acting in their interest or by simply not believing their diagnosis or prognosis.
Limitations	Serious limitations – unclear what precisely is encompassed by the phrase "end-of-life discussions".
Applicability of evidence	Context not specific to discussion of likelihood of entering last days of life but appears, from themes elicited, to be part of issues discussed within focus groups. Setting outside UK, therefore system barriers may not be appropriate for UK context.

Table 29: Aslakson 2012

Study (RefID)	Aslakson 2012[31]
Aim	To identify nurse perceived barriers to effective communication regarding prognosis and optimal end-of-life care for surgical ICU patients
Population	n=32 SICU nurses
Setting	Surgical intensive care unit, tertiary referral centre in USA
Study design	Focus groups.
Methods and analysis	Four focus group sessions were convened. Open-ended questions focused on the nurses' perceptions of communication regarding prognosis, "Prognosis" was defined as incorporating whether or not the person was likely to die during the hospitalisation and and what would be the quality of life during the hospitalisation and after discharge. Qualitative analysis of content. Written notes taken during discussion were compared and pooled and content analysis technique used to identify major themes emerging in the discussions. After initial validation of the domains by the study investigators these domains were disseminated to a subset of 10 nurses who participated in the focus groups for verification.
Themes with findings	**Logistics**
	• Surgical team rounds before family is present • Cannot assemble entire team (intensivists, surgeons, nurses) • Not all parties present when meetings do occur

Study (RefID)	Aslakson 2012[31]
	• Other support resources not always available (social work, pastoral care, palliative care) • Insufficient time during meeting • Poor availability of doctors or family for a meeting • Multiple decision makers in a family • Surrogate decision maker not at the meeting • Meetings interrupted by healthcare provider pagers and/or telephone calls • Lack of unbiased person • Patient cannot participate in conversations • Unclear what prior specialists and consultants have said regarding prognosis.
	Discomfort with discussion
	• Physician discussions with nurses and families are inconclusive • Family members do not want to "hear bad news" and avoid meeting • Prognoses are unrealistic and often portray "small victories" instead of overall prognosis • Unclear whose role it is to discuss prognosis and no one ends up doing so • Poorly defined goals of care, even prior to surgery.
	Perceived lack of skill or training
	• Physician discussions are rushed • Families are not given adequate time to ask questions • Communication is done "last minute" often before a procedure • Families are unaware of a patient's diagnosis • There is no accepted protocol about when and what to communicate • If families do not ask for meetings they will not receive them • Physicians both use language that the family do not understand and do not recognise it • Families do not remember to ask all their questions • Families do not know what resources are available to them • Fear of legal ramifications of bad outcomes
	Fear of conflict
	• Different opinions about prognosis between care providers

Study (RefID)	Aslakson 2012[31]
	• Inconsistencies between team members in communicating prognosis to families • Surgery and ICE teams rarely discuss prognosis but get angry when nurses discuss it • Difficult personalities of some healthcare providers.
Limitations	Serious limitations
Applicability of evidence	Population of intensive care unit not representative of review population, but many aspects explored in the analysis may be applicable to the wider population.

Table 30: Gutierrez 2012

Study (RefID)	Gutierrez 2012[191]
Aim	To describe the experiences and needs of family members surrounding prognostic communication for people at high risk of death in an ICU.
Population	n=20 family members of people with a greater than 50% chance of in-hospital mortality on the basis of clinical criteria. Female: 70%, white: 90%
Setting	22 bed adult medical/surgical ICU in a community hospital in the USA
Study design	Semi-structured interview.
Methods and analysis	Purposive sampling used; families were interviewed (either in the family waiting room in the ICU or in the patient's own room) until data saturation occurred. An iterative content analysis data process was implemented.
Themes with findings	Experiences with prognostic communication.
	• **Hearing and recalling information** Family members described cognitive difficulties and feeling overwhelmed by the situation. This was greatest for those who did not anticipate hospitalisation, when events happened unexpectedly. Their ability to think and process information was perceived as being much slower than usual. *"Communication is difficult for two reasons. One, as a family member you are so overwhelmed by what's just taken place especially if it's in a situation like this where it was so unexpected. There's not been a process of she's getting worse. This was a sudden thing…Cause you're so overwhelmed that you forget everything that has been in place (discussion of patients wishes) before this crisis happened".*
	• **Accessing information** Family members perceived a need to gather information regarding the person's condition, treatment plan and prognosis throughout the stay, representing a significant form of work. While easy access to nurses was appreciated it was noted that they were often too busy to sit down and talk with families. Most family members described wanting to talk to a physician. They described frustration with the amount of time waiting to talk to a physician as well as difficulties knowing who to ask questions of and knowing who was "in charge" of decisions (due to a number of specialities being involved

Study (RefID)	Gutierrez 2012[191]
	in care). Rotation of healthcare staff also provided difficulties to family members, having to get to know different providers in order to develop a relationship upon which to access information.
	• **Interpreting information** Once they were able to access and "hear" information, family members often struggled with making sense of it. Family members found it difficult to clarify their understanding since they did not possess a foundation of knowledge in order to be able to identify appropriate questions. If they did have questions many either did not know who to ask or did not want to ask due to a fear of "looking stupid". If information was unclear many family members formed interpretations based on assumptions or simply "wondered" about possible interpretations. Some families turned to the internet for clarity. *"I have seen nurses in different hospitals talk to my dad and explain information to him and he keeps nodding his head and no one ever asks "can you repeat back to me what I just told you? And I wish they would because I am sure my father did not understand anything he was just told. People just don't want to look unintelligent, so they don't always ask questions even though they don't understand the information being presented to them. Sometimes you don't know who to ask and you don't know what to ask".* *"It's difficult to interpret simple words like 'good'. Physicians say the patient is 'doing good' and that means 'doing good this hour', whereas the families interpret this as 'hooray he's recovering let's have a party' and then when the patient gets worse, they get really blown away".*
	• **Retaining new information** Most family members described significant difficulties retaining information even after then initial shock of admission had passed. Families often coped with this difficulty by utilising memory aids such as keeping notes.
	• **Utilising information for decision making** The availability of healthcare directives helped to decrease family members' perceptions of anxiety and burden in making decisions, but did not always fully obviate the cognitive struggle regarding the appropriateness of decisions, which was frequently ongoing. Often families' worries focused on the response of the person to the decisions if the person survived, especially how decisions might impact their relationship with the person and the person's quality of life after discharge. Thus, utilizing information for decision-making and on-going evaluation of decision-making was a significant type of information-related work for family members, which was perceived as extremely stressful. Families of 2 people who were very concerned with goals of quality of life for the person and following the person's wishes, which conflicted with the critical care physicians' goal of patient survival. Both families wanted to withdraw life support because they perceived it was what their loved ones would have wanted based on their healthcare directives, previous discussions with the people before they became ill, and past actions on the part of the person (for example, making themselves Do Not Resuscitate in previous hospitalisations).However, in both of these situations the people were showing signs of improvement, so the physicians were reluctant to withdraw support at that time.
	Needs related to prognostic communication
	• **Content** "There was a consistent message conveyed by families, which said, "You have to hear the hard news but it is not easy to hear." Only one family member did not want to hear any "bad news" for the first 2-3 days after her husband was admitted to the ICU. She was a registered nurse and

Study (RefID)	Gutierrez 2012[191]
	knew from the information communicated by the physician that her husband was dying. She stated her way of coping with this devastating news was to deny it was happening. Thus, she stayed in the family waiting room, would not go into her husband's room, and refused to listen to any "bad news". Instead, the rest of the family communicated with the providers on her behalf. Besides this exception, all family members interviewed described a desire to receive honest, realistic information first and foremost, tempered with hope only when appropriate. They wanted both the good news and the bad news in order to get a "perspective" of the situation, a "reality check," so they could use this information to prepare themselves for possible outcomes. Consistency of information provided was also important and influenced the level of trust family members perceived towards providers.
	• **Style of communication** "Families wanted information communicated in a manner that was respectful, compassionate, and caring. Family members described that it was much easier to hear and cope with bad news when it was communicated in a caring, sensitive, compassionate manner. For some, the desire and need to perceive that providers genuinely cared extended beyond the manner of verbal communication to include communication via body language, actions, and even the perceived type and level of energy of providers when they were around patients and families. Most families wanted to know that providers genuinely cared for both the person and family and that "it's not just your job"".
	• **Communicator of prognostic information: who is saying it?** Families suggested that being able to develop a relationship with only 1 or 2 healthcare providers would have facilitated families feeling "heard".
Limitations	No limitations
Applicability of evidence	Population of intensive care unit not representative of review population, but, many aspects explored in the analysis may be applicable to the wider population.

Table 31: Jackson 2010

Study (RefID)	Jackson 2010[236]
Aim	To explore the perceptions of relatives and health care professionals of care pathways in the last 48 hours of life.
Population	Bereaved carers and healthcare professionals
Setting	UK
Study design	Research nurses compiled through medical coding a list of all people who had died within 48 hours of admittance to hospital. Clinical consultants reviewed the patient notes and decided whether in their opinion the person could have been cared for at home. Demographic data was taken from the medical records. Semi-structured interviews were undertaken with the bereaved carers and 'key informants' including hospital consultants, chaplains, porters, hospital nurses, ambulance staff, hospice at home assistants, and nursing and residential home staff. Percentage of staff type included, or how the bereaved carers were recruited was not provided.
Methods and analysis	a 'collaborative approach' was used involving several team members (unclear if same across all interviews) reading the transcripts and identifying themes. These were then coded by the researchers.

Themes with findings	**Unpredictability:** *'"You know, I had asked how long [until death] and t[the doctor] said "how long is a piece of string". I mean, fair enough, but [other healthcare professionals] kept saying: "she is not ready to die."*
	Privacy: Relatives and staff did not perceive the acute environment to be the ideal place to die, in particular because of its lack of privacy, which was exacerbated by the use of paper curtains around beds: *"There was my dad, an 88 year old man, looking dreadful on oxygen and being moved. There were visitors everywhere and noise everywhere. [I do not know] why they had to move my dad from a very very peaceful area [while] telling me he only had hours left to live. [He was] pushed into a bay and all squashed in.'"*
Limitations	Poorly reported study. No information given on what questions were asked in the semi structured interviews, so hard to extract meaningful conclusions from data provided.
Applicability of evidence	Very applicable setting, as UK hospital based, including those important to the dying person and a multiprofessional team involved in their care. However, the subject is potentially not applicable as it is far wider than communication of prognosis, and no information about what questions were asked is provided.

Table 32: Houttekier 2014

Study (ref id)	Houttekier 2014[223]
Aim	To examine to what extent physicians are aware of the impending death of their dying patients and if awareness is related with communication and quality of dying in the last 3 days of life.
Population	Physicians at a University Hospital asked to complete questionnaires regarding 228 people who had died between Jun 2009 and February 2011
Setting	University Hospital in the Netherlands
Study design	Retrospective survey
Methods and analysis	Thirty five-item survey instrument used. Physician and patient characteristics were recorded about as well as physician awareness of impending death of the person and communication about impending death with their relatives and family. Treatment during last days of life and physician's rating of the person's quality of life during final 3 days and quality of dying (using a numerical rating scale 0-10) Bivariate association between awareness of impending death and physician communication in the last days of life were analysed using Pearson's chi squared test.
Survey findings	More likely that physicians discuss death with patients when physician is aware of impending death than unaware (57% versus 39%) More likely that physicians discuss death with relatives when physician is aware of impending death than unaware (5+% versus 39%)
Limitations	Very serious limitations.

Study (ref id)	Houttekier 2014[223]
Applicability of evidence	Setting outside UK, but, findings applicable to UK context.

Table 33: Sullivan 2007

Study (ref id)	Sullivan 2007[426]
Aim	To describe whether and when physicians report recognizing and communicating the imminence of death and identify potential barriers and facilitators to recognition and communication about dying in the hospital
Population	n=196 physicians as part of teams caring for 70 people who died in hospital, USA
Study design	Cross-sectional survey
Methods and analysis	Medical records of people recently deceased were randomly sampled for inclusion in the study and a median of 3 physicians participated in interviews about each sample patient case. Patient cases with a minimum of 2 responding clinicians were included in analysis. Clinicians participated in interviews 90 minute semi-structured interviews in which they were asked both closed and open ended question about the person's illness and death. Patient data from medical records were also abstracted. Variables for timing, recognition of and communication of likelihood imminent death were constructed from open-ended questions in physician interviews. Other quantitative physician-level variables were drawn from closed-ended survey questions. Bivariate analyses using chi squared tests of independence and t-test were used to analyse associations between physician or patient characteristics and recognition of imminent death. Then multiple logistic regression models were used to assess predictors for whether discussions occurred with the person.
Survey findings	Certainty of physician that the person would die during the hospitalisation was associated with discussion of possibility of death with patient and family. Proportion of people with whom possibility of death was discussed according to physician certainty of prognosis: Uncertain 0%, certain hours before death 30%, certain days before death 51.2% Proportion of families with whom possibility of death of relative was discussed according to physician certainty of prognosis: Uncertain 33%, certain hours before death 100%, certain days before death 97.7%, certain 92.9% Time at which physicians became aware of likelihood of death during hospitalisation was significantly associated with discussion: Controlling for person age and level of consciousness, OR 3.4 95%CI 1.28-9.08 comparing physician confident of prognosis 1 week prior to death and confident of prognosis days before death. Physicians were more likely to discuss possibility of death during hospitalisation the older the person was (p=0.06 Wald test in logistic regression).

Study (ref id)	Sullivan 2007[426]
Limitations	Very serious limitations.
Applicability of evidence	Setting outside UK, but, findings applicable to UK context.

H.3 Shared Decision Making

Table 34: Abbott 2001[6]

Study (ref id)	Abbott 2001[6,21]	
Aim	To identify critical psychosocial support and areas of conflict for families of intensive care unit patients during decisions to withdraw or withhold life sustaining treatment.	
Population	n=48 family members of a prospective cohort of critically ill people for whom the issue of withdrawing or withholding life- sustaining treatment was discussed in 1 of 6 ITU's. The person's 'next of kin' was identified and interviewed 18-22 months after this event.	
Setting	USA.	
Study design and methodology	Semi structured interview with the participant in person or by telephone. Respondents were asked to describe in their own words their experiences while their family member was hospitalised in the ICU and the decision making process for withdrawing or withholding life sustaining treatment.	
Analysis methods	The interviews were transcribed, and a random sample of these were analysed for potential themes. These were coded independently by two investigators. Disagreements were resolved by consensus on discussion.	
Themes with findings	Conflicts with the next of kin over decision making were present in 7 of the 48 cases (decisions include the decision to withdraw or withhold treatment, pain control, perception of care or communication).	
	Facilitators	Barriers
	Family and social support	Disrespect: *" there was one doctor… he found out she (the sister in law) was [a nurse], he turned directly away from me and giving her every bit of the information and asking her all of the questions and it was like I was not even there. This doctor really almost blew it… because I was the one that should have been; he should have been talking directly to."*
	Spiritual or faith support	Not enough information shared *" Me and [Attending].. had a major disagreement on o on one occasion*

Study (ref id)	Abbott 2001[6,21]	
		when [patient] came in, and it was only due to the fact that the doctors were not giving us enough information [patients] condition… that's a major point with a lot of these families is they're not getting enough feedback and it makes you get more tense and more upset when thing do happen, when you do not know what's going on".
	Previous knowledge of patients opinion *" But he made all the decision… I did not make a single decision because he said he did not want… me to feel that if I'd had it done this way things wouldn't have happened… And I did not… sign a single paper from the time he started, he did it all".*	
	Private space for discussion "*There was a critical need for space for family conferences. There was one family there when we were there and they clearly needed to have conversation and make big decisions. And there was nowhere for them to be,. We Left the waiting room and shut the door one time because they were having a serious conversation and they clearly needed privacy and the waiting room was so tiny".*	
	The quality of care received- the knowledge that everything possible was done to save the person eased the decision making process.	
Limitations	Serious limitations. The reliability was calculated using the Kappa statistic. Kappa scores were >0.5 for 12 of the 14 codes and >0.4 for the remaining two codes, indicating moderate or better agreement.	
Applicability of evidence	USA healthcare setting.	

Table 35: Additcott 2012[13]

Study (RefID)	Addicott 2012[13]	
Aim	To identify what particular barriers exist for non-cancer patients in accessing end of life care support.	
Population	n=141 NHS and other service providers:	
	Role	**n=**
	District nurse	10

	Healthcare assistant	2
	Hospice nurses	5
	General practitioner	3
	End of life care (or palliative) consultant	4
	Hospital specialist	4
	Practice nurse	6
	Delivering choice programme team member	11
	Service manager	39
	Specialists nurse	20
	Ward nurse	11
	Adult social care	7
	Care home staff	19
Setting	Three local health economies in England.	
Study design	Not described	
Methods and analysis	Not described	
Themes with findings	**Disease trajectory and patient identification-** It is more difficult for clinicians to identify the stage at which non-cancer patients enter the end of life phase, or when they may benefit from more palliative support. This was in relation to the unpredictable nature of the disease trajectories for non-malignant diseases such as chronic heart or respiratory failure which affects prognosis. Participants reported concerns about the cost and resource implications of referring non-cancer patients to end of life services, particularly those who could be receiving such care for a long time period. Clinicians were wary of repercussions from the local funding body if inappropriate or costly referrals were seen to have been made. One Macmillan nurse reported: "*If you're talking about palliative care for somebody with MS [multiple sclerosis] you're looking at a very long period of time and support and I don't know if [dedicated end of life care providers] can sustain that, that that palliative patient on, because that could be 10, 20 years of their time*"' Some participants believed that it was possible to identify when people were entering the end of life phase. These views were predominantly from disease-specialists from non-cancer areas, and they acknowledged that these clinical triggers would not necessarily be so easily identifiable to a generalist health professional who may have had less of a history of interaction with a particular person.	
	Care planning and prognostication- Participants reported that clinicians frequently fail to discuss the prognosis and subsequent preference and care planning with non-cancer patients for the following reasons: ● Non-cancer diagnosis acts as a barrier "*... what's going to have to change, what we're going to have to get better at, is being honest and open and having those discussions with people. There's more of an honesty in managing cancer patients about how things are, what the*	

	prognosis is, what the future holds, that doesn't exist in other diseases yet" ● "[clinicians] Shy away from those sorts of conversations because they are difficult conversations to have" ● Reticent to stopping treatment in non-cancer conditions as many people may be in the end of life phase for a prolonged period of time, and difficulty, particularly in hospital of 'admitting defeat': '*"What we've seen is that doctors are able to diagnose dying very successfully… but what they don't do necessarily is then put the appropriate management systems in place to support that. So for example they recognise that the patients dying, but they find it very difficult to take down the drip, to stop the drug, to communicate to the patient and the relative that that's actually happening"'* ● Many participants felt it should be the responsibility of the consulting doctor and specialists. One nurse reported: "*The family have got to be told that they are near to death. I would not go in and talk about discharge and fast track [funding] without that [conversation] being done first and I don't think it's a nursing job… because there are normally more questions coming back. And the last thing I want to say is 'actually I don't know".* ● Some clinicians found it easier to have discussions with the family and carers rather than the person directly: "*It is very difficult. If I am honest, I don't tend to ask the patient-which is awful. I should do, I know. I tend to ask the family what their views are and then hopefully they discuss it with the patient"* ● Some staff expressed anxiety about having discussion with people regarding their preferences as they were unsure what support services were available to meet these preferences, or knew that in that area these services were not available.
Limitations	Very serious limitations. Very poorly described method and analysis section. No information on data saturation.
Applicability of evidence	Unclear what definition of end of life care was used. The quotes suggest that it encompasses both the last days of life and the last months.

Table 36: Almack 2012[21]

Study (ref id)	Almack 2012[21]
Aim	To explore the factors influencing if, when, and how advance care planning (ACP) takes place between healthcare professionals, patients and family members from the perspectives of all patients involved and how such preferences are discussed and are recorded.
Population	The study identified subjects from an existing audit looking at care delivered in the last 4 weeks of life. The patients were asked to nominate a family carer/relative to be interviewed and a healthcare professional that was involved with their care at home. Participants ranged from 59-90 and included diagnosis ranging from cancer to cardiovascular disease such as heart failure or stroke. n=18
Setting	UK primary care
Study design and methodology	Interviews were initially with people regarding their understanding of their illness and current state of health/illness. They explored how they felt about the care and support they were receiving from family, friends and healthcare professionals and in their view how well informed they felt they had been from their healthcare professional.
Analysis methods	The transcribed interviews were initially read through and themes decided and a coding framework developed in collaboration between the

Study (ref id)	Almack 2012[21]	
	investigators.	
Themes with findings	Facilitators – from the healthcare professional	Barriers - from the healthcare professional
	Rapport with the patient "*It's important we've built up a rapport with the patient… and that's why we like early referrals so we get to know the person"*	Inexperience: the need for training and developing experience in advanced communication skills
		Unwillingness of person and relatives to have these conversations "*It's very much led by the patient: if they want to know…how they are doing whatever and be guided intuitively by them really. There are some patients who will be very open and frank with you and use all the right words but there are others that will day to you or indicate 'I know where you're going with this and I don't want to hear"*
		Uncertainty of trajectory with long term condition " *If you think they're coming towards end of life with all the uncertainty around heart failure, you want to discuss that, but at the same time, you don't want to take away all their hope"*
	Facilitators – from the patient	Barriers- from the patient
	Initiative of patient – From the healthcare professional- "*We've talked to them about where he wants to die and what the future possibly holds and how she is going to cope what services are available, that's been a conversation we've had right from the beginning and a couple of times they've initiated it to re-visit".*	Not accepting of prognosis/wanting to think far ahead. *"no not at this time because I don't see myself as being that far down the road yet, I'm still quite positive, well apart from when I'm feeling really ill".* Healthcare professional- *"he never actually asked him where he would like to die. It was always a case of let's see what's happening with you and he steered you away form that all the time".*
Limitations	Serious limitation. Data saturation not commented on.	
Applicability of evidence	Indirect population, unclear on whether information was drawn from those in the last days of life, or earlier then this time point.	

Table 37: Boot & Wilson, (2014)[58]

Study	Booth & Wilson, (2014)[58]

Study	Booth & Wilson, (2014)[58]
Aim	To identify the challenges experienced by clinical nurse specialists (CNSs) when facilitating advance care planning (ACP) conversations with terminally ill people.
Population	HEALTHCARE PROFESSIONALS: Twelve community-based CNSs with at least 1 years' experience working as a CNS. The participating nurses worked in two geographically separate teams caring for people with advanced progressive diseases.
Setting	One team was based in an urban location and one in a more rural area (Hertfordshire and London, UK).
Study design	Individual semi-structured interviews.
Methods and analysis	Interviews: It is stated that 'semi-structured interviews allowed the researcher to follow a theme raised by the participants and to incorporate questions in later interviews as particular ideas arose. Interviews were audio-recorded and transcribed verbatim. Data analysis: transcripts were analysed inductively meaning that they were read and individual words, phrases, and segments of text were assigned a code that described the issue being outlined (for example, timing). Codes were then discussed with another researcher and verified. Similar codes were then amalgamated into themes.
Themes with findings	**Opening the discussion (timing):** CNSs felt the issue of who to open a discussion about advance care planning a challenge. They experienced a balancing act of providing sufficient opportunity to engage with the person whilst also recognising that some people may not to discuss such topics. Quote: *'[I] feel there is a moral obligation to do the best you can to be in touch with what people would like so we can plan sensitively for their future. It is that kind of moral dissonance about getting the timing right. Not robbing of the opportunity but not stepping in insensitively.'*
	Personal issues (sociodemographic, family dynamic and emotional): Nurses believed that advance care planning was better if it took place in the context of a relationship. They felt that this was an important prerequisite and facilitator in this process. Getting to know the person allows the nurse to gauge when they are ready to discuss issues related to ACP. However, even when a person is known to the nurse it is possible to misread the cues. *'I really try and do it so that I keep a good relationship with people ….I think it is important that I hang on in a relationship and I am allowed to continue to visit and supporting people than to maybe get into a conversation that might destroy that because they don't' want me to have it.' Family dynamics were also seen as important and could be challenging. The nurses reported that there is a need to balance support to the family with prioritising patient needs'*.
	Ethical issues (organisational – policy, documentation, teamwork): This could be also related to family dynamics for instance when relatives insist on further treatment for the person who is dying because they are in denial.
Limitations	Very serious limitations. The interview procedure is poorly described. It is just described that it is semi-structured but the overall structure of the questions that were posed were not described. It is also unclear how often or how long interviews took place apart from a general time of 'over a 3 month period'.
Applicability of evidence	Directly applicable evidence from UK setting.

Table 38: Caron 2005[85]

Study	Caron 2005[85]
Aim	Examine the experience and preoccupations of family caregivers about end-of-life issues, and more specifically, about treatment decision-making processes in the context of advanced dementia.
Population	FAMILY: Research sample consisted of 24 family caregivers involved in the care decisions for an older family member with late-stage dementia, as documented in the person's medical record. A total of 20 care givers (4 spouses, 5 sons, 8 daughters, 2 nieces and a widowed daughter-in-law) agreed to be interviewed. The adult children and nieces ranged in age from early 40s to mid-70s. Among the caregiving spouses were 1 wife in her 60s, 2 women in their 70s and an 83-year-old man. At the moment of interview, 3 sons arrived with their wives and 1 wife requested that her son be present for their interview, resulting in interviews with 24 caregivers (17 women and 7 men) for 20 relatives with late-stage dementia. Regarding people with dementia, 15 women and 5 men aged from 63-96 years were receiving care in the long-term care facilities. Of these, 16 had died within the year prior and 4 were still alive at the time of the interview. The presence of dementia varied from 2 to 22 years and the period of institutionalisation ranged from 1 month to 16 years.
Setting	Canada. Two types of long-term care facilities were involved in the study – a university geriatric institute and a group of publicly funded long-term care centres.
Study design	Grounded theory method of qualitative research was used. This allows a substantive theory to be generated that depicts the actions of individuals in a given social context.
Methods and analysis	The recruitment strategy sought to interview the principal caregiver, as identified by two types of long-term care facilities involved in the study. Following the imperative of theoretical sampling, the selection criteria in this study evolved with the development of the theory as key factors appeared, including differing relationships (spouses, children, nieces) and genders. Each caregiver dyad participated in one in-depth interview, lasting approximately 1 hour and was recorded on audiotape in order to collect data in narrative form. The audiotapes were subsequently transcribed for analysis. IN the grounded theory approach, the questions posed during the early interviews were open-ended questions. As the research progressed through an iterative process, the analysis of each interview prompted questions for subsequent interviews. The constant-comparative method and line-by-line/dimensional analysis were used to code each interview. To ensure that personal beliefs of research team members were not imposed on the subject matter and to allow cross-validation in the interpretation of the interviews, at least two members of the research team participated in the data analysis sessions.
Themes with findings	One dimension that has an important influence on the decision-making process was the context of the interactions that caregivers had with healthcare providers. The 4 elements of this dimension are quality of the relationship, frequency of contact, values and beliefs and level of trust.
	Quality of the relationship: Family caregivers seek a personalised relationship with the care providers; personalised in the sense that the care team both understands the needs specific to the caregiver's situation and displays empathy. In the absence of a personalised relationship, it was more difficult for family caregivers to have a sense that their experience was understood and considered important by healthcare providers, and thus more difficult to

Study	Caron 2005[85]
	promote their viewpoint regarding care of their loved one. 'The first meeting [with the care team] was quite formal. I mean, we had forms that we had to fill out. It seemed pretty routine to them. I think that those people are really pressed for time. It would be nice to take the time with them, just to talk and get to know each other a little more, it would make a difference. But they just don't have time for that. If they'd taken the time, I think it would have changed everything. I mean you can't just put people in categories A B C D. You know, mark here and she's coded. C'mon, she's a human being! Each case needs to be looked at individually and each case analysed … according to what the family wants, who the person is, their past , how we will think tomorrow and then after her death … that would be really personalised, I think.' Niece 01. 'What I find with them [the care team], it's that they are a bit cold towards us, as if these things happen every day, and they have built up a shell to deal with all the complaints. I got that feeling, I felt a wall there. "Hey, say what you like but we did our best." For sure, I agree that they did their best, but I say to them "Just the same, you can't put all the patients in the same basket." Then they said "It's all in your head, because you are aware of it, but your mother, she isn't aware of it". Hey, just a minute! It's not as true as all that. So, it was difficult. From the first day I asked for a transfer.' Daughter 08.
	Frequency of contact: One of the greatest dissatisfactions expressed by the family caregivers who participated in this study relates to the limited contact between themselves and the providers working with their family members. Certain families met with the care team or the doctor at the time of their relative's admission to the centre in order to clarify family expectations with regard to treatment and to answer any questions about the person and his or her living conditions, whereas other families had no such meetings. Certain caregivers wished that regular meetings with the healthcare providers could have been planned. 'Well, for me, I think that in terms of the relationship [with the] family, it might have been good to have meetings with the staff, to see what is going on with [my relative], treatments, the evolution of the disease as well as getting to know each other a little bit. It would reassure us. When we can see that they really are interested in the patients and in us as well. But sometimes we get the impression that we are important but when it comes to the care of the patients, we don't have a lot of say. Perhaps if we met regularly, we'd have a little more say in the decisions being made.' Niece 01. 'It would have been good if, once a year, someone who really know what was going on with [my relative living in the long-term care setting] would have said to us "well, such and such a thing happened, things are like this now but we're expecting this to happen." Maybe we could get like an update once a year. It wouldn't be a bad thing. And if we wanted to know more, we could phone the doctor. But rather than having to do this ourselves, and there are certain people at certain times, who have trouble reaching the doctor … it would be … perhaps a good suggestion to have someone meet with us once a year. Anyway, it would be a minimum, if you will.' Son 05. It is important to note that nearly all the caregivers who took part in this study expressed the need to meet more often with the care team, in a formal manner. The caregivers do not specify a particular type of professional. In their view, such meetings would provide an understanding of the evolution of the condition or illness of their relative, an opportunity to receive answers to their questions from knowledgeable professionals, reassurance with doubts dispelled and a sense of being involved. Few care givers were fully aware of their role as decision maker. *Interviewer:* 'So you're saying that it was important for you in those last moments, first of all, to be sure that she was not in pain?'

Study	Caron 2005[85]
	Family caregiver: 'yes, and to have someone answer our questions. Like, for us, they answered our questions. We asked them if we give her this, do you think that…?" and they told us "She will be more comfortable, but we can't give her more than 1 dose. They explained why and that was fine. We have to have answers to our questions. We're suffering too, but we need to know what is going on.' Spouse 03.
	Values and beliefs: Another dimension in the context of interaction with the healthcare providers that influences decision making, in terms of considering a medical treatment, is the concordance of values and beliefs between caregiver and the professional. The results of this study indicate that concordance of values facilitates decision making.
	Level of trust: 'Pre-existing trust' is an implicit trust accorded on the basis of the professional status and medical knowledge of the care team. Some caregivers did not feel the need to participate in care decisions because they did not see themselves as competent in this area. 'So for me, I let them do their job. It is completely beyond my ability, I don't know how [to administer oxygen]. They are the ones who know how to do that. We leave it in their hands because they know what they are doing.' Son 05. Caregivers with pre-existing trust are the least likely to feel the need to participate in medical decisions, delegating these decisions to the professionals. However, for many caregivers, trust is built through interactions with the care team in the long-term care setting – referred to as 'acquired trust'. 'It's not easy to abandon someone we love to other hands, many other hands. And the personnel is changing all the time. It's not easy, it's not obvious. And then, at one point we all become like a little family. We can trust them more. But they were being tested. And they passed. There was even an orderly who remarked to me "oh I'm so happy that I passed your test".' Daughter 02. 'Myself, I like to be consulted. After all, she's a member of my family, someone I love, and before treatment, I would like to be consulted before making a decision. So that I can ask questions, afterward, well, I tell myself that I can let them go ahead as they see fit … because in the end, how can I trust them if they do whatever they want, as soon as my back is tuned, without talking to me about it? I might lose confidence. I find that, trust is really important for the family to be able to trust these people, because we aren't there every minute of the day. And if we know that they have consulted us it's because they take our feelings into account, that's really good.' Daughter-in-law 02. A number of elements facilitate enabling trust: regular contact with the family, providing patient information on the progression of the disease as well as treatments to control symptoms, advising families of changes in the loved one's condition, establishing a personalised approach and considering the family as a partner in the care of the person.
Limitations	Serious limitations- Small sample size from a limited geographical area.
Applicability of evidence	Indirect evidence. Not all people had end of life decision making experience as 4 were still alive at time of interview. Results are not transferrable to all family caregivers, as participants in this study had a good relationship with their older family member with dementia and sought to be involved in the care of their loved one. Results may not apply to families with a long history of family conflict.

Table 39: Caron 2005B[86]

Study (ref id)	Caron 2005B[86]	
Aim	To explore the meaning attributed by family care givers to the end of life experience of a loved one with dementia.	
Population	Family care givers involved in the care decisions for an elderly relative with late stage Alzheimer's disease or a related dementia who was either alive or had died within the previous year, although no less than 3 months prior to the interview. These were recruited from long term care facilities, 1 with more medical input available and 1 with less. n=24. 16/24 of the participants loved ones had died within the last year, 8/24 were still alive. Of those who died, 1 died suddenly without intervention from septic shock. The remaining were treated with morphine, and some had oxygen, and antibiotics given in the last days of life as well.	
Setting	Canada in care home facilities.	
Study design and methodology	In-depth interviews were undertaken, these were then transcribed. Open ended questions were posed examples included: • Tell me about the last few weeks of your relatives life • What were (are) your concerns about the care of your loved one? • What were some of the decisions that you had to make about the care of your loved one? • How did making these decisions go? • How difficult was it to have a sense of what your (relative) was experienced? How did this influence the decisions you made? These questions became more narrowed as the interviews progressed and initial themes were analysed helping shape further questioning.	
Analysis methods	Each interview was coded using the constant comparative method and line by line/dimensional analysis. Particular attention was paid to the conditions under which the decision making process occurred and the consequences of this process for the caregivers their loved ones and other affected by the decision making process. Between 2-03 members of the research team participated in the data analysis sessions.	
Themes with findings	Facilitators	Barriers
		Ambiguity in the role of the surrogate decision maker: *"To know what I should do, what my role is. In the end we get so that we don't know any more"* "*oh they keep them alive as long as they can. It should be the family that decide or the person himself, he should decide. Instead of dragging things on… for a long time even. They should hold a meeting with the family and ask everyone if they agree or not".*
		Lack of medical understanding on part of surrogate decision maker: "*.. For sure I want to be told about major changes in medication. I have no way of evaluating whether it's necessary for her to have it or not, so what could I say about it? I don't see it".*

Study (ref id)	Caron 2005B[86]	
		"… Leave it in their hands as they know what they're doing".
		Unavailable for support/discussion "*It seems to me that, when there is something, a, a decision to be made, they make it among themselves in their office. Why we are not included in what is going on… It becomes such a routine to them that they don't think to let us know. So we, we no longer know what is going on".*
Limitations	Serious limitations. Not all the barriers and facilitators listed in the discussion are supported by the quotes or results described.	
Applicability of evidence	Indirect population. 33% of those interviewed relative had not died, and was not in the last days of life. Canadian setting.	

Table 40: Fields, et al. (2013)[159]

Study	Fields, et al. (2013)[159]
Aim	To explore clinicians' experiences of discussing preferred place of death (PPD) with palliative care patients.
Population	Healthcare professionals: Six hospice clinicians (1 staff nurse, 2 community nurse specialists, 1 specialist palliative care consultant, 1 day services nurse, 1 foundation year 2 doctor.
Setting	A Marie Curie Hospice which provides specialist palliative care services to a population of 500,000 people. Edinburgh, Scotland, UK.
Study design	Semi-structured interviews.
Methods and analysis	Interviews: Individual face-to-face interviews lasting between 30-50 minutes took place at the hospice. The interview approach was flexible and non-directive and aimed to elucidate meaningful, participant-derived accounts. Three broad question areas were covered: (1) What are your feeling on discussing PPD with patients? (2) Tell me about how you discuss PPD? (3) Tell me a bit about your experiences of talking to patients about PPD. Probes were used to encourage participants to expand on certain areas. Data analysis: Interviews were transcribed verbatim and analysed using interpretative phenomenological analysis (IPA). This is grounded in participant data and aims to capture and explore the lived experiences of a relatively small, homogeneous sample without testing any predetermined hypotheses. From the transcripts significant information was underlined and the transcript margin used to note initial interpretations, followed by descriptive, linguistic, and conceptual comments. The next stage involved identifying emergent themes which conceptualise important areas identified during the initial analysis. Through clustering related emergent themes superordinate and sub-themes were identified.

Study	Fields, et al. (2013)[159]
Themes with findings	**Staff view that PPD discussions are important:** Staff recognised the need for this topic to be discussed and felt that the opportunity to discuss the choices could have a psychological benefit. Giving a topic a high level of importance could act as a facilitator: *'It allows us to provide more holistic care to patients because it's not just encompassing their symptom management or their psychological support, it's also where they want to be at the end….so I think it allows us to fit that final bit of the jigsaw.'*
	Identifying when and how to discuss PPD: Participants felt that the initiation of end-of-life care discussions was seen as depending on the context and how prepared people are to confront such topics. As such the context of the hospice setting in itself may be a facilitator since it may already provide greater awareness of the proximity of death and people therefore anticipate end-of-life conversations. Finding the optimal time was seen important with one of the participant describing that if the discussion is initiated too early it could be perceived as uncaring. 'I've gone through a phase of it's not right … to pitch up on the first visit to say – Where do you want to die? - …Maybe that's the only thing that they've heard in the whole conversation … And then other times I thought well actually if their condition deteriorated would I know what they wanted and be able to advocate for them?'
	Reflections on emotional aspects of discussing PPD: Addressing end-of-life issues was experienced as emotionally challenging for both health professionals and patients. Dealing with distress can be difficult. *'Doctors tend to try and make people happy … you don't want to make people cry.'*
	Staff experience/length of service: With experience participants have realised that although people may be upset, they often value staff for being brave enough to explore these matters. *'I was always a bit frightened…about upsetting the patient, but since I've been working here I now realise that you're not really upsetting the patient, it's just it's a really sad topic.'*
Limitations	Serious limitations. Only 1 researcher coded the data. The interview procedure is only vaguely described.
Applicability of evidence	Indirect topic. The focus of the paper is restricted to the topic of preferred place of death, but the themes are generalizable to the overall review topic of shared-decision making.

Table 41: Hsieh 2006[224]

Study	Hsieh 2006[224]
Aim	To identify inherent tensions that arose during family conferences in the intensive care unit and the communication strategies clinicians used in response.
Population	Clinician-family conferences (n=51) in the intensive care unit from 4 hospitals in which the attending physician believed discussion of withdrawing life-sustaining treatments or delivery of bad news would occur. All conferences were led by physicians. A total of 221 clinicians, including 36 physicians, participated in the conferences. The number of clinicians in each conference ranged from 1 to 12 (mean 4.3). A total of 50 nurses participated in 41 of the family conferences (range 0-2, mean 1). A total of 25 social workers participated in 24 of the family conferences and 12 chaplains, priests or nuns participated in 12 family conferences. Finally 227 family members participated in the conferences (range 1-13, mean

Study	Hsieh 2006[224]
	4.5). The mean length of the conference was 32 minutes (range 6-73).
Setting	Intensive care units Seattle
Study design	Family conferences were observed and themes drawn from the discussions.
Methods and analysis	Family conferences were eligible if the physician conducting the conference believed the issue of forgoing life-sustaining therapy would be discussed or the physician planned to break the bad news. Of the 111 families eligible to participate, 17 families were not approached at the request of the attending physician or nurse caring for the person. Because of concern of potential litigation, another 2 were excluded for risk-management reasons. Twenty-four families approached by the nurse caring for the person refused to speak with the study staff. An additional 17 families spoke with the study staff but declined participation. Of the 111 families eligible to participate, 51 (46%) participated in the study. Only 2 conferences were excluded because of refusal on the part of the clinician (1 clinician and 1 nurse refused to participate). Eligible conferences were audiotape recorded. The analysis used a directed approach to qualitative content analysis where an existing theory or prior research findings influence the initial approach to the data. The dialectical perspective was used to narrow the focus of the analysis to the portions of the text that addressed communication about a contradiction (hence text was excluded that primarily focused on reviewing the person's condition and planning for future meetings). The dialectic perspective was used to identify potential initial odes for contradictions such as those that appear extensively in the ethics literature, for example, prolonging versus, allowing death or ordinary versus. extraordinary treatment. Coding was done using an iterative process. First the investigator listened to the audiotapes of the family conferences and read the transcripts throughout at least twice. Initial categories were re-examined continuously to promote clustering around common themes. After contradictions raised by either family members or clinicians were identified, the communication strategies used by clinicians in response to these contradictions were identified and coded into common themes. To ensure trustworthiness, identified contradictions and communication strategies were reviewed repeatedly by the other investigators who were experts in the content area and qualitative methodologies to validate the classification system and study findings. Other techniques sued to establish trustworthiness included prolonged engagement, reflexive journaling and interdisciplinary review and feedback. Finally, agreement was done to address dependability/reliability. After a brief training exercise, a researcher who was naïve to the data verified and matched operational definitions with specific quotes from the transcripts. The percentage agreement between the two coders was 75%.
Themes with findings	The overarching contradiction present in the conferences was the tension between to-let-die-now and not-to-let-die-now, which reflects the clinical reality that even a decision to continue life-sustaining therapy may not ensure long-term survival for a critically ill person. Surrounding this major contradiction, 5 more specific contradictions emerged from the conferences; killing vs. allowing to die, death as a benefit or a burden, homering the person's wishes or following the family's wishes, weighing contradictory versions of the person's wishes and choosing an individual

Study	Hsieh 2006[224]
	family member or the family unit as decision maker. Evidence for at least 1 of these 5 contradictions was found in each of the 51 conferences
	Killing or allowing to die: This contradiction centred on the issue of whether withdrawing life support is an act of taking a person's life or allowing the person to die naturally. Both sides of the contradiction were explicitly raised infrequently 93 of 51 conferences), whereas in 9 additional conferences 1 side (allowing to die) was explicitly raised. The issue of whether withdrawing life support is synonymous to killing was raised only by family members, whereas both family members and clinicians raised the opposite side of the contradiction, that is, withdrawal is allowing the person to die. The concern about killing the person seemed to make family members hesitant or unwilling to withdraw or withhold life support. Withdrawing or withholding life support was uniformly perceived by clinicians as allowing the person to die.
	Death as a benefit or a burden: This contradiction was centred on the result of death, specifically what death would mean to the patent or family members. Both sides of the contradiction were addressed in 15 conferences and 1 side was addressed in another 18 conferences (33 in total). Death was viewed as a benefit, often from the perspective of the patient, if it offered the opportunity to honour the person's wishes, end suffering, prevent lingering, end a life without quality, permit a peaceful or natural death or allow the dying person to join deceased family members. Burdens included family members not having time to digest or prepare for the death, not being able to say goodbye, not being able to pay their respects, not being able to be with the dying person anymore, other family members not being able to be involved in decision making or the person not having a chance to recover or get better.
	Honouring the patient's wishes or following family's wishes: Discussions that centred on honouring the dying person's wishes vs. following family members' wishes in decision making were raised in 44 of 51 conferences (21 conferences with both sides of contradiction expressed and 23 with 1 side). The most common presentation was that the dying person would wish to limit life support whereas family members' preferences were not to limit life support.
	Weighing contradictory versions of the patient's wishes: This contradiction could only be identified when both sides were expressed; this occurred in 1 of 51 conferences. Families and clinicians struggled with which version represented the dying person's authentic choice and hence, should be honoured.
	Choosing an individual family member or the family unit as decision maker: Both sides of this contradiction were present in 2 conferences and 1 side in 6 additional conferences (total 8 of 51 conferences).
Limitations	Very serious limitations. Family conferences represent only a portion of the communication that occurred between the clinicians and family. There

Study	Hsieh 2006[224]
	may have been additional formal conferences and informal discussions between the healthcare team and the family that were not captured. Communication strategies focused on in this analysis were strategies that were used to respond to contradictions directly. Other types of communication strategies are potentially useful to address contradictions. Other strategies that could not be identified in this analysis include non-verbal ones such as attentive listening, allowing denial and presenting a compassionate presence. This analysis does not assess whether different healthcare providers tend to use different communication strategies. The nature of the ICU conference makes the physicians leading the conferences in the hospitals where this project was conducted. Yet, other members of the healthcare team, such as nurses, social workers or chaplains, are also vital in overcoming challenges surrounding EOL communication. These clinicians are likely to have encountered similar contradictions around EOL decision making yet may respond with different communication strategies. This analysis could not verify the findings with participants in the study directly. The interpretation of communication is subject to the understanding of the investigators. In lieu of confirmation with original study subjects, clinical and content experts were used to validate the emerging analytical framework.
Applicability of evidence	Indirect setting. American ITU, and participants were chosen by clinicians based on their belief of potential litigation.

Table 42: Lind 2011[289]

Study (ref id)	Lind 2011[289]
Aim	To examine family members' experiences of end-of-life decision-making processes in Norwegian intensive care units (ICUs) to ascertain the degree to which they felt included in the decision-making process and whether they received necessary information.
Population	Family: Twenty seven bereaved family members of 21 former ICU patients 3-12 months after the person's death.
Setting	Norwegian ICU.
Study design	A constructivist interpretive approach to the grounded theory method of qualitative research.
Methods and analysis	A constructivist interpretive approach to the grounded theory method of qualitative research was employed, with interviews of 27 bereaved family members of 21 ICU patients who died after a decision to withhold or withdraw life support. Three university hospitals and 1 district hospital participated in the study. Hospitals were selected based on their ICU size (>8 beds) and type of unit (general ICU). A sample size of family members was selected from each IC's patient database by local research coordinators. Inclusion criteria were age greater than 18 years for both the person and the family member. The decision to withdraw treatment was documented in the patient records. Families who had been asked to consent to organ donation were excluded. Most interviews took place in the participant's home. Due to long distances, two interviews were conducted via telephone.

Study (ref id)	Lind 2011[289]
	The interviews were held within 3-12 months after the person's death, with an average of 9 months. The interviewer used an interview guide as a background tool to ensure relevant topics were covered in the dialogue. The interviews lasted about 1 hour and were digitally recorded and transcribed verbatim. The data were organised using NVivo. First, individual interviews were thoroughly analysed by two researchers (G.F.L and R.L.) with relevant episodes then isolated and arranged into themes. Using the interpretive grounded theory method, the themes were coded and named. The concepts emerged within single interviews and between interviews, although the emphasis remained on the whole, as in a hermeneutic circle. In organising the data, initial codes were chosen to facilitate analysis. The cases were then labelled based on the participant's experience of inclusion in the decision-making process and then divided into two groups. The underlying assumptions of the different cases were compared. A common key concept emerged: 'wait and see.'
Themes with findings	Most participants were not included in end-of-life decision-making. The expression 'wait and see' was experienced by participants from both groups and it was related to communication with both physicians and nurses. Five subthemes demonstrate the variety in this main concept; unavailability, ambivalence, disparate comprehension, delayed communication, shared decision-making.
	Unavailability: Few participants experienced regular physician communication. The physicians often seemed busy, did not keep appointments and left the family waiting for hours. When family members did succeed in meeting a doctor, they found they were rarely given enough time for proper dialog. One daughter, who was with her father for 1 week in the ICU state: 'There was little … very little communication. The only time we talked with doctors was that time the two doctors sat down with us. We had no contact apart from what we heard from the discussion when they arrived on their rounds.' (no. 8). Many families felt that they needed more frequent discussions concerning the perspectives of the treatment. One family member said: 'There were … lots of questions I could ask, but I would not get an answer (from nurses). A doctor had to answer them … But then … then It seems a bit of an uphill path to get information and arrange a meeting with a doctor …' (no. 18). Nurses rarely participated in meetings between families and physicians.
	Ambivalence: In retrospect, many felt that uncertainty was hidden behind a focus on continued full treatment and the hope for improvement. A wife said that 'they never actually said it would not work out, to start with. They had hope and we clung to it.' (no. 9).
	Disparate comprehension: In retrospect, the families realised that 'wait and see' was in fact used to covey treatment termination at a given time, unless there were unexpected signs of improvement. Others had previously understood it as meaning that the doctors were uncertain about the outcome. However, several family members felt that the end-of-life discussion after the 'wait and see' period was over came up too abruptly.
	Delayed communication: The 'wait and see' period sometimes delayed the important part of the discussion regarding the decision-making process and made it difficult for the family to recognise their role as surrogates for the patient. Some family members were relieved to discover that the physicians are responsible for decisions, but still had a perception of the importance of their own contribution. One woman, married for more than 30 years, said: 'My

Study (ref id)	Lind 2011[289]
	husband and I were very conscious of wanting to be the closest relatives and part of this was to be confident that the spouse made the best decision'. (no. 1). Despite the fact that few people had previously discussed end-of-life goals within their family; the relatives believed they knew the end-of-life wishes of the patient. They based this on their previous generalised conversations on moral values and end-of-life goals. This carries with it a strong feeling of responsibility to communicate this knowledge to the clinicians. Several family members, while presuming that the correct decision had been made, would still have preferred greater involvement in the decision-making process. Looking back, 1 son said: 'Her quality of life was not part of the discussion … no, in fact it was not … They should have discussed it with me … that is what I think. It is actually a moral question. It is really difficult.' (no. 18). Several family members recall the situation as emotionally charged. Some were left with unanswered questions, leading to doubt about whether the correct decision had been made. They were unsure whether they had received all necessary information or if there were other aspects to be considered.
	Shared decision-making: For a few family members the 'wait and see' period worked as a preparation phase for the decision-making process. These families experienced early family meetings in which clinicians made efforts to establish a relationship and provide family with emotional support. In later meetings, the person's preferences were discussed and treatment goals were revised. Nurses sometimes took part in family meetings. An elderly man who lost his wife said: 'In a way, I was prepared by the process which went on continuously and the talks with those two fantastic professionals. And it was obvious to me that it was her life it was all about, and on the doctor's recommendation I saw no reason to continue the treatment.' (no 12).
Limitations	Serious limitations. Recall bias: impossible to know if participants recollect ion exactly describe their thoughts and feelings at the time of the decision.
Applicability of evidence	Indirect setting. (Norwegian ITU).

Table 43: Lind 2013 [290]

Study	Lind 2013[290]
Aim	To explore to what extent and in what ways can family members of alert and assumed competent people be involved in information and decision-making processes regarding possible termination of treatment.
Population	n=11, inclusion criteria: age over 18 years old of both the patient and the family member, daily visits by the family member. The family member was invited to interview within a year of the person dying, the person was alert and had assumed competence in the decision making process. Multiple members of the family who met the criteria were included, ranging from single participants to a 1 group of 3. This was part of a larger study which looked at 27 family members of 21 hospital patients. This study is also included in the report, but it is unclear

	whether these patients' data were reused in this study.
Setting	An ITU in Norway
Study design	Focus groups for each family were undertaken by two researchers. One researcher was an ITU nurse and it was unclear whether they had a prior relationship with the participants during the person's stay in ITU. A semi structured interview guide was used but not provided for extraction, but questions related to the interaction with healthcare professionals, experiences of the communication in the end of life discussions and the content of the conversations. The participants were also asked their experiences of how the clinicians assessed the person's autonomy and decision-making capacity. The starting questions was '*Can you tell me what happened?*'
Methods and analysis	The interviews were transcribed from digital recording and analysed using thematic narrative analysis, each analysed separately using hermeneutic approach. Emergent themes were then compared across the other interviews. Unclear who was involved in this process.
Themes with findings	**Transparency in communication-** Due to the alert condition of the person's condition, some of these 6 families experienced less attention paid to their informational needs, which then had ethical implications for their ability to support and protect the patient. The family members were often informed separately to the dying person. This lead to confusion over the information that had been given to the dying person, and concern from the family members that they were adequately informed to make decisions: *'"The doctor said he knew everything. That he got the same information as us. But he had great difficulty in talking. he had a tight mask on and was dependant on it. He had trouble making clear enough signs for us to understand him"'* There were also concerns raised by family members on how the competence of the patient had been assessed.
	Participation in the end of life decision making process, patient consent and the role of the family- the family members described a desire to be involved with the decision making process. There were 3 different experiences described: 1. Shared decision making- Between the patient family and critically ill person of a person who had given the decision making responsibility to her daughters *'"It is was absolutely crucial for us that we were included and we knew she was taken care of like that"'* 2. Acceptance of the physician's decisions- this included examples of uniformed participation in decision making, where not enough information had been provided to the family member and yet they were asked to make a decision on the dying person's behalf. 3. Information of the physician's decision- some families reported being informed of the physician's decision without any evidence of shared decision with the patient or themselves. These situations were described as offensive and these families struggled with the memory of the ways this was done. Nurses did not participate in these talks.
	Responsibility in the decision making, a matter of ethical intertwinement- When a person had capacity the family members main role was reported as supportive to facilitating decision between the patient and the healthcare provider. When the family members acted as surrogate decision makers their responsibility was firmly justified by acting in the person's prior informed wishes. When the family were not adequately informed or involved in the decision making they often felt responsible for the decision: '"*I've thought a lot about this. Did I do the right thing? Did I do the wrong thing? I understood that we were asked consent and I feel responsible for this. There and then, if I'd been asked there and then, I'd have said no. She seemed so much, much better. She was quite alert with bright eyes."'*.
Limitations	Serious limitations – Analysis process not fully described, no information given on theme saturation.
Applicability of	Indirect setting outside UK.

evidence	

Table 44: Minto 2011[324]

Study	Minto 2011[324]
Aim	To determine the factors associated that assist or hinder the primary care health professionals having discussions about the end of life.
Population	**Healthcare professionals:** One GP and 1 district nurse from each of 3 GP practices. SAMPLE: A purposive sample of GPs and DNs who care for people with life-limiting conditions in the primary care settings was selected. The rationale for the sampling was to locate participants who could provide appropriate data for the area being studied; therefore the process of sampling involved the researcher making a judgement regarding which potential participants would provide the most informative data. Those with experience of ACP for their patients approaching the end of life and who had been in their post for at least 6 months were considered.
Setting	The study was conducted in a primary care setting in an urban area of Scotland and involved GP practices that are signed up to using the Gold Standards Framework (GSF). The community palliative care clinical nurse specialists (CNS) based in a local hospice work closely with the GP practices in the area, with each CNS having several allocated GP practices. The study concentrated on 8 local GP practices. The CNS team regularly attend the GSF meetings of their allocated GP practices, meeting with the GPs and DNs. ACP is routinely discussed for patients at this time.
Study design	Qualitative study using Semi-structured interviews.
Methods and analysis	The qualitative and interpretive methodology of phenomenology was used, as the study focused on an exploration of experiences and perceptions. Individual face-to-face semi-structured interviews were the method of data collection. All participants chose to be interviewed in their own workplace. The interviews were conducted by the lead researcher. The interviews were digitally recorded and transcribed verbatim by the lead researcher. The transcripts were then returned to the participants to verify their authenticity. The participants at this stage had the opportunity to withdraw any or all of their data, but none did. The data were analysed by the lead researcher using Colaizzi's (1978) thematic approach. Notes were made on the transcripts to reflect the researcher's initial thoughts in regard to emerging themes. Validation of the findings is enhanced if they are returned to the participants to ensure that there has been no loss of meaning, but unfortunately this was not possible owing to time constraints. However, the analysis of 1 of the transcripts was externally verified by a researcher not involved in the study.
Themes with findings	The findings clearly depict two of the challenges faced by GPs and DNs in the community: emotional labour and balancing patients' and families' expectations about care provision in the community where limited resources are available.
	Four key themes emerged that appeared to illustrate the participants' experiences of ACP in end-of-life care. These were the evolution of palliative care, managing transitions of care, the emotional labour of ACP and balancing expectations. The first 2 themes address communication and the need for education and were not presented in depth. The second 2 themes were presented in depth.
	Emotional labour of ACP: The potential for health professionals to become distressed themselves owing to the sensitive nature of ACP discussions.

Study	Minto 2011[324]
	Some of the participants highlighted experience as a factor in being able to deal with the emotional impact of ACP. 'Personally I'm ok with it now … it definitely gets easier when you've don't it … read the leaflets and learned from other people's experiences as well.' (DN1). Learning from others how to approach end-of-life care issues can help to reduce professionals' anxieties. 'I think it will get easier and easier and easier … But certainly if you asked me three years ago, I'd be like "Oh dear god, no: I'm not prepared at all." And see how [a consultant] spoke so openly about death and dying and how much the patient really appreciated that rather than skirting round it.' (DN3).
	Balancing expectations: Most of the interviews highlighted a disparity between the resources available and the patients' and family's expectations. District nurses faced challenges when trying to prioritise their time to enable them to manage the person dying at home in conjunction with their regular workload. '…what their expectations are that can be provided for them as well … Sometimes that can be a big stumbling block in advance care planning because, particularly if place of death is to be at home, and obviously coming from the district nurse's perspective, that is a big difficulty … As well as doing palliative care we also have our normal caseload so that does make things very difficult for us' (DN3). 'Families are expecting to have a Marie Curie nurse and then have the equipment there to actually … If that's not there, does it stop them dying at home, if that's their preferred place?' (DN2). '…because you can just see their faces-you know, "I want this hospital bed for you and it would help your legs, it would ease the pain, it would do that but unfortunately, we just have to wait until one's available so …"'. (DN1). The DNs were unanimous in their views regarding respecting a person's choice to die at home, but they reported experiencing frustration when having to wait for the equipment required to achieve this. This aspect of patient care was not identified by the GPs. There was a strong sense that health professionals are committed to providing the care required for people at home at the end of life if that is the person's wish. However, some of the factors identified that hinder this include a lack of resources, balancing palliative care patients with the normal workload and supporting the family caregivers. The emotional toll it takes, along with feelings of guilt if the person does not achieve their wish to die at home is reflected in the following statement: 'Is the family going to be able to handle this? Because it is a huge emotional, physical, spiritual journey … and often in terms of you know, being able to escort somebody from this world into the next in putting in spiritual terms … there are very few families that actually have the resources to do the whole package.' (GP2) Palliative care has evolved to focus on care being delivered in the community setting. The primary healthcare team therefore is the main service provider and this may raise resource implications and feelings of failing both for the patient and the family. '… the main burden is with the family if they are going to do a whole anticipatory care … they sometimes struggle and struggle, it's the main factor.' (GP1). 'I think everything we can try to put into place in advance care planning, if you don't have the family on side with you … it can become extremely difficult.' (DN1).

Study	Minto 2011[324]
Limitations	Very serious limitations. Small sample size due to time restrictions. The lead researcher had limited experience in qualitative reviews. The lead researcher works as a clinical nurse specialist in palliative care and was known as such to the study participants.
Applicability of evidence	Direct evidence from UK setting.

Table 45: Nolan 2008[350]

Study (ref id)	Nolan 2008[350]
Aim	The study compared the preferences of people with amyotrophic lateral sclerosis (who normally maintain capacity for decision making until close to death) for involving family in healthcare decisions at the end of life with the actual involvement reported by the family after death
Population	People recently (within 8 weeks) diagnosed with ALS. They were excluded if they had an altered mental state. (n=16) The person's identified family members who might participate in healthcare decisions with them. (n=16)
Setting	USA
Study design and methodology	The patients were interviewed every 3 months prior to death *or* 2 years have elapsed, and the final interview (0 to 3 months prior to death) was included. The patients were asked to think of the most important decision that they had recently made or were about to make regarding their healthcare. Using a modified version of the Control Preferences scale (using picture cards) they were asked to rate how they preferred to make this decision with their family as either independent, through shared decision making, or through surrogate decision making. After death, the researchers interviewed the family member identified by the patient using the Family Member Decision Making Survey, a 30 items comprised of open questions and multiple choice questions. Asking the family member to think about the most important healthcare decision made near death, they were asked to indicate whether the person had made this decision independently, through shared decision making with family, or through decision making that was reliant on family. Using an in-depth qualitative interview they asked whether they had previous experience in decision making with or for another family member at the time of death, whether they had observed another person making decisions with or for a family member or whether they had received positive feedback from anyone about their ability to participate in these types of decisions. They were also asked to rate how satisfied they were with the decision making experience.
Analysis methods	Descriptive statistics used a Cohen's kappa to measure agreement between the patient and the family member's ratings for involvement in decision making. The qualitative data were analysed using content analysis. The investigator who conducted the interview and another independent investigator reviewed the transcript separately and then together. They stopped when theme saturation was reached.
Themes with findings	The actual involvement of the family was concordant with the patients preference in 78% of cases if the person preferred and independent style (n=9), 50% if the person preferred shared decision making (n=6), and 0% if the person preferred to rely on the families judgement (n=0).

Study (ref id)	Nolan 2008[350]	
	Facilitators for family members decision making.	Barriers for family members decision making.
	Confidence in decision making usually brought by prior experience in making end of life care decisions.	Lack of support from family or healthcare professionals.
Limitations	Serious limitations. No quotes from the qualitative interviews provided, but summaries. No information from the descriptive elements (the Family Member Decision Making survey) were provided although listed in the methods.	
Applicability of evidence	Direct evidence from the family members as this occurred after the patients died. The information from the dying people is indirect given it could of occurred up to 3 months prior to death. Indirect setting outside of the UK.	

Table 46: Royak-Schaler 2006[398]

Study (ref id)	Royak-Schaler 2006[398]
Aim	To assess healthcare provider communication about end-of-life (EOL) and hospice care with people with terminal cancer and their families, from the perspective of the family members.
Population	FAMILY: 24 spouses and first degree relatives of deceased people with cancer who had been treated at the cancer centre from 2000-2002.
Setting	USA
Study design	Exploratory qualitative study using focus group discussion.
Methods and analysis	A qualitative study design was used to examine communication and decisions about EOL and hospice care from the perspective of spouses and first-degree relatives of deceased people with cancer. A list of potential participants was generated from the medical records of 300 people with cancer who had died from October 2000-August 2002. In these records, 149 spouses or first degree relatives were identified. Of the 77 who were contacted successfully, 24 completed the study, resulting in a 31% response rate. The most common reasons people gave for declining to participate were that they were still in too much pain related to the death or that they lived too far away to attend the focus groups. Participants ages ranged from 26-77 years 9mean 57.3); most were female (79%); Caucasian (71%) and spouses (75%) of a deceased person; all had graduated from high school; more than half were college graduates and most earned less than $35,000 a year. Sixteen participants (67%) reported that their loved ones received hospice care delivered by a hospice team at EOL, 8 in their homes, give in an inpatient hospice and 3 in a hospital setting. Family members participated in 1 of 2 focus group discussions and completed a short self-administered questionnaire regarding their sociodemographic characteristics and the type of EOL care their deceased relative had received. Two 2-hour focus groups were conducted during March 2003 at the University of Maryland Medical Centre. Group leaders facilitated discussion, following a moderator guide that was designed to allow for the standardisation of questions and data collection methods for the 2 groups. In both groups, the same patient vignette was used to open group discussions.

Study (ref id)	Royak-Schaler 2006[398]
	Qualitative data were audiotaped and analysed by comparing, contrasting and summarising content themes from the focus groups using NUD*IST 5 (N5) software.
Themes with findings	**Access to healthcare team and quality of provider communication:** Some participants believed that the staff was too busy to adequately explain their loved one's status to too busy to provide quality care. As a result, some participants questioned the competency of the healthcare team. 'I had to be the manager of her care, and you do because you don't have an advocate in the hospital. Doctors are too busy and nurses are too busy to be an advocate for a particular person, so the caregiver is the advocate and you've got to watch every single thing.' 'You start feeling like you have to be a nurse of your own to get through the situation. We never saw the doctor, but I guess we saw the resident who had been working 36 hours straight … that may be part of the hospital life, but sometimes it's hard, it rubs you a little. You just feel like, God, am I getting the right care?' Accurate information that was communicated clearly to patients and family members was appreciated. According to 1 participant, 'the staff are excellent … they know, I could call them and they would direct me in the way that I should go, and I thought that was really nice.'
	Communication about disease progression and available care options: Focus group participants repeatedly commented about the need for more information from the healthcare team regarding the stage of disease and treatment decisions. When available, sufficient and accurate information helped them make informed decisions and feel comfortable with their loved one's care, even when the final outcome was death. When information was freely available and compassionately shared, perceptions were more positive. 'Everyone that we had to deal with was kind and considerate, and they answered our questions and they helped us to understand what was going on, what his options were.' '[My father] didn't complain or ask questions, and it was important for me to get this information or to have the doctors explain everything to him very clearly because he was able to make a decision on his own and I didn't want to have to make a decision for him. When he was informed, and the family members were informed, and he made the choice, we felt more comfortable as to whatever happens. We were thoroughly informed, and my father chose not to go with chemotherapy. He decided that he wanted to live his life but the way he wanted and be in control, so I thought that was very, very good.'
	Language, timeliness and sensitivity of communication: Many participants reported difficulty understanding the information that healthcare professionals provided. In addition, they indicated that such difficulty affected the ability of patients, when possible, or relatives (on behalf of the patients) to make EOL decisions. Unfortunately the language and medical terminology used by healthcare providers sometimes impeded understanding. 'I think the medical people assume that we know a lot about these disease and thing, but we don't … and thank God for the internet, because I went home and I became, not an expert, but knowledgeable of cancer and stage IV … I had all the printouts and everything, but something like that, why do they assume that I know what stage IV cancer is?'

Study (ref id)	Royak-Schaler 2006[398]
	Participants reported that time was an important obstacle to effective communication. 'I had a complaint too, about, in fact, one of my very few complaints was getting information results of [computed axial tomography] scans to see whether the treatment was working or wasn't working. I found it very difficult to get a timely output from the oncologists … the difficulty was getting the information in a timely fashion.' Although some focus group participants preferred healthcare professionals to openly communicate information about the stage of disease and treatment decisions, the data indicated that others preferred just the opposite – especially when the information was shared in the presence of the patient. Some participants described experiences in which they felt that healthcare providers used language or shared information that was inappropriate because of its potential impact on the patient. 'After it was mentioned the he may have 2 weeks to live, that's when my husband started saying, "Leave me alone. Let me die in peace." That's when he gave up, and I think those situations should be discussed away from the patient so they can have some hope.'
	Sources of bias in patient- and family –provider communication: Participants were asked whether they believed that healthcare providers demonstrated any biases or beliefs that affected patient EOL communication. No one reported racial or gender discrimination, although several mentioned possible age biases by healthcare professionals. One man explained that because his dying brother was young and had a close relationship with his healthcare providers, they had difficulty telling the dying person that he was close to death. Another participant believed that information to promote informed decision-making about hospice care was given only to older people.
Limitations	Serious limitations. Sample size was small.
Applicability of evidence	Indirect population- In addition, the educational back group of the participants (42% high school graduates, 58% college or beyond) was higher than that of the general population. All participants were family members of deceased people with cancer who were treated at 1 site both of which limit generalizability. Setting outside of UK.

Table 47: Seymour 2010[408]

Study	Seymour 2010[408]
Aim	To examine how community palliative care nurses in England understand ACP and their roles within ACP. To identify factors that may facilitate or constrain community nurses' implementation of ACP and nurses' educational needs.
Population	**Healthcare professionals:** Twenty three community nurses from 2 Cancer Networks in England.
Setting	UK.
Study design	Focus groups conducted under an action research framework (places emphasis on collaborative working between multiple partners in gaining

Study	Seymour 2010[408]
	practical knowledge to effect change).
Methods and analysis	Twenty three community nurses from 2 Cancer Networks in England were recruited to 6 focus group discussions and 3 follow-up workshops. A meeting was held for those interested in hearing more about the study, which provided an opportunity for nurses to shape the objectives of the study. Roles of nurses who took part included: clinical nurse specialist in palliative care (Macmillan nurses), heart failure or respiratory care (9), hospice nurses (4), community matrons (4), district nurses (3), community staff nurse (1), community psychiatric nurse (1), end-of-life care programme facilitator (1). Each of the nurses had received some level of training about ACP although this varied in terms of its depth and content. For most, it had taken the form of attendance at local study days about the Mental Capacity Act or local practice development meetings. The nurses took part in 6 focus group discussions about their experiences of providing end-of-life care and views about ACP. Three follow-up workshops with nurses who had participated in the discussion focused on collaborative interpretation of the focus group data and identification of key themes and developing ideas about educational resources for ACP. Focus groups were transcribed with nurses' permission and analysed with the qualitative data analysis package NVIVO. Authors used Strauss and Corbin's constant comparative method to generate categories, patterns and themes from the transcribed textual data relating to experiences and perceptions. Emerging categories and themes were subsequently verified by the research team at dedicated project meeting and then discussed with the nurses at the follow-up workshops. This acted as a form of respondent validation and also generated new insights.
Themes with findings	Nurses saw their role in ACP as engaging with patient to elicit care preferences, facilitate family communication and enable a shift of care focus towards palliative care. Challenges perceived to ACP included: timing, how to affect team working within ACP, the policy focus on instructional directives which related poorly to patients' concerns, managing different patients' and family's views. Perceived barriers included: lack of resources, lack of public awareness about ACP, difficulties in talking about death.
	First encounters and understanding of ACP: Nurses reported not feeling confident they properly understood the various possible components of ACP. 'I think, maybe for me, it was when I worked in (locality) which was over 2 years ago, we started to go to GSF meetings … over the last 2 or 3 years it's becoming in but now a little bit more formally and a little bit more structured I suppose.' (Community staff nurse). Some recalled being confused about the differences between day-to-day 'care planning', which they regarded as a key aspect of their role, and the more unfamiliar ACP. 'I think one of the problems-sort of being on the outside looking in – is that a lot of DNs think, oh not another project, not more paperwork, and it's been in a way perhaps not greeted with huge enthusiasm, although as some people have said here before, it's something that a lot of district nurses and healthcare professionals say; we've been doing this for, we've done this but haven't actually formalised it, and that's very much how I see the ACP.' (Hospice nurse).
	Challenges: **Identifying the best time and most appropriate person to introduce ACP issues to patients.**

Study	Seymour 2010[408]
	'I found it interesting, on a GSF form in one practice we've got preferred place of death, and often GPs will say "oh no, it's too early to talk about that yet"'. (District nurse). 'But when do they need it? Is it a form of diagnosis? And I think that's the difficult thing because obviously consultants don't have time to do it, and obviously it comes down to [Macmillan] nurses doesn't it, [or] support nurses within the hospital, because that's usually where the diagnosis is made'. (Macmillan nurse). **Managing differences in staff understanding of ACP in the wider healthcare team.** GPs are often reluctant to consider and discuss specific decisions relating to ACP with patients or their representatives. It was felt that this reluctance arose from discomfort raising ACP issues with patients for fear of raising issues about the end of life 'too soon'. Nurses were especially aware of difficulties of prognostication in people with non-cancer long term conditions and the risk of raising issues about the end-of-life care at an inappropriate time that would harm the person and not be congruent with their coping strategies. 'Patients with heart failure and COPD may be living for 10-15 longer years. So I suppose it's pitching just when it's appropriate to have those dialogues, and I think it's very different for every person, and I think the same as has been said earlier that there are some people who are going to be very happy, for want of a better work, to discuss that, and there are other patients who don't want to go there.' (Community nurse). **Managing the emphasis on instructional directives and the drive to bureaucratize ACP practice.** Concerns were raised about the bureaucratisation of ACP leading to a potentially blunt, harmful 'one size fits all' approach. '… what I have seen unfortunately is sometimes it's used as more of a checklist, you know, with tick boxes…'. (End-of-life care programme facilitator). One Macmillan nurse perceived that if nurses and other practitioners were encouraged to regard ACP as a set of procedures or a 'check list of questions' this could effectively subvert the goals of good end-of-life care practice. In particular they perceived that some people, on admission to hospital were being asked about resuscitation decisions inappropriately and in the absence of any wider discussions about care. 'It's interesting though when a patient's take into hospital now there is a resus status put on them straightaway'. (Heart failure nurse specialist). 'But straightaway they were talking to her daughters about her resus status, you know, that was the first thing that when she got out of the admissions hall that happened…'. (District nurse). **Documentation and communication of ACP discussions across healthcare systems.** Nurses also observed that GPs were often reluctant to engage in discussions about resuscitation or any other end-of-life issues. Nurses perceived a general reluctance to disengage from the 'active' curative mode of care resulted in GPs not acting on the perceptions of nurses or relatives about patients' wishes, even when these had been recorded in an advance care plan. '… a duty doctor was called out in the middle of the night, and they took him to hospital, and unfortunately he died in hospital, which is not what

Study	Seymour 2010[408]
	he wanted, [it] caused a lot of issues for his family as well … And I think the care home staff at the time were pretty adamant his wishes are that he doesn't but the duty doctor was: "no he is going", and sort of overruled it all…'. (Community psychiatric nurse). Lack of readily available or clear documentary evidence of a person's advance statements and uncertainty about the status of the wishes of close family members in relation to the person's best interests were seen as reasons why medical staff and senior nursing staff might take the least 'risky' course of action when presented with an unfamiliar person who was acutely ill towards the end of life. '(My colleague) was actually put into a bit of dilemma because [patient] was really ill, and he subsequently died … she wanted to send him to hospital because he needed hospital treatment. But the daughter had said expressly … she preferred him to stay in the residential home and got very angry when he was admitted to hospital, but it wasn't recorded anywhere.' (District nurse). Documentation, storage and retrieval of ACP records were perceived as a significant issue across systems of care, especially when people had many sets of notes and multiple hospital admissions. A lack of resources to support family carers was perceived as 1 reason why there may be a disjuncture between patients' and carers' views. '… the family were so concerned, worried, although we assured them they'd have a great care package, in reality … it doesn't always come to fruition and there isn't always the care there to support those families … We can't guarantee 24-hour cover but we will try our utmost.' (District nurse). **Barriers:** **Lack of resources (including time and end-of-life services) with which to meet patients' preferences and support family carers.** Nurses perceived that ACP could only be implemented authentically if there were adequate services and resources in place. '…you can try and get the services together and coordinate them, but often they're not there. And I think people can manage very well at home if that's where they want to die as long as we've got the services to keep them at home and to support them.' (Macmillan nurse). 'Certainly, around heart failure at the minute we do struggle for palliative care support. There isn't a specific unit that patients can go into. When they talk about the hospice, there's actually only day care hospice, X hospice is only for cancer patients.' (Heart failure nurse specialist). **Lack of public and patients' awareness about ACP and other end-of-life issues.** Nurses perceived lack of knowledge among the general public, patients and their family members about the availability of help and support during illness and end-of-life care and a contemporary tendency to not think about one's reaction to serious illness until it actually occurs. 'People don't know … what they want until they're in that situation. Because often people will say to me I didn't know there were all the services out there.' (Macmillan nurse). Nurses also perceived that patients and the public lacked knowledge about the course and outcomes of common life-limiting conditions. This created a further barrier to ACP conversations as many people perceived they were irrelevant to their situation. **Taboos and fears about death and dying among public and patients.**

Study	Seymour 2010[408]
	Nurses perceived that people had many fears about death and illness, which combined to create a taboo surrounding the subject. Fears identified included being frightened of death, fears about going into hospital, about being alone and dying alone. Nurses described how fears could be alleviated once people were encouraged to put into words what they were most worried about. 'And it's also sort of about unpicking why people are … maybe to facilitate the talk [there is a need] to actually unpick that, what is the fear around, for those people who don't want to talk about it yet.' (Macmillan nurse).
	Perceptions to training and education: Among the greatest challenges that nurses perceived to be associated with ACP were their own and colleagues' knowledge and skills about communication practice, recording and follow-up. '… we've still got – when you look at teams – a lot of nurses that aren't confident to have those conversations. They say: "well you like palliative care, you're good at it", and they back off … That's my worry – the confidence of the staff, teaching them to do it and then following it through.' (Macmillan nurse). 'I've been in post three years, so for me it's the uncertainty or where you do document all this information and actually how you can get it through to other people so the patient's wishes are respected – the documentation is a big thing for me'. (Community matron). Alongside formal training and education, whether by face-to-face teaching or distance learning, some saw the use of mentorship and apprenticeship styles of training as crucial. 'I think there is so much to learn about communication skills and dealing with patients which you can emulate from a role model. And I feel very passionately that junior nurses need to work with senior nurses much more at the bedside, not in the classroom because I think there's a theory and practice divide.' (Macmillan nurse).
Limitations	Serious limitations. the authors do not claim to have achieved data saturation and recommend further research takes place to check the transferability of results.
Applicability of evidence	Indirect population. nurses who participated were self-selecting and therefore likely had a particular interest in the topic in hand. The authors note that their focus group design may have obscured possible differences between specialist palliative care nurses (who mainly looked after people with cancer) and non-specialist community nurses (who looked after people with cancer and many others).

Table 48: Stevens 2011[421]

Study	Stevens 2011[421]
Aim	To investigate the views of healthcare professionals regarding ACP.
Population	**Healthcare professionals:** 34 Healthcare professionals:

Study	Stevens 2011[421]
	Focus group 1: HCPs working with people affected by non-malignant disease (GP, motor neurone disease CNS, heart failure CNS, district nurse, Parkinson's disease CNS, palliative care community CNS x2) Focus group 2: HCPs working with people affected by COPD (GP, palliative care CNS, respiratory CNS x2, physiotherapist, district nurse, practice nurse). Focus group 3: HCPs working with people affected by lung cancer (respiratory physician, GP, lung CNS x2, palliative care CNS, palliative care community CNS, occupational therapist, physiotherapist, specialty doctor – respiratory medicine, care home manager, ward manager – community hospital, district nurse, community staff nurse). Focus group 4: HCP working with people affected by metastatic breast cancer (oncologist, breast care CNS, district nurse, student district nurse, chemotherapy nurse, breast care CNS). HCP: Healthcare professional, CNS: clinical nurse specialist.
Setting	West of Scotland.
Study design	Focus group discussions.
Methods and analysis	Healthcare professionals were identified by key personnel in the west of Scotland and invited to participate in focus group discussions. The focus groups were designed to obtain the views of professionals who may become involved in ACP scenarios. Each focus group lasted between 1 and 1 and a half hours, and had a skilled facilitator and observer/note taker. A semi-structured interview schedule was used to encourage discussion. Comments were tape-recorded, transcribed verbatim and analysed independently by the authors.
Themes with findings	Common themes reported: Malignant vs. non-malignant disease, knowing the patient, communication, education and training, primary/secondary care interface.
	Malignant vs. non-malignant disease: One doctor worried about when it would be appropriate to introduce ACP to her patients: 'My only worry is, with malignant patients you have a time frame whereas with non-malignant you really don't have a time frame, especially chronic obstructive pulmonary disease (COPD)'. Specialty doctor in respiratory medicine. Due to improvements in treatments, professionals no longer felt confident at accurately making a prognosis. 'It's very difficult, they keep getting new treatments; it would have been easier ten years ago because you would only have 2 treatments, now we've got about six.' Oncologist. 'Breast cancer is becoming kind of chronic.' District nurse. However, some participants identified ways round an uncertain prognosis and believed there can be similarities between different patient groups. prognostic indicators [could be used] as a prompt' as well as 'looking at the rate of chance/decline' of a particular individual. 'Intuition' was thought to play a part in identifying deteriorating people. Respiratory clinical nurse specialist. There were inconsistencies around perceived 'capacity'; that is, the ability to care for the potentially large numbers of people who could be added to the palliative care register.

Study	Stevens 2011[421]
	'If you went from the relatively small number of patients that the average practice has in the terminal phase with cancer, to the large numbers of patients with severe COPD, there's a huge capacity issue.' GP.
	Knowing the patient: Most participants felt that a relationship with the patient was paramount when initiating sensitive conversations around ACP. 'It's about having a relationship with somebody and that is [developed] over years.' Palliative care CNS. 'I think it's important to that whoever does [the ACP discussion] knows exactly what they are doing … it's a discussion between a team, not just one person.' Oncologist. Some agreed it was up to the person to decide who to have these discussions with. 'Anyone can lead the discussion; I think it's very much who the patient feels comfortable with.' Respiratory physician. There was consensus that views of the carer should be sought, as they have the expertise regarding the person being cared for. 'The person that's been telling me about the patient's deterioration is the carer.' Palliative care CNS.
	Communication: Almost all focus group participants expressed the need for improved communication for patients and their families, between teams and across care settings. They described people constantly asking: 'When am I going to get better, when is my breathlessness gonna improve?' Respiratory CNS. While participants expressed that communication could be better and there was recognition that information needs to be sensitively assessed, some were hesitant: 'You're frightened to open a can of worms; what if they fall to pieces?' Physiotherapist. 'I certainly wouldn't want to inhibit anyone's lifestyle when they grasp that they've got a life-limiting illness, twenty years before it's going to limit their life.' GP. Where hospital palliative care teams were involved, communication appeared timelier and reference was made in the letters to discussions that had taken place with a person while in hospital. 'The discharge letter includes the discussions we've had with the patient and the plan for the future…' Palliative care CNS.
	Education: Almost all participants expressed the need for improved education regarding ACP, communication skills and in some cases education related to specific diseases, such as COPD. '…difficult conversations which nobody trains you for.' GP. 'I've never done [ACP] … we've not been taught how to use it in practice.' GP.
	Primary/secondary care interface Many participants recognised that there was tension between primary and secondary care.

Study	Stevens 2011[421]
	'Historically there has been a lot of stuff about primary and secondary care not working optimally.' GP. There was real concern from community staffs regarding the time hospital discharge letters take to arrive, meaning that people could have been re-admitted before they had received correspondence pertaining to the first admission. 'It can take weeks to get discharge letters.' GP. However, communication across settings was good in some areas. 'Our discharge letters go out within 48 hours of the clinic appointment.' Oncologist.
Limitations	Serious limitations. No comment as to whether data saturation achieved.
Applicability of evidence	Direct evidence from UK setting with non-cancer and cancer populations.

Table 49: Tan 2013[427]

Study (ref id)	Tan 2013[427]	
Aim	To describe the conflict experience that family physicians have with substitute decision makers of dying people and to identify the factors that may facilitate or hinder the end of life decision making process.	
Population	Family physicians with experience of dealing with conflict with surrogate decision makers of dying people n=11	
Setting	Canada	
Study design and methodology	Semi-structured interviews using a guide created by the researchers. The initial questions asked was "could you please tell me in an anonymous manner about the time(s) when you experienced conflict during an end of life decision making discussion with a substitute decision maker of a dying person.	
Analysis methods	The transcripts were analysed individually by the researchers and discussed to come to a joint analysis. An outside researcher of the study coded the transcripts to confirm initial coding of themes.	
Themes with findings	**Facilitators**	**Barriers**
	Building mutual trust and rapport (using communication techniques) "*So I think you can enable the patients and families to digest things in smaller chunks so you can basically give them more information over time, and you see them over time, and they*	Families denial of the patients terminal illness: "The *wife wasn't really grasping it and probably in some denial… so she was sort of saying 'can we do this? Can we do this? Can we do more?"'* *"I think a lot of it has to do with unrealistic expectations for the patients and family though… they expect of medicine what medicine cannot do…".*

Study (ref id)	Tan 2013[427]	
	have a trust in you… to come to a better understanding of things."	
	Understanding one another as a facilitator *" and tell me a little bit about… what you're understanding is of what's going on here and what are your sorts of thoughts about what's going to happen now?... then I learn kind of where we're at".*	Lack of prior relationship between the physician and the dying patient and family: *" … Because I take on "orphan" palliative patients a lot of the time, you're meeting people for the first time at precisely the most emotionally stressful time of the patient and usually the family's life… the potential for me for conflict is greater when I'm coming in as a new physician*".
	Building common ground: Using time: *"It takes time. I think understanding the perspective of the substitute decision- maker or even the patient. And time. And that whole thing of finding common ground. I think it is important. And it takes time to find that common ground."* Using Other MDT such as nurses social workers and chaplains: "*Don't think that you're by yourself in these situations… If you ever feel that you're coming into conflict with someone, always just ask for help and get different perspectives on situations and different ways of dealing with things… don't ever get angry with it. You know just stop the conversation it you feel like you're not getting anywhere and leave and ask for help."*	No previous effective advance care planning by the patient and family: "*So I really think it is our responsibility, first and foremost, we are the people that know them the best. We are the people that can have this discussion and we've got the continuity and the longevity. We know how to bring this up, we know when to bring it up…"* *"It really has to be the family physician… in an ideal world, it would always be brought up by the family physician and we would have clear understandings about future wishes of patients".*
	Experience of the doctor: "*Conflict, dealing with conflicts, I think, makes you more grounded, makes you more experienced to deal with these kind of situations in the future. That's how I feel… I learn a lot. We all learn a lot from conflicts."*	Barriers to understanding one another (listed but not detailed in report0: • Language barriers • Cultural/religious barriers • Value difference • Legal concerns • Taking conflict personally • Being inflexible • Prior negative healthcare experiences

Study (ref id)	Tan 2013[427]	
		• Mistrust of system • Family discord/dysfunction • Unattainable goals and expectations • Denial of patients condition • Physician internal conflict.
Limitations	No limitations. Data saturation met during the study, and results triangulated through field notes to capture observations not taken in the audiotapes. Theoretical sampling also used.	
Applicability of evidence	Direct population, although the study only explores physicians who had experience of dealing with conflict, and did not speak to those who reported no conflict, this group may have had refined skills in preventing or handling conflict. Setting outside the UK.	

Table 50: Thompson et al. (2003)[431]

Study	Thompson et al. (2003)[431]
Aim	To discover the views of health professionals on advance directives.
Population	**Healthcare professionals:** Twelve participants were interviewed (4 hospital doctors, 4 general practitioners, and 4 nurses). There were also 6 focus groups comprising hospital nurses (in care of the elderly and general medicine), hospice staff, GPs, consultant geriatricians, geriatricians in training grades and an interdisciplinary group (34 persons in total).
Setting	Great Glasgow area, Scotland, UK.
Study design	Semi-structured interviews and focus groups.
Methods and analysis	Interviews lasted 1 hour and focus groups 90 minutes on average. All research encounters were recorded and transcribed verbatim and analysed according to a modified grounded theory approach. This entailed coding of all data for both literal and interpretative meaning with the synthesis of these concepts into the broader themes.
Themes with findings	The only relevant theme from this paper is Advance directive as an agent of communication: The presence of an AD in any clinical situation will induce discussion. This also helps trigger conversations on end-of-life issues that professionals can find difficult to initiate. *'…the main advantage of an advance directive is as a tool for communication between the medical staff, the rest of the multi-disciplinary team, the patient and the patient's loved ones.'*
Limitations	Serious limitations. The 'modified' grounded theory approach used is not described.
Applicability of evidence	Indirect topic of advanced directives rather than shared decision making. UK setting.

Table 51: Tilden 1995[432]

Study	Tilden 1995[432]
Aim	To describe how families reason about a decision to withdraw life support. To describe the positive and negative effects of physicians' and nurses' behaviours on families during the process
Population	Family members (n=32) of people (n=12) without advance directives whose deaths followed a stay in the intensive care unit and withdrawal of treatment. PATIENTS: Eligibility criteria of patients: aged 21 years or older, unable to make decisions at the time of death, had been hospitalised at least 3 days before death, were without formal advance directives and had family who participated in a decision to withdraw life support. The deceased people whose families participated were all white, 2 thirds were male, half had private insurance and half had public sponsorship or were without payment coverage. Although the length of hospitalisation before death varied widely (range: 5-79 days, mean 24.9 days, SD 24.6 days), half of the patients were hospitalised for 12 days or less. Diagnoses included cancer, gastrointestinal disease, cardiac disease, heroin overdose and motor vehicle accident trauma. Half the patients were on the medical service and half were on the surgical service. All patients spent at least a brief period of time in the ICU, although half of all deaths occurred in the acute treatment unit. Although the mean age was moderately advanced (64.3 years, SD 16.03, range 41-94), three quarter of patients were between 41-69 years. FAMILY MEMBERS: More than half the family members were adult children of the dead people, about a quarter were spouses and the rest were parents, adult siblings or extended kin. The mean age of family subjects was 50.4 years.
Setting	USA Tertiary hospital in a major university medical centre and level I trauma centre.
Study design	Semi structured interviews.
Methods and analysis	Families were contacted 2 to 6 months following the death of the eligible person. Informed consent was obtained from 55% of the families who were contacted. Intensive 1- to 2-hour-long individual interviews were conducted using a semi-structured interview protocol and focused on the family's decision to limit life support and their experiences of the person's final days. Demographic information of participant was also collected at the beginning of the interviews. The majority of family members were interviewed individually in their homes or places of work. About a quarter of participants lived a long distance from the hospital and were interviewed by telephone. None of the authors were directly involved with any of the patients or their family members. Interviews were conducted by 1 author. Interviews were tape recorded and transcribed verbatim, producing more than 700 pages of narrative data. Content analysis was used to analyse the data. Multiple readings of the first 5 interviews by the authors led to an agreement of 10 main categories of data, which were further divided using 38 codes. Each transcript was then read and coded separately by 2 of the authors. Comparison of the 2 sets of coded data indicated 90% inter-rater reliability on codes independently selected from data segments. The 2 raters then jointly reviewed and discussed each code transcript until full agreement was achieved on the selection of codes for the data. Once all data were in final coded form, a computer software program (Ethnograph) was used to cut and sort the data by code and category.

Study	Tilden 1995[432]
Themes with findings	**Dawning awareness:** Subjects said that physicians and nurses usually eased the family gradually toward the understanding of the possibility of withdrawing life support through tentative and cautionary statements that laid the ground work for patient's death. Subjects reported that clinicians typically used phrases such as "he's starting to fail", "it doesn't look good" and "I think he's not fighting anymore." The idea of withdrawal followed soon after, typically preceded by statements from physicians such as "let's try another day of treatment and then see" and "we'll try one more test and see what it shows us." Acknowledgement of withdrawal as an option came from either the nurses or the physicians or both more or less simultaneously. Typically, phrasing at first was cautious, diplomatic and open-ended, for example "we'll probably have to make some sort of decision …" Most families realised a time for decision-making of some kind was approaching but felt it was up to the clinical team to lead the way. For example: 'I can't remember which nurse brought it up but they did it very diplomatically and of course I knew it was going to have to be done. But it was nice that someone else could sort of start the process for me. And I think then I talked to Dr X and he said, "You know, that is one option" and they were very, very careful about it.' Most families greatly appreciated the thoughtful and unhurried approach to withdrawal taken by staff, for example: 'The doctors brought the subject up just a little bit, and of course I think they knew that I was aware, but sometimes it's a little hard to say. I thought they handled it very well.'
	Framing the question: In some families, being asked the question lead to feelings of burden, while in others it led to feelings of inclusion in the care-giving team and empowerment to look after their family member's interests. A subject said that the feeling she remembered when the physician asked the question was "Oh my god, you know, then *we're* deciding life and death here …?" Families who experienced being asked the question as indicative of inclusion and empowerment spoke of being an active and contributing part of the clinical team and not having to fight to be heard. One husband said that he feared he would have to fight the physicians for what he thought his wife would want and was relieved to find the physicians completely open and honouring of his input.
	Reasoning about the decision: Some families wondered about legal constraints ("We didn't know … what was legal or not legal about how far to go") and needed to be told that withdrawal of life support was legally permissible before they were able to further reason about decision options.
	Families' interactions with physicians and nurses: Subjects described overwhelmingly positive opinions of providers. Physicians and nurses were described with great feeling by families as inclusive and involved. Supportive behaviours: Many families noted how well staff included them in both the day-to-day care of the person and the decision-making processes about the person's

Study	Tilden 1995[432]
	treatment. The fact that staff gave both expert medical care *and* sensitive emotional care was valued highly. As 1 daughter said: 'They treated him [the patient] as if he were their own father. They treated me as if I were part of the healing team.' Even as prognosis worsened and staffs' efforts shifted toward comfort care, families felt tremendous support rather than abandonment. 'we just can't say enough about the hospital and the nurses and the care. They never lost their cool or never gave up. They were fighting just as hard as she [the patient] and we were.' Families valued physicians especially for their effectiveness in communication, which they described as timely, frequent, unhurried, honest, compassionate and available. Families were hungry for information, even small details and spoke warmly of physicians who: '…answered every question we ever wanted to ask without acting like it was foolish or they didn't have time…' Burdening behaviours: Although positive experiences predominated and were more often described spontaneously by subjects, with further questioning families described a variety of experiences with staff that led to feelings of burden and exclusion. The experiences most often related to problems with attitude, communication, timing of withdrawal and dealing with family conflict. Regarding attitude, several families commented negatively about some physicians (interns, residents) who seemed to view the person's death as a failure and who acted defensively or who distanced themselves. A few families noted that some physicians do not seem comfortable saying 'I'm sorry' after the death: '… doctors just don't say I'm sorry, and I don't know why, except that perhaps they feel that they have lost a patient and they would be admitting a failure.' Problems with communication were not common but when they occurred they were distressing. Occasionally families did not understand staffing rotations and found it confusing to talk with different staff members who provided different information or perspectives. 'You got different messages, depending on what particular doctor it was and what that doctor was looking at. So sometimes that might be positive and then the next doctor would come in and say well, this isn't so good" and so that was real confusing …' Two families were upset that information regarding prognosis and the possibility of withdrawal was presented to them at the person's bedside. A granddaughter said: 'The one doctor, the way he was talking in front of [the patient], I felt like hitting him over the side of the head and saying "wait a minute, this is a person here …"' Regarding timing of withdrawal, several problems occurred. One family, for whom the withdrawal of the ventilator from the person had been postponed several times for reasons unclear to them, blamed the staff for the emotionally difficult delays, saying the staff were afraid of the responsibility and: '… wanted the patient to live at least a few hours after they took it off to save their own nerves so they wouldn't feel like they were killing him.' Another family felt that the staff waited too long before coming to grips with withdrawal. When the family brought up withdrawal of the ventilator because they thought that the patient was suffering, the intern on duty quickly dismissed the idea: 'The young ones are gung ho and they're going to save his patient no matter what. The doctor's position was "As long as there's life there's hope." And we thought, well, hum, yeah, but this is painful, you know, for him and for us to watch him being in pain … as long as there's true hope, that's

Study	Tilden 1995[432]
	great, but if there isn't … so that was frightening.'
	Communication and information transmission: Families were, as 1 man said, 'starving for information.' Many families spoke of the need for more information, more timely information and better coordination. Although they appreciated, on the whole, that clinicians are understandably reluctant to give information prematurely that may later change, many subjects appealed for early and direct talk. Families wanted physicians to be honest about poor prognosis as soon as possible so that they could be prepared. Families requested more reading material in lay language about the person's condition and hospital policies, and more specifically directions about ICU expectations (for example, appropriate length of visits, best timing of visits, how to touch the person, how they could participate in the person's care, where to wait during procedures).
	Families in conflict: Significant conflict was found in several families regarding who exactly compromised the family or who had decision-making authority. These families advised physicians and nurses to take more time to clarify the composition of family, to provide a private setting for discussions so that conflicts within the family can surface and to limit the involvement of others peripheral to the decision.
Limitations	Serious limitations. Only 55% of those included in the study participated in interviews
Applicability of evidence	Indirect setting, outside of the UK.

Table 52: Vig 2007[449]

Study (ref id)	Vig 2007[449]
Aim	To gain an understanding of the experience and challenges of surrogate decision making.
Population	n=50, Surrogate decision makers of older, chronically ill, veteran people. Eligibility criteria included being identified as a surrogate decision maker by the veteran, being fluent in English, being able to participate in a telephone interview, being free of moderate to severe cognitive impartment (as determined by fewer than 5 errors on Short Portable Mental Status Questionnaire) and previous experience with surrogate decision making (as determined by asking potential participants if they had ever made a medical decision for someone who was too ill to make their own decisions). 76% of those included had made end of life decisions, 10% surgical management decisions and 14% medical management decisions. 68% of those included were spouses, 14% adult children, 8% other family, and 10% friend.
Setting	USA.
Study design and methodology	Participants were identified from an additional study on veterans. Semi structured telephone interviews were conducted asking participants to tell the story of their loved ones illness, to describe their experiences making medical decisions for others and to reflect on what made decision-making easier and harder for them. Interviews were recorded and transcribed. Further participants were recruited until data saturation was reached.

Study (ref id)	Vig 2007[449]		
Analysis methods	A content analysis of surrogate's reports of barriers and facilitators was undertaken- the research team independently read 3 of the transcripts and then met to draft coding schemes, and continued coding until consensus was reached. Remaining transcripts were then coded by 2 of the researchers with quality assurance in place- the percentage agreement ranged from 68%-75%.		
Themes with findings	Theme	Facilitators to decision making	Barriers to decision making
	Surrogates characteristics and life circumstances	Previous decision making experiences "*I had lost both parents of the same thing, so I had been through it before. And so I knew how to talk to him and bring up stuff that I knew that I'd been through and so it did help a lot".*	Physical distance between surrogate and the patient *"I wasn't there with him to really talk to him person to person"*
		Positive coping strategies /managing stress/hobbies "*I think my own strength [helped me make the decision], because to not do something that someone has asked to me would be a harder thing to live with than not doing it".*	Competing responsibilities (aging parents, or surrogates own health).
		Religious community support/spiritual beliefs.	
		Decision the surrogate can live with.	Financial barriers.
	Surrogates social networks	Support and others to talk to and working towards consensus.	Family conflict "*Family's family and when they're dying they want to have their say… it was a hard time… But [my brother] and I finally came to an agreement because I found some sort of a way to wait for him to come to terms with losing our mother".*
	Surrogate – patient relationship and communication	Responsibility, keeping a promise to the patient *"I had made a promise to him. It was that simple… You make that kind of commitment and you've got to do what you've got to do to see that its fulfilled… he was helpless, there was nothing more he could do".*	Not being able to follow the patients preferences *" I think the only thing that made it difficult was that I did know his wishes… to have his demise here at home, and we couldn't do it for him. We had to make the decision to take him into the hospital so that he would be more comfortable in his last hours".*
		Decision will result in a good outcome (that is, reduced suffering).	Emotions or attachment to the patient.
		Being involved- keeping up on the patients' medical condition *" I don't think I could've made those [decisions] if we hadn't*	Weighing a person's preferences against their quality of life.

Study (ref id)	Vig 2007[449]		
		discussed it".	
	Surrogate-clinician communication and relationship	Clinician availability	Too many involved clinicians "*There was just too many people: there were too many different stories. I was being told one thing and when another team would come through, they'd tell me something else. I was so confused during that time, I didn't know what was going on. At that point I said 'I want to speak to one person and one person only. I can't take in all this stuff'".*
		Frank information from clinicians in lay terms (prognosis, chances of recovery, how a person would die after withdrawal of ventilator support)	
		Recommendations from clinicians "*I talked to the doctors, and they all were very helpful in giving me proper information, and telling me that he probably wouldn't come out of it because his cancer had spread and plus he'd had pneumonia on top of it*"	
		Positive reinforcement for decision making	
		Respect from clinicians "*Dr f. was fairly new to me, but when a doctor treats the spouse with a lot of respect and answers questions like they're important, they give you the feeling of competence. And I think Dr F made me feel like a very important part of the team".*	
Limitations	No limitations. Well designed and analysed study.		
Applicability of evidence	Indirect population. Only 76% had made end of life decisions, unclear if there were themes directed towards this particularly or in general. Unclear if the patients had died or where in the last days of life in the study. Setting outside of the UK.		

Table 53: Willard 2006[470]

Study	Willard 2006[470]
Aim	Discuss the challenges to appropriate EOL care in acute hospitals in the UK, highlighting how this setting contributes to the patients' and families' care and treatment requirements being excluded from decision-making.
Population	**Healthcare professionals:** 29 cancer nurse specialists from 5 hospital trusts. Eligible CNSs were hospital-based registered nurses, whose roles appeared to involve a high level of expertise within the field of cancer and palliative care. Participants included: 3 nurse practitioners, 2 research nurses, 11 tumour-specific CNSs, 9 palliative care CNSs, 4 CNSs with combined tumour-specific and palliative care roles.

Study	Willard 2006[470]
Setting	UK.
Study design	Grounded theory study using observation and semi-structured interviews.
Methods and analysis	Data collection: Participants were selected according to the principles of purposive and theoretical sampling. Data collection involved 135 hours of observation followed by semi-structured interviews. Some CNSs agreed to both observation and interviews, resulting in observations with 15 CNSs and interviews with 17 CNSs. Observation took place in hospital outpatient and inpatient areas and included observing 73 CNS-patient interactions and numerous professional interactions. Participants were those at various stages of the disease process, from those recently diagnosed with cancer, to those who were in the final stages of their illness. The interviews were tape recorded and lasted between 30-90 minutes. Analysis: Field notes from observation and transcribed interviews were thematically analysed using a constant comparative method used in grounded theory. The qualitative data analysis package NVivo, was used to facilitate data management and analysis. Emerging categories were reviewed by KL and preliminary findings discussed with study participants who were able to attend a feedback session prior to compiling a final report.
Themes with findings	**Prioritization of treatment:** CNSs reported there was minimal discussion either within teams or with patients, about the overall aim and rationale of treatment. 'I deal with haematology patients as well, and the perception there is that it's treatment, treatment, treatment, right until, sometimes they don't actually stop, people die having active treatments, when maybe somebody should have at some point said "Well look, where are we going?".' Palliative care CNS. For CNSs, compliance with routine practice was a source of considerable frustration and contradictory to their beliefs about dying well, where comfort and control of symptoms take precedence. 'A lot of my work is in the surgical area, and thoughts are very surgical-moulded, so for example things like intravenous fluids, at the EOL, 3 or 4 litres a day, and they're actually prompting symptoms such as ascites and fluid overload and breathlessness, because their thoughts are still post-operatively rather than in EOL situations.' Palliative care CNS. For professionals geared to meeting the demands of treatment, there was a perception that palliative care was 'giving up' on the person when there was still much that could be done. 'Rather than palliative care being a good thing, it's actually seen in a very negative way and therefore kept at a distance. If the language of palliative care is difficult, it may be fair to assume that the language of treatment is quite the opposite perhaps pro-active and positive, there's more to be done, there is more to be given. It's still very much this separate camp – them and us camps.' Palliative care CNS. Prioritizing treatment and routine care also appeared to prevent attention to symptom management and discussion of patents' views and preferences about their treatment and care, even when there was opportunity to do so due to the person's expected deterioration. 'We went to see an elderly lady who had metastatic oesophageal cancer and bowel obstruction. She had been in hospital for about a week, was aware she was dying and had put her affairs in order. She told the CNS she wanted to die at home, but ward staff had not explored the

Study	Willard 2006[470]
	practicalities of this or other options of care. The person was still nil by mouth, subcutaneous fluids were being given and analgesia prescribed when necessary rather than regularly.' Tumour-specific/palliative care CNS. Although in this case the CNS had been able to elicit the person's preferences, it was too late for these to be acted upon.
	Critical junctures: Critical junctures are described as points in the course of a serious illness where current treatment could be evaluated in relation to changes in the person's condition. Critical junctures are not always recognised as opportunities to review and reset the treatment plan to one more appropriate to the person's deterioration or explore the patients' or families' preferences. 'A patient with lung cancer was admitted and had surgery for a suspected space-occupying lesion but it turned out she had brain metastases. The nurses were still continuing to do neuro-obs, and there was a train in the lady's head. The daughter was absolutely frantic you know, "is she dying?" She was vomiting and she had headaches and you know her treatment was very medicalised really. The family, they didn't want treatment to continue and wanted to get her off this really busy acute ward where no-one spend any time with them.' Palliative care CNS.
	Ethical challenges: While critical junctures provide opportunities to review current treatment plans, they also raise complex and uncomfortable ethical questions about what a person's deteriorating condition represents and whether it should be treated. A CNS describes how she and the consultant differed in their perception of a situation concerning a very ill person with dysphagia and the most ethical course of action. 'The consultant felt as though he couldn't let her die in that way, so I just said I thought she was dying, and it isn't pleasant having a feeding tube put in, they don't always work, there are complications and the risk of having all that for the outcome, I didn't feel that it was justified. He could understand where I was coming from and it did make him think about it, but he still was saying well you know we should give it a go.' Palliative care CNS. Even when people are capable of expressing their wishes, it appears that the treatment ethos of the acute setting may contribute to the paternalistic professional stance, in which the views of certain categories of people may be overlooked and, therefore, excluded from the decision –making process. 'We went to see an elderly man admitted (not for the first time) with bleeding oesophageal varices. The patient looked very ill and frail: he had also been diagnosed with bladder cancer 3 years earlier but had refused treatment. In the medical notes, a treatment plan involving further investigations and surgery for the varices had been documented, but according to nursing staff, the patient just wanted to return home where he lived with his brother. The CNS talked to the patient about the proposed surgery, he was very sure he did not want any treatment that he thought he was dying but had to die of something, and would rather spend his remaining time at home. When the CNS discussed his case with the senior doctor, she said she believed he had been mismanaged in the past and that the proposed surgery was essential. The CNS pointed out that the person was very clear about what he wanted and if he was aged 25 and mobile, he would simply discharge himself. While the doctor accepted this, she was also keen to pursue the banding to prevent further bleeding.' Palliative care CNS.
Limitations	Serious limitations. Analysis of themes conducted by 1 individual only.
Applicability of	Direct UK setting.

Study	Willard 2006[470]
evidence	

H.4 Assisted Hydration

Table 54: Bruera et al 2005. trial: Bruera 2005[73]

Study	Bruera et al 2005. trial: Bruera 2005[73]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=51)
Countries and setting	Conducted in USA; Setting: Multicentre trial based in hospitals.
Duration of study	Intervention + follow up: 2 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis.
Stratum	Cancer.
Subgroup analysis within study	Not applicable: Not done.
Inclusion criteria	A diagnosis of advanced cancer with no further treatment planned; an oral intake of less the 1000 ml/day; evidence of mild to moderate dehydration (decreased skin turgor in subclavicular region more than 2 seconds, plus at least 1 of the following findings: dry mouth, thirst, decreased volume of urine, in the absence of reasons for jaundice or haematuria, and biochemical values consistent with dehydration).
Exclusion criteria	Refusal to participate. The presence of severe dehydration, defined as a decreased systolic resting BP 30 mmHg or lower from baseline value, low perfusion of limbs and no UO for 12 hours or longer, a decreased level of consciousness or evidence of severe renal failure or bilateral hydronephrosis.
Recruitment/selection of patients	Not mentioned.
Age, gender and ethnicity	Age - Mean (range): 63 years (28-90 years). Gender (M:F): 24:27.
Indirectness of population	No indirectness: Compares intervention with control on symptom control using appropriate scales.
Interventions	(n=28) Intervention 1: Clinically assisted hydration - Parenteral hydration. 1000 ml of normal saline given over 4 hours, once daily. Duration 2 days. Concurrent medication/care: Given IV if IV access available, subcutaneous if no IV access

	available. (n=23) Intervention 2: Placebo - Clinically insignificant amounts. 100 ml of normal saline. Duration 2 days. Concurrent medication/care: IV if IV access available, subcutaneous if no IV access
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARENTERAL HYDRATION VERSUS CLINICALLY INSIGNIFICANT AMOUNTS Protocol outcome 1: Quality of life - Actual outcome for cancer: Global patient perception of benefit at 2 days; Group 1: mean 3.8 1-7 scale rating (SD 2.2); n=27, Group 2: mean 3.6 1-7 scale rating (SD 2.4); n=22; Overall wellbeing 1-7 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for cancer: Global investigators perception of benefit at 2 days; Group 1: mean 4.5 1-7 (SD 2.3); n=27, Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for cancer: Patients perception of wellbeing at 2 days; Group 1: mean 1.4 (SD 4.1); n=27, Group 2: mean 0.8 (SD 3.1); n=22; Perception of wellbeing 1-10 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for cancer: Investigators perception of wellbeing at 2 days; Group 1: mean 1.2 (SD 3.9); n=27, Group 2: mean 0.9 (SD 2.7); n=22; Quality of life 1 (worst possible) -10 (best possible) Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Symptom improvement - Actual outcome for cancer: hallucinations at 2 days; Group 1: 9/11, Group 2: 7/14; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for cancer: sedation at 2 days; Group 1: 15/18, Group 2: 5/15; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for cancer: myoclonus at 2 days; Group 1: 15/18, Group 2: 8/17; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for cancer: symptoms totalled together at 2 days; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Adverse events procedural at end of study - Actual outcome for cancer: Pain at injection site at 2 days; Group 1: mean 1.41 (SD 2.9); n=27, Group 2: mean 1.75 (SD 2.55); n=22; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for cancer: swelling at injection site at 2 days; Group 1: mean 0.82 (SD 1.13); n=27, Group 2: mean 1.41 (SD 1.66); n=22; NRS 0-10 Top=--; Risk of bias: High; Indirectness of outcome: No indirectness	

Table 55: Bruera et al 2013 trial: Bruera 2013[68]

Study	**Bruera et al 2013 trial: Bruera 2013[68]**

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=129)
Countries and setting	Conducted in USA, Setting: Home
Duration of study	Intervention time: 7 days
Stratum	Cancer
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged>18. Admitted to hospice. Reduced oral intact of fluids with evidence of mild or moderate dehydration as defined by a) decreased skin turgor in subclavicular region (2 seconds) and a score of >2 of 5 in the clinical dehydration assessment. Intensity of >1 on a 0 to 10 scale for fatigue and 2 of the 3 other target symptoms (hallucinations, sedation and myoclonus). Life expectancy 1 week. Availability of a primary carer. MDAS score <13. Ability to give written informed consent. Geographic accessibility (within 60 miles of the University of Texas MD Anderson Cancer Centre.
Exclusion criteria	Severe dehydration defined as decreased blood pressure or low perfusions of limbs, decreased level of consciousness or no urine output for 12 hour, history or clinical evidence of renal failure with creatinine more than 1.5 x upper normal limit, history or clinical evidence of congestive heart failure, or history of bleeding disorders demonstrated by clinical evidence of active bleeding, haematuria, hematoma, ecchymoses, and petechiae.
Recruitment/selection of patients	Recruited from inpatients at hospice within the geographical area of MD Anderson Cancer Centre.
Age, gender and ethnicity	Age - Mean (range): 67 (41-92). Gender (M:F): 68:61
Indirectness of population	No indirectness.
Interventions	(n=63) Intervention 1: Clinically assisted hydration - Parenteral hydration. 1000 ml normal saline administered subcutaneously over 4 hours daily. Duration 7 days. Concurrent medication/care: usual palliative care, visited daily by research nurse to start fluids. (n=66) Intervention 2: Placebo - Clinically insignificant amounts. 100 ml of normal saline administered subcutaneously over 4 hours, daily. Duration 7 days. Concurrent medication/care: Usual palliative care received, and daily visits from the research nurse to start the infusion.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARENTERAL HYDRATION VERSUS CLINICALLY INSIGNIFICANT AMOUNTS Protocol outcome 1: Quality of life	

- Actual outcome for cancer: Quality of life using FACT G scale. Measured difference at baseline and 7 days; Group 1: mean 6.7 (SD 11.2); n=44, Risk of bias: Low; Indirectness of outcome: Serious indirectness

Protocol outcome 2: Symptom improvement
- Actual outcome for cancer: Global symptom evaluation. Measured difference at baseline and 7 days; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for cancer: Change in the sum of 4 dehydration symptoms at difference at baseline and 7 days; Group 1: mean -4.9 (SD 9.2); n=44, Group 2: mean -3.8 (SD 9.05); n=49; ESAS composite for fatigue, drowsiness, hallucinations and myoclonus 1-10 for each outcome, 4-40 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
outcome; Risk of bias: low; Indirectness of outcome: No indirectness

Protocol outcome 3: Adverse symptoms related to dehydration at end of study
- Actual outcome for cancer: Delirium using MDAS score at difference at baseline and 7 days; Risk of bias; Indirectness of outcome: No indirectness
- Actual outcome for cancer: Delirium using NuDESC score at difference at baseline and 7 days; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Hydration assessment
- Actual outcome for cancer: change in dehydration assessment score difference at baseline and 7 days.; Group 1 mean -1 (SD 1.7) n=44; Group 2 -0.5 (SD 1.4) n=49 Risk of bias: high; Indirectness of outcome: No indirectness

Protocol outcome 5: Biochemistry at end of study
- Actual outcome for cancer: change in urea difference at baseline and 7 days.; Group 1 median -2 (range -7 to 3) n=44; Group 2, median 2 (range -1 to 8) n=49 Risk of bias: very high; Indirectness of outcome: No indirectness
- Actual outcome for cancer: change in sodium difference at baseline and 7 days.; Group 1 mean 1.9 (SD 5.0) n=44; Group 2 0.7 (SD 5.0) n=49 Risk of bias: very high; Indirectness of outcome: No indirectness
- Actual outcome for cancer: change in creatinine difference at baseline and 7 days.; Group 1 median -0.1 (range -0.2 to 0) n=44; Group 2 –0.1 (range -0.1 to 0.1) n=49 Risk of bias: very high; Indirectness of outcome: No indirectness

Protocol outcome 6: Survival at end of study
Actual outcome for cancer, survival; Group 1 median 21 (range 13 to 29) n=44; Group 2, median 15 (range 12 to 18) n=49 Risk of bias: very high; Indirectness of outcome: No indirectness

Table 56: Cerchietti et al 2000 trial: Cerchietti 2000[88]

Study	Cerchietti et al 2000 trial: Cerchietti 2000[88]

Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in USA; Setting: Not specified.
Duration of study	48 hours.
Stratum	Cancer.
Subgroup analysis within study	Not applicable
Inclusion criteria	People with terminal stage advanced cancer. More than 1 of the following symptoms: thirst, chronic nausea (>4 weeks) or delirium, dehydration diagnosed on physical examination, with our without renal failure, and an inability to maintain adequate hydration (<50 ml/day fluid).
Exclusion criteria	Uncontrolled symptoms (pain in 2 of the participants, sever dyspnoea in 2), 1 bowel obstruction syndrome require surgery, 3 severe constipation.
Recruitment/selection of patients	Not specified.
Age, gender and ethnicity	Age - Mean (SD): 55.8 (7.5) and 51.7 (4.5) hydration: no hydration. Gender (M:F): 17:25.
Further population details	1. Setting: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness.
Interventions	(n=20) Intervention 1: Clinically assisted hydration - Parenteral hydration. 1000 ml of 5 % dextrose with 140 nEq/litre sodium chloride per day, at an infusion rate of 42 ml/hour subcutaneous. Duration 48 hours. Concurrent medication/care: Continued taking medication as already prescribed via subcutaneous route. Haloperidol 2.5 mg 4 hourly and/or 10 mg metoclopramide 4 hourly. Thirst control achieved by daily antiseptic mouth rinsing, and administration of 2 ml water every 30-60 minutes. (n=22) Intervention 2: Placebo - No intervention. No treatment. Duration 48 hours. Concurrent medication/care: Continued taking medication as already prescribed via subcutaneous route. Haloperidol 2.5mg 4 hourly and/or 10mg metoclopramide 4 hourly. Thirst control achieved by daily antiseptic mouth rinsing, and administration of 2 ml water every 30-60 minutes. Comments: Morphine was not controlled between the 2 groups, or mentioned in analysis.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARENTERAL HYDRATION VERSUS NO INTERVENTION Protocol outcome 1: Adverse events procedural at end of study	

- Actual outcome for cancer: Local adverse reactions due to subcutaneous administration at 48 hours; Group 1: 1/20, Group 2: 0/22; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Adverse events, over hydration at end of study - Actual outcome for cancer: Severe adverse reactions that required the interruption of hydration. at 48 hours; Group 1: 0/20, Group 2: 0/22; Risk of bias: Very high; Indirectness of outcome: No indirectness.	

Table 57: Morita et al 2005 trial: Morita 2005[327]

Study	**Morita et al 2005 trial: Morita 2005[327]**
Study type	Prospective cohort study
Number of studies (number of participants)	(n=226)
Countries and setting	Conducted in Japan; Setting: oncology units, palliative/home care settings.
Duration of study	21 days
Stratum	Cancer
Inclusion criteria	Age >20 years; life expectancy estimated by a physician to be <3 months; and incurable malignancy of abdominal origin
Exclusion criteria	Liver cirrhosis of any aetiology, renal failure, nephrotic syndrome, protein losing enteropathy, intra-abdominal shunt for ascites, hypercalcaemia, adrenalopathy, thyroid diseases, and other complications of the circulatory, respiratory, hepatic, or renal system unrelated to underlying malignancies. Surgical, radiological or oncological treatments with the primary intent of tumour reduction in the 3 weeks prior to study inclusion; existing communication difficulty such as aphasia or aphonia; and the use of assisted enteral nutrition.
Recruitment/selection of patients	From patients already being treated at the institutions.
Age, gender and ethnicity	Age - Mean (SD): 68. Gender (M:F): 101:109.
Indirectness of population	No indirectness.
Interventions	(n=59) Intervention 1: Clinically assisted hydration - Parenteral hydration. More than 1 litre/ day of clinically assisted hydration or more at both 1 week and 3 weeks before death. Duration 3 weeks. Concurrent medication/care: Usual Care

	Further details: 1. Route of administration: 2. Volume of fluid administered: (n=167) Intervention 2: Placebo - Clinically insignificant amounts. People who received less the 1/day of clinically assisted hydration at both 1 week and 3 weeks before death. Duration 3 weeks. Concurrent medication/care: Usual treatment Further details: 1. Route of administration: 2. Volume of fluid administered:
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARENTERAL HYDRATION VERSUS CLINICALLY INSIGNIFICANT AMOUNTS Protocol outcome 1: Adverse symptoms related to dehydration at end of study - Actual outcome for cancer: Hyperactive delirium at 3 weeks; Group 1: 7/59, Group 2: 22/167; Risk of bias: Very high; Indirectness of outcome: serious Protocol outcome 2: Adverse events, over hydration at end of study - Actual outcome for cancer: Pleural effusion at 3 weeks; Group 1: mean 0.36 (SD 0.61); n=59, Group 2: mean 0.31 (SD 0.63); n=167; Pleural effusion score 0-2 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: serious - Actual outcome for cancer: Oedema at 3 weeks; Group 1: mean 6.1 (SD 6.4); n=59, Group 2: mean 5.2 (SD 5.2); n=167; Peripheral oedema score 0-21 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: serious Protocol outcome 3: Hydration status at end of study Actual outcome for cancer: Dehydration assessment Group 1: mean 2.7 (SD 1.6); n=59, Group 2: mean 3.2 (SD 1.5); n=167; Ad hoc dehydration score 0-5 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: serious Protocol outcome 4: Biochemistry at end of study Actual outcome for cancer: Urea/creatinine, Group 1: mean 44 (SD 18); n=37, Group 2: mean 39 (SD 20); n=56; urea/creatinine mg/dl, Risk of bias: Very high; Indirectness of outcome: serious	

Table 58: Viola 1997 trial: Viola 1997[450]

Study	**Viola 1997 trial: Viola 1997[450]**
Study type	Prospective cohort study
Number of studies (number of participants)	(n=66)
Countries and setting	Conducted in Canada; Setting: Hospices. Took place in 2 hospices, located in Edmonton, and Ottawa.

Duration of study	14 days
Stratum	Cancer
Subgroup analysis within study	Not applicable
Inclusion criteria	Advanced cancer. Inpatients of either Edmonton or Ottawa palliative care units with advanced cancer, not aphasic, MMSE >24, and subjectively competent (as judged by physicians), able to understand English if at the Edmonton site, or English or French at Ottawa site. Has a history of poor oral fluid intact, or excess fluid loss or both, plus a history of decreased urine output, dry mouth sensation, thirst sensation postural dizziness, or combination, or resting heart rate >100 BPM, dry mucous membranes, enophthalmos, or combination.
Exclusion criteria	Receiving enteral tube feedings, acute renal failure, pulmonary oedema, or bleeding disorders, aphasic, MMSE <24. Immediate discharge planned.
Recruitment/selection of patients	People were recruited from existing inpatients at 2 hospice sites.
Age, gender and ethnicity	Age - Mean (SD): 63.5. Gender (M:F): 29:35. Ethnicity: NA
Further population details	1. Setting: Hospice
Extra comments	Most participants were excluded because of cognitive defects. 2 from incomplete data, and 1 from a bleeding disorder
Interventions	(n=33) Intervention 1: Clinically assisted hydration - Parenteral hydration. Subcutaneous fluids titrated to participant needs. Either 0.9% NaCl, or 0.3% NaCl with 3.3% dextrose. Hyaluronidase 750 units added to each 1 litre of fluid solution. The median volume was approximately 1000 ml/day. Duration-Until death/no longer having a fluid deficit or discharge from palliative care unit. Concurrent medication/care: usual care. Further details: 1. Route of administration: Subcutaneous 2. Volume of fluid administered: 1 litre a day or more (n=33) Intervention 2: Placebo - No intervention. No administered fluids. Duration Until death/no longer having a fluid deficit or discharge from palliative care unit. Concurrent medication/care: Usual Care. Further details: 1. Route of administration: Not applicable / Not stated / Unclear. 2. Volume of fluid administered: Not applicable / Not stated / Unclear
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARENTERAL HYDRATION VERSUS NO INTERVENTION Protocol outcome 1: Symptom improvement - Actual outcome for cancer: Wellbeing during the afternoon at Day 14; Group 1: mean 52.5 (SD 26.4); n=17, Group 2: mean 80 (SD 21.4); n=6; Risk of bias: Very high; Indirectness of outcome: No indirectness	

- Actual outcome for cancer: Nausea during afternoon. at Day 14; Group 1: mean 23.8 (SD 30.5); n=20, Group 2: mean 21.3 (SD 40.2); n=8; VAS 1-100 Top=High is poor outcome; Risk of bias: --; Indirectness of outcome: No indirectness
- Actual outcome for cancer: Thirst during the afternoon at Day 14; Group 1: mean 47.4 (SD 32.4); n=18, Group 2: mean 61.2 (SD 12.1); n=4; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for cancer: Anxiety during the afternoon at Day 14; Group 1: mean 17 (SD 19); n=20, Group 2: mean 27.5 (SD 34.5); n=6; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for cancer: Pain during the afternoon at Day 14; Group 1: mean 20 (SD 15.3); n=20, Group 2: mean 29.4 (SD 27.2); n=8; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for cancer: Dyspnoea during afternoon at Day 14; Group 1: mean 20.9 (SD 24); n=20, Group 2: mean 12.9 (SD 24.8); n=7; VAS 1-100 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness

Table 59: Waller 1994 trial: Waller 1994[463]

Study	**Waller 1994 trial: Waller 1994[463]**
Study type	Prospective cohort study
Number of studies (number of participants)	(n=68)
Countries and setting	Conducted in Israel; Setting: Hospice.
Duration of study	2 days.
Method of assessment of guideline condition	Method of assessment /diagnosis not stated.
Stratum	Cancer.
Subgroup analysis within study	Not applicable.
Inclusion criteria	People receiving palliative care admitted to hospice from other hospitals or GPs in whom blood and urine samples collected less the 48 hours before their death.
Exclusion criteria	No blood tests/urine samples available.
Recruitment/selection of patients	Prospective controlled single centre study.
Age, gender and ethnicity	Age - Other: Unclear. Gender (M:F): Unclear. Ethnicity: NA

Further population details	1. Setting: Hospice
Indirectness of population	Serious indirectness: Only looked at people who had their blood taken in the last 48 hours of life, unclear why taken, whether there were concerns about this population's serology in the first place and are not usual patients.
Interventions	(n=55) Intervention 1: Placebo - Clinically insignificant amounts. Oral hydration only, volumes not described. Duration 48 hours. Concurrent medication/care: Normal palliative treatment. (n=13) Intervention 2: Clinically assisted hydration - Parenteral hydration. 1-2l/day IV fluids. Duration 48 hours. Concurrent medication/care: Normal palliative treatment
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARENTERAL HYDRATION VERSUS CLINICALLY INSIGNIFICANT AMOUNTS Protocol outcome 1: Adverse symptoms related to dehydration at end of study - Actual outcome for cancer: State of consciousness at 48 hours. Impossible to extract data from the study but listed as no significant difference between the groups; Risk of bias: Very high; Indirectness of outcome: Serious indirectness Protocol outcome 2: Actual outcome for cancer: urea/creatinine at 48 hours; Group 1: mean 33 (SD 13.4); n=13, Group 2: mean 33.5 (SD 14); n=55; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Actual outcome for cancer: sodium during at 48 hours; Group 1: mean 148.5 (SD 10); n=13, Group 2: mean 139 (SD 7.3); n=54; Risk of bias: Very high; Indirectness of outcome: No indirectness	

H.5 Pharmacological Intervention

Table 60: Booth 1996[59]

Study	**Booth 1996[59]**
Study type	RCT (randomised; Crossover: No formal washout period. Duration of each treatment was 15 minutes in order to allow sufficient time for previously administered gas to wash-out before assessment).
Number of studies (number of participants)	1 (n=38)
Countries and setting	Conducted in United Kingdom; Setting: Two hospices.
Line of therapy	Unclear.

Duration of study	Intervention time: <1 day.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Mean survival time 19 days.
Stratum	Breathlessness management: A person's breathless at rest.
Subgroup analysis within study	Post-hoc subgroup analysis: History of cardiopulmonary disease.
Inclusion criteria	Hospice inpatients with advanced cancer and breathlessness at rest.
Exclusion criteria	Already receiving chronic oxygen therapy.
Recruitment/selection of patients	Unclear.
Age, gender and ethnicity	Age - Median (range): 71 (54-90). Gender (M:F): 58/42%. Ethnicity: Not stated.
Further population details	
Extra comments	20 had primary lung cancers, 2 had mesothelioma, and 16 had other primary cancers with metastases to the lung. 13 had significant COPD and 4 had significant cardiac disease. Modified Borg scale may not be appropriate in this setting.
Indirectness of population	Serious indirectness: Majority of people in last 15-30 days.

Interventions	(n=38) Intervention 1: Breathing gas - Oxygen. Oxygen from camouflaged cylinders via nasal cannulae at 4 litres/minute. Duration 15 minutes. Concurrent medication/care: Morphine: 13; benzodiazepine: 6; morphine and benzodiazepine: 14 Further details: 1. Delivery system: Delivery system: nasal tube 2. Drug class: Breathing gas 3. Route of administration: Route of administration: transmucosal. (n=38) Intervention 2: Breathing gas - Air. Air from camouflaged cylinders via nasal cannulae at 4l/min. Duration 15 minutes. Concurrent medication/care: Morphine: 13; benzodiazepine: 6; morphine and benzodiazepine: 14 Further details: 1. Delivery system: Delivery system: nasal tube 2. Drug class: Breathing gas 3. Route of administration: Route of administration: transmucosal. (n=20) Intervention 3: Breathing gas - Oxygen. Oxygen followed by air from camouflaged cylinders via nasal cannulae at 4l/min. Duration 30 minutes. Concurrent medication/care: Unclear Further details: 1. Delivery system: Delivery system: nasal tube 2. Drug class: Breathing gas 3. Route of administration: Route of administration: transmucosal. (n=18) Intervention 4: Breathing gas - Air. Air followed by oxygen from camouflaged cylinders via nasal cannulae at 4l/min. Duration 30 minutes. Concurrent medication/care: Unclear Further details: 1. Delivery system: Delivery system: nasal tube 2. Drug class: Breathing gas 3. Route of administration: Route of administration: transmucosal.
Funding	Academic or government funding.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OXYGEN versus AIR Protocol outcome 1: Adverse events/withdrawal of the medication due to adverse events at Any - Actual outcome for Breathlessness management: Adverse effects relating to study procedure at Unclear; Group 1: 0/38, Group 2: 0/38; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Control of breathlessness at Any - Actual outcome for Breathlessness management: Vertical 100 mm VAS (0 - no shortness of breath; 100 - shortness of breath as bad as can be) at 15 minutes; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Breathlessness management: Modified Borg scale at 15 minutes; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Time to death at Any - Actual outcome for Breathlessness management: Mean survival time at Unclear; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at Any; Sedation (GCS/AVPU) at Any; Control of anxiety at Any; Control of agitation at Any; Control of delirium at Any; Duration of symptom control at Any; Time to symptom control at Any; Duration of institutional care at Any; Carer satisfaction at Any; Pain control at Any

Table 61: Clemens 2009[106]

Study	**Clemens 2009[106]**
Study type	Non-randomised comparative study.
Number of studies (number of participants)	1 (n=46)
Countries and setting	Conducted in Germany; Setting: Palliative care unit inpatients.
Line of therapy	Not applicable.
Duration of study	Intervention time.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Mean survival.
Stratum	Breathlessness management.
Subgroup analysis within study	Not stratified but pre-specified: Hypoxic (SaO2 <90%)/non-hypoxic and opioid naive/pre-treated.

Inclusion criteria	Advanced terminal cancer or other terminal incurable disease and dyspnoea at rest; normal cognitive status; Hb at least 10 g/dl measured within 2 weeks.
Exclusion criteria	Evidence of non-compensated congestive heart failure, severe renal or haptic failure, other uncontrolled symptoms that could require opioids.
Recruitment/selection of patients	Not stated.
Age, gender and ethnicity	Age - Median (range): Hypoxic: 66.5 (40-90); non-hypoxic: 70.5 (40-86). Gender (M:F): 50/50. Ethnicity: Not stated.
Further population details	
Indirectness of population	Serious indirectness: Mean (SD) survival 16.2 (11.9) days and 28.4 (22.4) days, hypoxic and non-hypoxic groups.
Interventions	(n=46) Intervention 1: Breathing gas - Oxygen. Oxygen 4 l/min via nasal cannula. Duration 60 minutes. Concurrent medication/care: Unclear Further details: 1. Delivery system: Delivery system: nasal tube 2. Drug class: Breathing gas 3. Route of administration: Route of administration: transmucosal Comments: Unclear washout period. (n=46) Intervention 2: Breathing gas - Room air. Baseline conditions. Duration Initial assessment. Concurrent medication/care: Unclear Further details: 1. Delivery system : Not applicable / Not stated / Unclear 2. Drug class: Breathing gas 3. Route of administration: Not applicable / Not stated / Unclear Comments: Unclear washout period. (n=46) Intervention 3: Opioids - Morphine. Initially immediate-release opioids every 4 hours and rescue doses if required (1/6 of daily dose) for breakthrough dyspnoea, followed by sustained release preparations q8-12h once dyspnoea and pain had reached tolerable levels. Initial dose defined according to dyspnoea intensity and performance status, and was increased in the titration phase. The choice of opioid (morphine or hydromorphone) was also based on dyspnoea intensity and performance status (patients pre-treated with high dose opioids or with low performance status, severe dyspnoea and/or mild renal dysfunction were given hydromorphone). Duration Ongoing. Concurrent medication/care: Rescue doses permitted. Further details: 1. Delivery system: Delivery system: oral tablet or liquid 2. Drug class: Opioid 3. Route of administration: Route of administration: enteral Comments: Unclear washout period.

Funding	Academic or government funding.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OXYGEN versus ROOM AIR.

Protocol outcome 1: Control of breathlessness at Any
- Actual outcome for Breathlessness management: Dyspnoea intensity at rest (patient-rated 0-10 scale) in opioid-naive hypoxic patients at During 60 minutes oxygen vs. baseline; Group 1: mean 5.8 (SD 2); n=11, Risk of bias: Very high; Indirectness of outcome: Serious indirectness.
- Actual outcome for Breathlessness management: Dyspnoea intensity at rest (patient-rated 0-10 scale) in opioid-pretreated hypoxic patients at During 60 minutes oxygen vs. baseline; Group 1: mean 5.5 (SD 2.3); n=7, Risk of bias: Very high; Indirectness of outcome: Serious indirectness.
- Actual outcome for Breathlessness management: Dyspnoea intensity at rest (patient-rated 0-10 scale) in opioid-pretreated non-hypoxic patients at During 60 minutes oxygen vs. baseline; Group 1: mean 5.5 (SD 2.3); n=11, Risk of bias: Very high; Indirectness of outcome: Serious indirectness.
- Actual outcome for Breathlessness management: Dyspnoea intensity at rest (patient-rated 0-10 scale) in opioid-naïve non-hypoxic patients at During 60 minutes oxygen vs. baseline; Group 1: mean 6 (SD 2); n=17, Risk of bias: Very high; Indirectness of outcome: Serious indirectness.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OXYGEN versus MORPHINE

Protocol outcome 1: Control of breathlessness at Any
- Actual outcome for Breathlessness management: Dyspnoea intensity at rest (patient-rated 0-10 scale) in opioid-naive non-hypoxic patients at During 60 minutes oxygen vs. 120 min after opioid; Group 1: mean 6 (SD 2); n=17, Risk of bias: Very high; Indirectness of outcome: Serious indirectness.
- Actual outcome for Breathlessness management: Dyspnoea intensity at rest (patient-rated 0-10 scale) in opioid-pretreated non-hypoxic patients at During 60 minutes oxygen vs. 120 min after opioid; Group 1: mean 5.5 (SD 2.3); n=11, Risk of bias: Very high; Indirectness of outcome: Serious indirectness.
- Actual outcome for Breathlessness management: Dyspnoea intensity at rest (patient-rated 0-10 scale) in opioid-pretreated hypoxic patients at During 60 minutes oxygen vs. 120 min after opioid; Group 1: mean 5.5 (SD 2.3); n=7, Risk of bias: Very high; Indirectness of outcome: Serious indirectness.
- Actual outcome for Breathlessness management: Dyspnoea intensity at rest (patient-rated 0-10 scale) in opioid-naive hypoxic patients at During 60 minutes oxygen vs. 120 min after opioid; Group 1: mean 5.8 (SD 2); n=11, Risk of bias: Very high; Indirectness of outcome: Serious indirectness.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MORPHINE versus ROOM AIR

Protocol outcome 1: Control of breathlessness at Any
- Actual outcome for Breathlessness management: Dyspnoea intensity at rest (patient-rated 0-10 scale) in opioid-naive non-hypoxic patients at 120 min after opioid vs. baseline; Group 1: mean 1 (SD 1.07); n=17, Risk of bias: Very high; Indirectness of outcome: Serious indirectness.
- Actual outcome for Breathlessness management: Dyspnoea intensity at rest (patient-rated 0-10 scale) in opioid-pretreated non-hypoxic patients at 120 min after opioid vs. baseline; Group 1: mean 1.3 (SD 1); n=11, Risk of bias: Very high; Indirectness of outcome: Serious indirectness.
- Actual outcome for Breathlessness management: Dyspnoea intensity at rest (patient-rated 0-10 scale) in opioid-pretreated hypoxic patients at 120 min after opioid vs. baseline; Group 1: mean 2 (SD 0.5); n=7, Risk of bias: Very high; Indirectness of outcome: Serious indirectness.

- Actual outcome for Breathlessness management: Dyspnoea intensity at rest (patient-rated 0-10 scale) in opioid-naive hypoxic patients at 120 min after opioid vs. baseline; Group 1: mean 2 (SD 1.07); n=11, Risk of bias: Very high; Indirectness of outcome: Serious indirectness.	
Protocol outcomes not reported by the study	Quality of life at Any; Sedation (GCS/AVPU) at Any; Adverse events/withdrawal of the medication due to adverse events at Any; Control of anxiety at Any; Control of agitation at Any; Control of delirium at Any; Duration of symptom control at Any; Time to symptom control at Any; Duration of institutional care at Any; Carer satisfaction at Any; Time to death at Any; Pain control at Any

Table 62: Navigante 2006[345]

Study	**Navigante 2006[345]**
Study type	RCT (Patient randomised; Parallel.)
Number of studies (number of participants)	1 (n=101)
Countries and setting	Conducted in Argentina; Setting: Cancer Institute.
Line of therapy	Unclear.
Duration of study	Intervention time: 48 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Life expectancy <1 week.
Stratum	Breathlessness management: Severe dyspnoea at rest.
Subgroup analysis within study	Not applicable.
Inclusion criteria	People who could provide informed consent and who were 18 years of age or older, with a documented diagnosis of terminal advanced cancer, life expectancy less than a week, Mini-Mental Status Exam (MMSE) > 23/30, severe dyspnoea at rest, and a performance status of 4 (Eastern Cooperative Oncology Group categorical scale, where 0 is “fully active” and 4 is “completely disabled”).
Exclusion criteria	Chronic obstructive pulmonary disease with hypercapnia, non-compensated congestive heart failure, severe renal or hepatic failure (clinically and/or biochemically detected), and other uncontrolled (numerical rating scale > 3/10) symptoms (excepting anxiety associated with dyspnoea) that could require the use of opioids, benzodiazepines, glucocorticosteroids, phenothiazines, bronchodilators, or methylxanthines.
Recruitment/selection of patients	Not stated.

Age, gender and ethnicity	Age - Mean (SD): 57.3. Gender (M:F): 47/53%. Ethnicity: Not stated.
Further population details	
Extra comments	11% were opioid naive. Modified Borg scale may not be appropriate in this population.
Indirectness of population	No indirectness.
Interventions	(n=35) Intervention 1: Opioids - Morphine. Around-the-clock morphine (2.5 mg every 4 hours for opioid-naïve patients or a 25% increment above the daily subcutaneous equivalent dose of morphine (DsEDM)for those receiving baseline opioids) with midazolam rescues (5 mg) in case of breakthrough dyspnoea. Total daily opioid dose was calculated and converted to oral morphine equivalents. A 3:1 ratio was used to convert oral dose to subcutaneous dose of morphine. If the DsEDM was lower than 15 mg, then people were considered opioid naïve. If the DsEDM was equal to or higher than 15 mg, people received an increase in dose equal to 25% of their respective DsEDM. All drugs were given subcutaneously through a butterfly needle located in the infraclavicular space. . Duration 48 hours. Concurrent medication/care: Psychological, spiritual, and non-pharmacological support (air therapy, breathing therapy, relaxation exercises) were offered by nurses or caregivers. None of the participants received oxygen therapy and/or steroids and/or pharmacological treatment to control respiratory symptoms during the study or prior to their inclusion but people who received morphine were systematically premedicated with laxatives. Further details: 1. Delivery system: Delivery system: SC delivery 2. Drug class: Opioid 3. Route of administration: Route of administration: subcutaneous Comments: The treatment was suspended for people who developed somnolence Grade 3 (a person sleeping between 6 and 11 hours during the day) or more at the moment of receiving the corresponding dose of medication. (n=33) Intervention 2: Benzodiazepines - Midazolam. Around-the-clock midazolam (5 mg every 4 hours) with morphine rescue doses (2.5 mg) in case of breakthrough dyspnoea. All drugs were given subcutaneously through a butterfly needle located in the infraclavicular space.. Duration 48 hours. Concurrent medication/care: Psychological, spiritual, and non-pharmacological support (air therapy, breathing therapy, relaxation exercises) were offered by nurses or caregivers. None of the participants received oxygen therapy and/or steroids and/or pharmacological treatment to control respiratory symptoms during the study or prior to their inclusion. Further details: 1. Delivery system: Delivery system: SC delivery 2. Drug class: Benzodiazepine 3. Route of administration : Route of administration: subcutaneous Comments: The treatment was suspended for people who developed somnolence Grade 3 (a person sleeping between 6 and 11 hours during the day) or more at the moment of receiving the corresponding dose of medication. (n=33) Intervention 3: Opioid + benzodiazepine - Morphine + midazolam. Around-the-clock morphine (2.5 mg every 4 hours for opioid-naïve patients or a 25% increment above the DsEDM) plus midazolam (5 mg every 4 hours) with

	morphine rescue doses (2.5 mg) in case of breakthrough dyspnoea. Duration 48 hours. Concurrent medication/care: Psychological, spiritual, and non-pharmacological support (air therapy, breathing therapy, relaxation exercises) were offered by nurses or caregivers. None of the participants received oxygen therapy and/or steroids and/or pharmacological treatment to control respiratory symptoms during the study or prior to their inclusion, but people who received morphine were systematically premedicated with laxatives. Further details: 1. Delivery system: Delivery system: SC delivery 2. Drug class: Not applicable / Not stated / Unclear (Combination). 3. Route of administration: Route of administration: subcutaneous Comments: The treatment was suspended for people who developed somnolence Grade 3 (a person sleeping between 6 and 11 hours during the day) or more at the moment of receiving the corresponding dose of medication.
Funding	Funding not stated.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIDAZOLAM versus MORPHINE Protocol outcome 1: Adverse events/withdrawal of the medication due to adverse events at Any - Actual outcome for Breathlessness management: Somnolence at 48 hours; Group 1: 2/33, Group 2: 6/35; Risk of bias: High; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Nausea/vomiting at 48 hours; Group 1: 1/33, Group 2: 4/35; Risk of bias: High; Indirectness of outcome: No indirectness. Protocol outcome 2: Control of breathlessness at Any - Actual outcome for Breathlessness management: Intensity of dyspnoea (Borg scale) at 24 hours; Risk of bias: Very high; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Intensity of dyspnoea (Borg scale) at 48 hours; Risk of bias: Very high; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Dyspnoea relief at 48 hours; Group 1: 17/23, Group 2: 21/24; Risk of bias: High; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Dyspnoea relief at 24 hours; Group 1: 12/26, Group 2: 20/29; Risk of bias: High; Indirectness of outcome: No indirectness. RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MORPHINE + MIDAZOLAM versus MORPHINE Protocol outcome 1: Adverse events/withdrawal of the medication due to adverse events at Any - Actual outcome for Breathlessness management: Somnolence at 48 hours; Group 1: 3/33, Group 2: 6/35; Risk of bias: Very high; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Nausea/vomiting at 48 hours; Group 1: 0/33, Group 2: 4/35; Risk of bias: High; Indirectness of outcome: No indirectness.	

Protocol outcome 2: Control of breathlessness at Any - Actual outcome for Breathlessness management: Intensity of dyspnoea (Borg scale) at 24 hours; Risk of bias: Very high; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Intensity of dyspnoea (Borg scale) at 48 hours; Risk of bias: Very high; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Dyspnoea relief at 48 hours; Group 1: 22/23, Group 2: 21/24; Risk of bias: High; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Dyspnoea relief at 24 hours; Group 1: 23/25, Group 2: 20/29; Risk of bias: High; Indirectness of outcome: No indirectness. RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MORPHINE + MIDAZOLAM versus MIDAZOLAM Protocol outcome 1: Adverse events/withdrawal of the medication due to adverse events at Any - Actual outcome for Breathlessness management: Somnolence at 48 hours; Group 1: 3/33, Group 2: 2/33; Risk of bias: High; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Nausea/vomiting at 48 hours; Group 1: 0/33, Group 2: 1/33; Risk of bias: High; Indirectness of outcome: No indirectness. Protocol outcome 2: Control of breathlessness at Any - Actual outcome for Breathlessness management: Intensity of dyspnoea (Borg scale) at 24 hours; Risk of bias: Very high; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Intensity of dyspnoea (Borg scale) at 48 hours; Risk of bias: Very high; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Dyspnoea relief at 48 hours; Group 1: 22/23, Group 2: 17/23; Risk of bias: High; Indirectness of outcome: No indirectness. - Actual outcome for Breathlessness management: Dyspnoea relief at 24 hours; Group 1: 23/25, Group 2: 12/26; Risk of bias: High; Indirectness of outcome: No indirectness.	
Protocol outcomes not reported by the study	Quality of life at Any; Sedation (GCS/AVPU) at Any; Control of anxiety at Any; Control of agitation at Any; Control of delirium at Any; Duration of symptom control at Any; Time to symptom control at Any; Duration of institutional care at Any; Carer satisfaction at Any; Time to death at Any; Pain control at Any.

Table 63: Twycross 1977[439]

Study	**Twycross 1977[439]**
Study type	RCT (Patient randomised; Crossover: 1 day).
Number of studies (number of participants)	1 (n=699)

Countries and setting	Conducted in United Kingdom; Setting: Hospice.
Line of therapy	Not applicable.
Duration of study	Intervention time: 5 days.
Method of assessment of guideline condition	Method of assessment /diagnosis not stated.
Stratum	Pain management.
Subgroup analysis within study	Post-hoc subgroup analysis: Male/female.
Inclusion criteria	People with terminal cancer prescribed diamorphine for pain relief.
Exclusion criteria	Not stated.
Recruitment/selection of patients	Not stated.
Age, gender and ethnicity	Age - Median (range): 67 years. Gender (M:F): 43/57%. Ethnicity: Not stated.
Further population details	
Extra comments	Very high rate of attrition.
Indirectness of population	Serious indirectness: Only states that median survival of people admitted to the unit is <2 weeks.
Interventions	(n=350) Intervention 1: Opioids - Diamorphine. Standard diamorphine hydrochloride elixir as prescribed; supplied in a series of doses from 2.5 to 60 mg and increased until pain free throughout 4-h between drug rounds. Elixir also contained cocaine hydrochloride 10 mg/dose. Duration 2 days. Concurrent medication/care: Prochlorperazine or chlorpromazine as antiemetic. Other drugs prescribed as required. Further details: 1. Delivery system : Delivery system: oral tablet or liquid 2. Drug class: Opioid 3. Route of administration: Route of administration: enteral. Comments: After 2 days participants were crossed over to the other intervention. (n=349) Intervention 2: Opioids - Morphine. Morphine sulphate supplied in a series of doses from 3.75 to 90 mg and increased until pain free throughout 4-h between drug rounds. Elixir also contained cocaine hydrochloride 10 mg/dose. Duration 2 days. Concurrent medication/care: Prochlorperazine or chlorpromazine as antiemetic. Other drugs prescribed as required. Further details: 1. Delivery system: Delivery system: oral tablet or liquid 2. Drug class: Opioid 3. Route of administration: Route of administration: enteral. Comments: After 2 days participants were crossed over to the other intervention.

Funding	Academic or government funding.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIAMORPHINE FIRST versus MORPHINE FIRST Protocol outcome 1: Pain control at Any - Actual outcome for Pain management: Difference on pain VAS (0-100) before and after crossover (pre- minus post- crossover scores) at 5 days; Risk of bias: Very high; Indirectness of outcome: No indirectness. Protocol outcome 2: Adverse events/withdrawal of the medication due to adverse events at Any - Actual outcome for Pain management: Difference on nausea VAS (0-100) before and after crossover (pre- minus post- crossover scores) at 5 days; Risk of bias: Very high; Indirectness of outcome: No indirectness. - Actual outcome for Pain management: Difference on sleep VAS (0-100) before and after crossover (pre- minus post- crossover scores) at 5 days; Mean Male subgroup D to M: -3.8 (SE 3.5); M to D 6.0 (SE 5.5); difference -9.8 favouring morphine Female subgroup D to M: -5.8 (SE 4.3); M to D: 0.6 (SE 3.2); difference -6.2 favouring morphine; Risk of bias: Indirectness of outcome: No indirectness.	
Protocol outcomes not reported by the study	Quality of life at Any; Control of breathlessness at Any; Control of anxiety at Any; Control of agitation at Any; Control of delirium at Any; Duration of symptom control at Any; Time to symptom control at Any; Duration of institutional care at Any; Carer satisfaction at Any; Time to death at Any; Sedation (GCS/AVPU) at Any.

H.5.1 Noisy Respiratory Secretions

Table 64: Back 2001[37]

Study	**Back 2001[37]**
Study type	Non-randomised comparative study.
Number of studies (number of participants)	One unit (n=191)
Countries and setting	Conducted in United Kingdom; Setting: Palliative care unit.
Line of therapy	Not applicable.
Duration of study	Other: 11 months in the first period (using Hyoscine Hydrobromide and 9 months in the second (using Glycopyrrolate).

Method of assessment of guideline condition	Unclear method of assessment/diagnosis.
Stratum	Overall.
Subgroup analysis within study	Not applicable.
Inclusion criteria	Dying people who developed noisy respiratory secretions.
Exclusion criteria	Not explicitly stated.
Age, gender and ethnicity	Age - Median (range): Hyoscine Hydrobromide: 71 (33 - 92); Glycopyrrolate: 71 (35 - 89). Gender (M:F): 105/97. Ethnicity:
Extra comments	Even though the inclusion criteria were not restricted to people with cancer, almost all participants had a diagnosis of cancer.
Indirectness of population	No indirectness.
Interventions	(n=129) Intervention 1: Anti-muscarinic - Hyoscine hydrobromide. 0.4 mg subcutaneous bolus, repeated after 30 minutes if noisy breathing persisted. Duration Until no longer clinically indicated or death. Concurrent medication/care: Not explicitly specified. (n=75) Intervention 2: Anti-muscarinic - Glycopyrronium bromide. 0.2 mg subcutaneous bolus, repeated after 30 minutes if noisy breathing persisted. Duration Until no longer clinically indicated or death. Concurrent medication/care: Not explicitly specified.
Funding	Other (It is described that there were no conflicts of interest).

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HYOSCINE HYDROBROMIDE versus GLYCOPYRRONIUM BROMIDE

Protocol outcome 1: Subjective or objective improvement in respiratory secretions at hours/days.
- Actual outcome: Subjective rating of noisy breathing on a 4 point scale (none to very severe) at 1 hour; Group 1: 59/103, Group 2: 22/55; Risk of bias: Very high; Indirectness of outcome: No indirectness.
- Actual outcome: Subjective rating of noisy breathing on a 4 point scale (none to very severe) at To final score (median time to final score < 2 hours before death); Group 1: 46/103, Group 2: 24/57; Risk of bias: Very high; Indirectness of outcome: No indirectness.

Protocol outcomes not reported by the study	Quality of life at hours/days; Hospitalisation at hours/days; Subjective ratings from people on distress related to noisy

	breathing /respiratory secretions at hours/days; Sedation (patient-rated, clinician-rated, carer-rated) at hours/days; Adverse events (particularly paradoxical agitation, failure to expectorate, dry mouth at hours/days; Subjective ratings from informal carers' on distress relating to noisy breathing/respiratory secretions at hours/days; Hydration status at hours/days; Length of survival at hours/days; Length of stay at hours/days.

Table 65: Clark 2008[97]

Study	**Clark 2008[97]**
Study type	RCT (Patient randomised; Crossover: Insufficient).
Number of studies (number of participants)	One (n=10)
Countries and setting	Conducted in Australia; Setting: Hospital.
Line of therapy	Not applicable.
Method of assessment of guideline condition	Unclear method of assessment/diagnosis.
Stratum	Overall.
Subgroup analysis within study	Not applicable.
Inclusion criteria	People over the age of 18 years with an expectation that the terminal phase of illness (defined as the last 48-72 hours of life) would occur during the admission.
Exclusion criteria	People already participating in another trial, people unwilling to discuss the potential of death, people without family members who could also provide consent, and people with known hypersensitivity to the intervention drugs.
Age, gender and ethnicity	Age - Median (range): 79 years (63 - 88). Gender (M:F): 3/7. Ethnicity:
Extra comments	All participants had advanced cancer (n = 6 gastrointestinal, n = 2 haematological, n = 1 breast, n = 1 prostrate).
Indirectness of population	No indirectness.
Interventions	(n=21) Intervention 1: Anti-muscarinic - Hyoscine hydrobromide. Hyoscine hydrobromide 400 mcg subcutaneously. Duration Injections at 30 minutes, 1 hour, 4 hours, and 6 hours. Concurrent medication/care: In conjunction with usual care which included non-pharmacological approaches (such as re-positioning). (n=21) Intervention 2: Somatostatin analogue - Octreotide. Octreotide 200 mcg subcutaneously. Duration Injections at 30 minutes, 1 hour, 4 hours, and 6 hours. Concurrent medication/care: In conjunction with usual care which included

	non-pharmacological approaches (such as re-positioning).
Funding	Funding not stated.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HYOSCINE HYDROBROMIDE versus OCTREOTIDE Protocol outcome 1: Subjective or objective improvement in respiratory secretions at hours/days - Actual outcome: Intensity of noisy breathing (none, mild, moderate, severe, very severe) at the time of each injection; Group 1: 2/5, Group 2: 2/5; Risk of bias: High; Indirectness of outcome: No indirectness.	
Protocol outcomes not reported by the study	Quality of life at hours/days; Hospitalisation at hours/days; Subjective ratings from people on distress related to noisy breathing /respiratory secretions at hours/days; Sedation (patient-rated, clinician-rated, carer-rated) at hours/days; Adverse events (particularly paradoxical agitation, failure to expectorate, dry mouth at hours/days; Subjective ratings from informal carers' on distress relating to noisy breathing/respiratory secretions at hours/days; Hydration status at hours/days; Length of survival at hours/days; Length of stay at hours/days.

Table 66: Heisler 2013[203]

Study	**Heisler 2013[203]**
Study type	RCT (Patient randomised; Parallel).
Number of studies (number of participants)	Single centre (n=137)
Countries and setting	Conducted in USA.
Line of therapy	Not applicable.
Duration of study	Intervention + follow up: 4 hours.
Method of assessment of guideline condition	Unclear method of assessment/diagnosis.
Stratum	Overall.
Subgroup analysis within study	Not applicable.

Inclusion criteria	Terminally ill people who developed audible respiratory tract secretions with a noise intensity score of at least 1 (audible only very close to the patient). They were required to be capable of or have an acceptable surrogate capable of providing informed consent.
Exclusion criteria	People were excluded if they had been treated with other antimuscarinic medications within the current inpatient admission.
Age, gender and ethnicity	Age - Mean (SD): 77.2 (11.5). Gender (M:F): 51/86. Ethnicity:
Extra comments	Diagnosis - cancer (43.1%); Baseline noise score (ranging from 0 - inaudible to 3 - clearly audible at about 20 feet): 1 (19%); 2 (58%); 3 (23%)
Indirectness of population	No indirectness
Interventions	(n=74) Intervention 1: Muscarinic acetylcholine receptor antagonist - Atropine. One-time dose sublingually. Two drops of atropine (1 mg). Duration One-time dose. Concurrent medication/care: Not explicitly specified. (n=63) Intervention 2: Placebo. Saline. Duration One-time. Concurrent medication/care: Not explicitly stated.
Funding	No funding (The authors declared no conflicts of interest).

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATROPINE versus PLACEBO

Protocol outcome 1: Subjective or objective improvement in respiratory secretions at hours/days
- Actual outcome: Reduction (1 point or more) on a 4 point scale at 4 hours; Group 1: 27/68, Group 2: 31/60; Risk of bias: Low; Indirectness of outcome: No indirectness.
- Actual outcome: Reduction (1 point or more) on a 4 point scale at 2 hours; Group 1: 28/74, Group 2: 26/63; Risk of bias: Low; Indirectness of outcome: No indirectness.

Protocol outcomes not reported by the study	Quality of life at hours/days; Hospitalisation at hours/days; Subjective ratings from people on distress related to noisy breathing /respiratory secretions at hours/days; Sedation (patient-rated, clinician-rated, carer-rated) at hours/days; Adverse events (particularly paradoxical agitation, failure to expectorate, dry mouth at hours/days; Subjective ratings from informal carers' on distress relating to noisy breathing/respiratory secretions at hours/days; Hydration status at hours/days; Length of survival at hours/days; Length of stay at hours/days.

Table 67: Hugel 2006[226] (Kass 2003[253])

Study (subsidiary papers)	Hugel 2006[226] (Kass 2003[253])
Study type	Non-randomised comparative study.
Number of studies (number of participants)	2 (n=72)
Countries and setting	Conducted in United Kingdom; Setting: Hospital.
Line of therapy	Not applicable.
Method of assessment of guideline condition	Unclear method of assessment/diagnosis.
Stratum	Overall.
Subgroup analysis within study	Not applicable.
Inclusion criteria	People with terminal advanced cancer who were managed using the Liverpool Care Pathway.
Exclusion criteria	Not described.
Age, gender and ethnicity	Age - Mean (SD): Hyoscine hydrobromide 70 (10) Glycopyrronium 71 (10). Gender (M:F): 40/32. Ethnicity:
Indirectness of population	No indirectness.
Interventions	(n=36) Intervention 1: Anti-muscarinic - Hyoscine hydrobromide. Hyoscine hydrobromide 0.4 mg subcutaneously, followed by 1.2 mg/24 hour period continuous subcutaneous injection. Duration Until death or until no longer clinically indicated. Concurrent medication/care: Other interventions on the Liverpool Care Pathway. (n=36) Intervention 2: Anti-muscarinic - Glycopyrronium bromide. Glycopyrronium bromide 0.2 mg subcutaneous followed by 0.6 mg/24-hour continuous subcutaneous injections. Duration Until death or until no longer clinically indicated. Concurrent medication/care: Other interventions on the Liverpool Care Pathway.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GLYCOPYRRONIUM BROMIDE versus HYOSCINE HYDROBROMIDE

Protocol outcome 1: Subjective or objective improvement in respiratory secretions at hours/days
- Actual outcome: Drug response (defined as absence of symptoms) categories into: immediate (within 4 hours), late (more than 4 hours, but before death), transient

(symptom free episodes after treatment but symptoms at death), no response at Immediate; Group 1: 13/36, Group 2: 11/36; Risk of bias: Very high; Indirectness of outcome: No indirectness. - Actual outcome: Drug response (defined as absence of symptoms) categories into: immediate (within 4 hours), late (more than 4 hours, but before death), transient (symptom free episodes after treatment but symptoms at death), no response at Late; Group 1: 13/36, Group 2: 10/36; Risk of bias: Very high; Indirectness of outcome: No indirectness. - Actual outcome: Drug response (defined as absence of symptoms) categories into: immediate (within 4 hours), late (more than 4 hours, but before death), transient (symptom free episodes after treatment but symptoms at death), no response at Transient; Group 1: 10/36, Group 2: 7/36; Risk of bias: Very high; Indirectness of outcome: No indirectness. Protocol outcome 2: Adverse events (particularly paradoxical agitation, failure to expectorate, dry mouth at hours/days - Actual outcome: Agitation (Number of episodes as a proportion of all episodes) at Until death or until no longer clinically indicated; Other: Median number of agitated episodes from first observed symptoms to death: 1 (range 0-5) in the glycopyrronium and 0 (0-3) in the hyoscine hydrobromide group.; Risk of bias: Very high; Indirectness of outcome: No indirectness.	
Protocol outcomes not reported by the study	Quality of life at hours/days; Hospitalisation at hours/days; Subjective ratings from people on distress related to noisy breathing /respiratory secretions at hours/days; Sedation (patient-rated, clinician-rated, carer-rated) at hours/days; Subjective ratings from informal carers' on distress relating to noisy breathing/respiratory secretions at hours/days; Hydration status at hours/days; Length of survival at hours/days; Length of stay at hours/days.

Table 68: Hughes 2000[227]

Study	**Hughes 2000[227]**
Study type	Non-randomised comparative study.
Number of studies (number of participants)	1 (n=111)
Countries and setting	Conducted in United Kingdom; Setting: Hospice.
Line of therapy	Not applicable.
Duration of study	Until death or cessation of symptoms.
Method of assessment of guideline condition	Unclear method of assessment/diagnosis.
Stratum	Overall.

Subgroup analysis within study	Not applicable.
Inclusion criteria	People with advanced terminal cancer judged to be within a few days of death. Participants were unconscious with noisy retained secretions that persisted despite repositioning.
Exclusion criteria	Not stated.
Age, gender and ethnicity	Age - Other: Not stated. Gender (M:F): Not stated. Ethnicity:
Indirectness of population	No indirectness.
Interventions	(n=39) Intervention 1: Anti-muscarinic - Hyoscine hydrobromide. Hyoscine hydrobromide 0.4 mg subcutaneously stat, followed by 0.6 mg stat and 2.4 mg/24 hour by syringe driver. Duration Until death or no longer clinically indicated. Concurrent medication/care: Not stated. (n=39) Intervention 2: Anti-muscarinic - Hyoscine butylbromide. Hyoscine butylbromide 20 mg subcutaneously stat, followed by 20 mg stat and 20 mg/24 hour by syringe driver . Duration Until death or no longer clinically indicated. Concurrent medication/care: Not stated. (n=39) Intervention 3: Anti-muscarinic - Glycopyrronium bromide. Glycopyrronium bromide 0.2 mg subcutaneously stat, followed by 0.4 mg stat and 0.6 mg/24 hour by syringe driver. Duration Until death or no longer clinically indicated. Concurrent medication/care: Not stated.
Funding	Funding not stated.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HYOSCINE BUTYLBROMIDE versus HYOSCINE HYDROBROMIDE

Protocol outcome 1: Subjective or objective improvement in respiratory secretions at hours/days
- Actual outcome: Level of change in noise intensity of respiratory secretions: absent, much better, slightly better, same, slightly worse, or much worse at Only specified as at death; Group 1: 24/37, Group 2: 20/37; Risk of bias: Very high; Indirectness of outcome: No indirectness.

Protocol outcome 2: Subjective ratings from informal carers' on distress relating to noisy breathing/respiratory secretions at hours/days
- Actual outcome: Change in relatives' distress: absent, much better, slightly better, same, slightly worse, or much worse at Only specified as at death; Group 1: 24/27, Group 2: 27/29; Risk of bias: Very high; Indirectness of outcome: No indirectness.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GLYCOPYRRONIUM BROMIDE versus HYOSCINE HYDROBROMIDE

Protocol outcome 1: Subjective or objective improvement in respiratory secretions at hours/days - Actual outcome: Level of change in noise intensity of respiratory secretions: absent, much better, slightly better, same, slightly worse, or much worse at Only specified as at death; Group 1: 24/37, Group 2: 20/37; Risk of bias: Very high; Indirectness of outcome: No indirectness. Protocol outcome 2: Subjective ratings from informal carers' on distress relating to noisy breathing/respiratory secretions at hours/days - Actual outcome: Change in relatives' distress: absent, much better, slightly better, same, slightly worse, or much worse at Only specified as at death; Group 1: 22/25, Group 2: 27/29; Risk of bias: Very high; Indirectness of outcome: No indirectness. RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GLYCOPYRRONIUM BROMIDE versus HYOSCINE BUTYLBROMIDE Protocol outcome 1: Subjective or objective improvement in respiratory secretions at hours/days - Actual outcome: Level of change in noise intensity of respiratory secretions: absent, much better, slightly better, same, slightly worse, or much worse at Only specified as at death; Group 1: 24/37, Group 2: 24/37; Risk of bias: Very high; Indirectness of outcome: No indirectness. Protocol outcome 2: Subjective ratings from informal carers' on distress relating to noisy breathing/respiratory secretions at hours/days - Actual outcome: Change in relatives' distress: absent, much better, slightly better, same, slightly worse, or much worse at Only specified as at death; Group 1: 22/25, Group 2: 27/29; Risk of bias: Very high; Indirectness of outcome: No indirectness.	
Protocol outcomes not reported by the study	Quality of life at hours/days; Hospitalisation at hours/days; Subjective ratings from people on distress related to noisy breathing /respiratory secretions at hours/days; Sedation (patient-rated, clinician-rated, carer-rated) at hours/days; Adverse events (particularly paradoxical agitation, failure to expectorate, dry mouth at hours/days; Hydration status at hours/days; Length of survival at hours/days; Length of stay at hours/days.

Table 69: Likar 2002[287]

Study	**Likar 2002[287]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=31)
Countries and setting	Conducted in Germany.
Line of therapy	Not applicable.

Duration of study	Intervention time: 10 hours.
Method of assessment of guideline condition	Unclear method of assessment/diagnosis.
Stratum	Overall.
Subgroup analysis within study	Not applicable.
Inclusion criteria	People with advanced terminal cancer with life expectancy of less than 3 days (N= 31). With life expectancy of less than 3 days.
Exclusion criteria	Fully conscious people were excluded from the study. People who are already receiving drugs from the same class.
Age, gender and ethnicity	Age - Mean (SD): Hyoscine hydrobromide: 66 (standard error 4); Placebo: 65 (standard error 5). Gender (M:F): 15/16. Ethnicity:
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Anti-muscarinic - Hyoscine hydrobromide. Hyoscine hydrobromide 0.5 mg (in 1 ml saline) iv/sc. Duration Given at 0, 4 and 8 hours. Concurrent medication/care: Usual care in which analgesic and/or sedative medication was documented. (n=16) Intervention 2: Placebo. Normal saline 1 ml iv/sc. Duration Given at 0, 4 and 8 hours. Concurrent medication/care: Usual care in which analgesic and/or sedative medication was documented.
Funding	Funding not stated.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HYOSCINE HYDROBROMIDE versus PLACEBO

Protocol outcome 1: Quality of life at hours/days
- Actual outcome: Level of pain: 1 = mild 2 = moderate; 3 = severe at Measured every 2 hours; Group 1: 13/15, Group 2: 2/16; Risk of bias: High; Indirectness of outcome: No indirectness.

Protocol outcome 2: Subjective or objective improvement in respiratory secretions at hours/days
- Actual outcome: Death rattle assessed using scale of 1 to 5: 1 = noisy breathing; 2 = minimal rattle; 3 = moderate rattle; 4 = severe rattle; 5 = very severe rattle at Measured every 2 hours; Other: Intervention group demonstrated tendency to reduced death rattle more than control group during the first 10 hours (not statistically significant).; Risk of bias: High; Indirectness of outcome: No indirectness.

Protocol outcome 3: Adverse events (particularly paradoxical agitation, failure to expectorate, dry mouth at hours/days - Actual outcome: Level of restlessness: 1 = mild 2 = moderate ; 3 = severe at Measured every 2 hours; Group 1: 9/15, Group 2: 6/16; Risk of bias: High; Indirectness of outcome: No indirectness. Protocol outcome 4: Length of survival at hours/days - Actual outcome: Length of survival at Start of treatment until death; Group 1: mean 907 Minutes (SD 526.73); n=15, Group 2: mean 611 Minutes (SD 456); n=16; Risk of bias: High; Indirectness of outcome: No indirectness.	
Protocol outcomes not reported by the study	Hospitalisation at hours/days; Subjective ratings from people on distress related to noisy breathing /respiratory secretions at hours/days; Sedation (patient-rated, clinician-rated, carer-rated) at hours/days; Subjective ratings from informal carers' on distress relating to noisy breathing/respiratory secretions at hours/days; Hydration status at hours/days; Length of stay at hours/days.

Table 70: Likar 2008[288]

Study	**Likar 2008[288]**
Study type	RCT (Patient randomised; Parallel).
Number of studies (number of participants)	Single centre (n=13)
Countries and setting	Conducted in Germany; Setting: Hospital.
Line of therapy	Not applicable.
Duration of study	Intervention time: 12 hours.
Method of assessment of guideline condition	Unclear method of assessment/diagnosis.
Stratum	Overall.
Subgroup analysis within study	Not applicable.
Inclusion criteria	Semi-conscious or unconscious people with advanced terminal cancer with predicted life expectancy of 3 days or less.
Exclusion criteria	Fully conscious people with a life expectancy of more than 3 days or people who are already receiving a drug from the

	same drug class.
Age, gender and ethnicity	Age - Mean (SD): Glycopyrronium bromide 72 (standard error 5); Hyoscine hydrobromide 71 (standard error 4). Gender (M:F): 10/3. Ethnicity:
Indirectness of population	No indirectness.
Interventions	(n=6) Intervention 1: Anti-muscarinic - Glycopyrronium bromide. Glycopyrronium bromide 0.4 mg every 6 hours intravenously. Duration Every 2 hours up to 12 hours. Concurrent medication/care: The use of analgesics/sedatives was documented. (n=7) Intervention 2: Anti-muscarinic - Hyoscine hydrobromide. Hyoscine hydrobromide 0.5 mg every 6 hours intravenously. Duration Every 2 hours up to 12 hours. Concurrent medication/care: The use of analgesics/sedatives was documented.
Funding	Other (It was described that the authors have no conflicts of interest.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GLYCOPYRRONIUM BROMIDE versus HYOSCINE HYDROBROMIDE

Protocol outcome 1: Subjective or objective improvement in respiratory secretions at hours/days
- Actual outcome: Death rattle assessed using scale of 1 to 5: 1 = noisy breathing; 2 = minimal rattle; 3 = moderate rattle; 4 = severe rattle; 5 = very severe rattle at Measured every 2 hours up to 12 hours; Risk of bias: High; Indirectness of outcome: No indirectness.

Protocol outcome 2: Adverse events (particularly paradoxical agitation, failure to expectorate, dry mouth at hours/days
- Actual outcome: Pain: 1 = slight; 2 = moderate; 3 = severe at Measured every 2 hours up to 12 hours; Other: It is only described that the percentage of people with pain in each group was not different between groups (no p-value or graph provided); Risk of bias: High; Indirectness of outcome: No indirectness.
- Actual outcome: Restlessness: 1 = slight; 2 = moderate; 3 = severe at Measured every 2 hours up to 12 hours; Other: It is described that the incidence of restlessness was not statistically different between groups.; Risk of bias: High; Indirectness of outcome: No indirectness.

Protocol outcomes not reported by the study	Quality of life at hours/days; Hospitalisation at hours/days; Subjective ratings from people on distress related to noisy breathing /respiratory secretions at hours/days; Sedation (patient-rated, clinician-rated, carer-rated) at hours/days; Subjective ratings from informal carers' on distress relating to noisy breathing/respiratory secretions at hours/days; Hydration status at hours/days; Length of survival at hours/days; Length of stay at hours/days.

Table 71: Wildiers 2009[468]

Study	Wildiers 2009[468]
Study type	RCT (Patient randomised; Parallel).
Number of studies (number of participants)	Multicentre (n=333)
Countries and setting	Conducted in Belgium; Setting: Hospital.
Line of therapy	Not applicable.
Duration of study	Intervention time: Until death - data were reported up to 120 hours.
Method of assessment of guideline condition	Unclear method of assessment/diagnosis.
Stratum	Overall.
Subgroup analysis within study	Not applicable.
Inclusion criteria	People at the end of life with noticeable death rattle.
Exclusion criteria	People with clear clinical indications of a secondary cause of rattle, including respiratory infection, food/fluid aspiration or cardiac failure with pulmonary oedema.
Age, gender and ethnicity	Age - Mean (SD): Mean 72.5. Gender (M:F): 158/175. Ethnicity:
Extra comments	N = 316 cancer, N = 17 non-cancer
Indirectness of population	No indirectness.
Interventions	(n=112) Intervention 1: Anti-muscarinic - Hyoscine hydrobromide. Scopolamine (hyoscine hydrobromide) 0.25 mg subcutaneous bolus, followed by 1.5 mg/24 hours. Duration Until death or until no longer clinically indicated. Concurrent medication/care: Not described. (n=106) Intervention 2: Anti-muscarinic - Hyoscine butylbromide. Hyoscine butylbromide 20 mg subcutaneous bolus, followed by 60 mg/24 hours). Duration Up to death or no longer clinically indicated. Concurrent medication/care: Not stated. (n=115) Intervention 3: Muscarinic acetylcholine receptor antagonist - Atropine. Atropine 0.5 mg subcutaneous bolus, followed by 3 mg/24 hours. Duration Until death or no longer clinically indicated. Concurrent medication/care: Not stated.

Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HYOSCINE BUTYLBROMIDE versus HYOSCINE HYDROBROMIDE

Protocol outcome 1: Subjective or objective improvement in respiratory secretions at hours/days
- Actual outcome: Subjective rating of noisy breathing on a 4 point scale. at 4 hours; Group 1: 46/85, Group 2: 44/94; Risk of bias: High; Indirectness of outcome: No indirectness.
- Actual outcome: Subjective rating of noisy breathing on a 4 point scale. at 12 hours; Group 1: 35/68, Group 2: 40/70; Risk of bias: High; Indirectness of outcome: No indirectness.
- Actual outcome: Subjective rating of noisy breathing on a 4 point scale. at 24 hours; Group 1: 28/47, Group 2: 36/53; Risk of bias: High; Indirectness of outcome: No indirectness.

Protocol outcome 2: Sedation (patient-rated, clinician-rated, carer-rated) at hours/days
- Actual outcome: Worsening levels of consciousness - rated by attending nurse at 24 hours; Group 1: 11/45, Group 2: 25/52; Risk of bias: High; Indirectness of outcome: No indirectness.
- Actual outcome: Worsening levels of consciousness - rated by attending nurse at 12 hours; Group 1: 14/66, Group 2: 31/68; Risk of bias: High; Indirectness of outcome: No indirectness.

Protocol outcome 3: Adverse events (particularly paradoxical agitation, failure to expectorate, dry mouth at hours/days
- Actual outcome: Improvement in confusion (for those with sufficient level of consciousness to assess) - rated by attending nurse at 12 hours; Group 1: 4/12, Group 2: 0/2; Risk of bias: High; Indirectness of outcome: No indirectness.
- Actual outcome: Improvement in confusion (for those with sufficient level of consciousness to assess) - rated by attending nurse at 24 hours; Group 1: 1/9, Group 2: 0/4; Risk of bias: High; Indirectness of outcome: No indirectness.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATROPINE versus HYOSCINE HYDROBROMIDE

Protocol outcome 1: Subjective or objective improvement in respiratory secretions at hours/days
- Actual outcome: Subjective rating of noisy breathing on a 4 point scale. at 4 hours; Group 1: 46/92, Group 2: 44/94; Risk of bias: High; Indirectness of outcome: No indirectness.
- Actual outcome: Subjective rating of noisy breathing on a 4 point scale. at 12 hours; Group 1: 46/65, Group 2: 40/70; Risk of bias: High; Indirectness of outcome: No indirectness.
- Actual outcome: Subjective rating of noisy breathing on a 4 point scale. at 24 hours; Group 1: 41/54, Group 2: 36/53; Risk of bias: High; Indirectness of outcome: No indirectness.

Protocol outcome 2: Sedation (patient-rated, clinician-rated, carer-rated) at hours/days
- Actual outcome: Worsening levels of consciousness - rated by attending nurse at 12 hours; Group 1: 18/62, Group 2: 31/68; Risk of bias: High; Indirectness of outcome: No indirectness.
- Actual outcome: Worsening levels of consciousness - rated by attending nurse at 24 hours; Group 1: 19/51, Group 2: 25/52; Risk of bias: High; Indirectness of outcome: No indirectness.

Protocol outcome 3: Adverse events (particularly paradoxical agitation, failure to expectorate, dry mouth at hours/days
- Actual outcome: Improvement in confusion (for those with sufficient level of consciousness to assess) - rated by attending nurse at 12 hours; Group 1: 1/5, Group 2: 0/2; Risk of bias: High; Indirectness of outcome: No indirectness.
- Actual outcome: Improvement in confusion (for those with sufficient level of consciousness to assess) - rated by attending nurse at 24 hours; Group 1: 0/6, Group 2: 0/4; Risk of bias: High; Indirectness of outcome: No indirectness.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATROPINE versus HYOSCINE BUTYLBROMIDE

Protocol outcome 1: Subjective or objective improvement in respiratory secretions at hours/days
- Actual outcome: Subjective rating of noisy breathing on a 4 point scale. At 4 hours; Group 1: 46/92, Group 2: 46/85; Risk of bias: High; Indirectness of outcome: No indirectness.
- Actual outcome: Subjective rating of noisy breathing on a 4 point scale. At 12 hours; Group 1: 46/65, Group 2: 35/68; Risk of bias: High; Indirectness of outcome: No indirectness.
- Actual outcome: Subjective rating of noisy breathing on a 4 point scale. At 24 hours; Group 1: 41/54, Group 2: 28/47; Risk of bias: High; Indirectness of outcome: No indirectness.

Protocol outcome 2: Sedation (patient-rated, clinician-rated, carer-rated) at hours/days
- Actual outcome: Worsening levels of consciousness - rated by attending nurse at 12 hours; Group 1: 18/62, Group 2: 31/68; Risk of bias: High; Indirectness of outcome: No indirectness.
- Actual outcome: Worsening levels of consciousness - rated by attending nurse at 24 hours; Group 1: 19/51, Group 2: 25/52; Risk of bias: High; Indirectness of outcome: No indirectness.

Protocol outcome 3: Adverse events (particularly paradoxical agitation, failure to expectorate, dry mouth at hours/days
- Actual outcome: Improvement in confusion (for those with sufficient level of consciousness to assess) - rated by attending nurse at 12 hours; Group 1: 1/5, Group 2: 0/2; Risk of bias: High; Indirectness of outcome: No indirectness.
- Actual outcome: Improvement in confusion (for those with sufficient level of consciousness to assess) - rated by attending nurse at 24 hours; Group 1: 0/6, Group 2: 0/4; Risk of bias: High; Indirectness of outcome: No indirectness.

Protocol outcomes not reported by the study	Quality of life at hours/days; Hospitalisation at hours/days; Subjective ratings from people on distress related to noisy breathing /respiratory secretions at hours/days; Subjective ratings from informal carers' on distress relating to noisy breathing/respiratory secretions at hours/days; Hydration status at hours/days; Length of survival at hours/days; Length of stay at hours/days.

H.6 Anticipatory Prescribing

Table 72: Faull et al. (2013)[156]

Study	Faull et al. (2013)[156]
Aim	The aim was to explore the issues that arise for all practitioners working in the community in relation to the prescribing, dispensing and administering of subcutaneous midazolam and diamorphine or morphine for the anticipated need of dying people to have timely and effective symptom management.
Population	A total of 63 participants were recruited from the Leicester and Rutland area. There were 22 GPs, 4 'Hospice at Home' nurses, 4 community matrons, 5 Marie Curie nurses, 16 community nurses 4 specialist palliative care nurses, 1 nursing home matron, 3 community pharmacists, 3 heart-failure nurses and 1 student nurse.
Setting	Various (see above).
Study design	Eight focus groups and 9 individual interviews.
Methods and analysis	**Method of recruitment:** Purposive sampling was used to ensure that there was at least one participant from each of the following areas: district nursing, specialist nursing in palliative care and heart failure, Marie Curie nursing, 'Hospice at Home' nursing, community matrons, nursing home nursing, pharmacy and general practice. **Data collection:** Data collection took place in 2007. focus groups and individual interviews were used so the research process could benefit from the advantages of each approach and to provide participants with choice, given the potential sensitivity of the area. A topic guide was developed utilising research team and steering group discussions, clinical and qualitative I interviewing experience, significant event analysis, educational interactions with primary care professionals and analysis of available 'best practice' guidance developed by some services. Guides were used flexibly so that unanticipated issues of importance to individual participants could be explored. The topic guide evolved in response to new data. **Data analysis**: Focus groups and interviews were audio recorded and interviewers (3 of the authors) maintained reflexive diaries. Data from transcripts were analysed by constant comparison based on grounded theory to identify themes. Open coding summarised the ways that participants talked about the processes that mattered. These codes were progressively focussed into broad categories forming the initial coding frame, further shaped by steering group discussion. The coding frame was systematically applied by the first author using QSR N6 software and continuously developed in response to new information. No new issues were elicited after 8 individual interviews and 6 focus groups (n=51

Study	Faull et al. (2013)[156]
	participants) transcripts had been coded.
Themes with findings	**Perceived resourcing problems**: Perceived lack of resources and the associated need to avoid waste were seen as challenging in 12 transcripts. These challenges could be subdivided into 3 further sections: (1) prescriptions not being written in advance of need because of concerns about waste since some had found that people did not actually require them. (2) a delay in dispensing because of limited availability of drugs in pharmacies and (3) a delay in administering drugs through a lack of syringe drivers.
	Reflections on expertise and experience: There were 10 transcripts in which participants emphasised the importance of learning both by formal education and from experience. This theme had 4 separate subthemes: • **Knowing when to prescribe or administer medication –** including uncertainties about recognising dying and fear about it being the wrong time to administer it. • **Knowing what should be prescribed or administered** – including concerns about inappropriate admissions to hospital if the wrong medications were selected, distressing symptoms (such as secretions) may occur if medications are missed out • **Concerns about accountability** – including who would take responsibility, fears about being accused of overdosing people, legal responsibilities about how much to prescribe. • **Non-cancer conditions** – including perceived greater difficulty in knowing when and what to prescribe because the deteriorating process is less predictable
	Patient professional links: In 12 transcripts, lack of opportunity to build and maintain patient-professional links was seen as contributing to failure to prescribe sufficiently in advance. Having enough contact with people to develop longer term, trusting relationships was seen as important because it enabled sensitive communications and provided a way of ensuring that past, present and future treatment was timely and coherent and that care felt 'human' and personal. 'Going in blind' was a huge challenge in making care effective, in the justification of prescribing decisions and in the stress it caused professionals. GPs felt they were less likely to admit their own patients than those of their colleagues especially with the confidence that they could review the situation the following day. There were 4 transcripts that described that getting to know patients and their family had prevented prescribing because that knowledge gave rise to grave concerns about placing controlled drugs in a house where there were reasons to think they might be misused. In another interview the opinion was expressed that an established trusting professional-patient relationship was not always necessary so long as the professional involved had knowledge of and could trust other professionals' judgements and communications about previous medical history.
	Failing to build or maintain trusting and responsive links between professionals: Participants had experienced many occasions when the success of anticipatory prescribing or dispensing, with its ultimate aim of enabling a person to stay at home had been threatened by the failure of reliable links between or within professional teams or disciplines. The importance of this issue is illustrated by that fact that the only 2 transcripts in which it did not arise were interviews in which the participants had almost no direct experience of pre-emptive prescribing. The challenges arising from not knowing or trusting other professionals whether within teams or between teams, tended to be those that caused greatest concern and promoted most discussion among participants. There were 3 areas where links were seen as particularly vulnerable: (1) Links between out-of-hours

Study	Faull et al. (2013)[156]
	care and usual care providers presented considerable challenges in joined-up decision making and care planning. (2) Links between community professional and hospital professionals were seen as a challenge in anticipatory planning for care at home with people and their families. This was especially so when the more 'trusted' relationship for the patients was with hospital providers. It was very difficult for community providers to change the direction of care and prepare and plan with the person and family for deterioration. (3) Links between specialist and generalist teams could also pose a challenge in anticipatory prescribing. A professional's title or role was not sufficient in itself for others to trust their advice.
Limitations	Well designed study, good use of providing quotes and data saturation reached.
Applicability of evidence	The topic and setting are directly applicable but the main focus is on barriers rather than facilitators.

Table 73: Wilson et al., (2015)[472]

Study	Wilson et al., (2015)[472]
Aim	To examine nurses' decisions, aims and concerns when using anticipatory medications.
Population	Registered nurses providing end-of-life care (UK Lancaster and Cumbria, and Midlands); data included 61 interviews and 83 observations.
Setting	Community care and nursing homes in 2 regions in England. The first, Lancaster and South Cumbria covered a large semi-rural area serving a largely dispersed population. The Midland was the second area which was a socio-demographically varied area with a dense and varied population in urban districts, as well as a more dispersed population in rural areas. In each of the 2 geographic areas 2 community nursing teams, involving district nurses and specialist palliative care nurses, and 2 care homes for older people registered to provide nursing care (that is, nursing homes) were invited to take part using a convenience sampling approach. The authors employed a recruitment approach used successfully in a previous study of end-of-life in care homes, namely, working with key local end-of-life care stakeholders to publicise the study, identify potential participating sites and then invite participation via the team leader or care home senior nurse.
Study design	An ethnographic study in 2 regions of the UK using observations and interviews.
Methods and analysis	Ethnographic study design, which demands that the researcher becomes involved in the daily activities of the particular group under study (in this case community nurses). The researcher then records, according to specified research objectives, aspects of the group's work and experiences in a detailed way, before making analytical interpretations that allow consideration of the broader implications. Observations: Approximately 4 weeks were spent with each nursing team in each nursing home to observe incidences of when prescriptions were written in advance of symptoms, as well as how, when and in what circumstances the prescriptions were activated. These observations allowed the study team to understand how the process of prescribing and using anticipatory medication unfolded in situ. Interviews: The aim of the interviews was both to complement the observational data and to gain their perceptions of the practical, organisational, ethical and communication issues they experienced. Sampling was dependent upon who was involved in writing, dispensing and using anticipatory medications at the study sites. The study team used a flexible interview schedule, adapted on the basis of the observations and informed by a literature review (using a set of aide-memoires). Interviews took place at the participant's place of work and lasted between 10 min and 2 hours. In addition to single interviews 6 small group interviews were held: 4 with 2 nurses, 1 with 3 nurses and 1 with 6 nurses. Two interviews were

Study	Wilson et al., (2015)[472]
	conducted over the telephone with nurses working out-of-hours for the convenience of the participants. Of the 61 nurses interviewed 5 were interviewed twice as directed by observations.
Themes with findings	Necessary conditions identified by nurses in order to administer anticipatory medications: • Irreversible symptoms due to the dying phase – the nurse had to be satisfied that the person had entered 'the dying phase'. • Inability to take oral medications • Where possible gain the person's consent • Decisions are independent of demands or requests from relatives – nurses acknowledged that although relatives often provided the majority of personal care to patients and had considerable insights into their needs, they took great care not to be 'unduly' swayed by relatives' judgements or requests.
	Nurses' aims in using anticipatory medications • To comfort and settle • Prevent transfer to hospital and avoid medical call-out • Start at the lowest dose and work within guidelines.
	Nurses concerns when using anticipatory medications: • Using the most appropriate drug for the presenting symptom • Used at the most appropriate time • Under medication • Over medication • Hastening death.
Limitations	High risk of bias- Data saturation not met at 1 of the 4 sites and limited provision of supportive quotes.
Applicability of evidence	The evidence is directly applicable. However, it only covers a subsection of anticipatory prescribing, that is, about administering the drugs. In other words when the decision to prescribe has already been made.

Appendix I: Economic evidence tables

I.1 Recognising Dying

No relevant economic evaluations were identified.

I.2 Communications

No relevant economic evaluations were identified.

I.3 Shared Decision Making

No relevant economic evaluations were identified.

I.4 Assisted Hydration

No relevant economic evaluations were identified.

I.5 Pharmacological Intervention

No relevant economic evaluations were identified.

I.6 Anticipatory Prescribing

No relevant economic evaluations were identified.

Appendix J: GRADE tables

J.1 Recognising Dying

None.

J.2 Communications

None.

J.3 Shared Decision Making

None.

J.4 Assisted Hydration

Table 74: Clinical evidence profile: clinically assisted hydration versus placebo

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Assisted hydration	Clinically insignificant amounts	Relative (95% CI)	Absolute	Quality	Importance
Change in Quality of Life (follow-up mean 7 days; measured with: FACT G; Better indicated by higher values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	44	49	-	MD 4.1 higher (1.63 lower to 9.83 higher)	LOW	CRITICAL
Wellbeing - Self reported (follow-up 2 days; measured with: NRS; Better indicated by higher values)												

1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	27	28	-	MD 0.2 higher (1.1 lower to 1.5 higher)	LOW	
Wellbeing - Physician rated (follow-up 2 days; measured with: NRS; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	27	22	-	MD 0.3 higher (1.66 lower to 2.26 higher)	VERY LOW	CRITICAL
Symptom Improvement - anxiety (follow-up 7 days; measured with: ESAS; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	44	49	-	MD 1.36 higher (0.1 lower to 2.82 higher)	LOW	CRITICAL
Symptom Improvement - Dyspnoea (follow-up mean 7; measured with: ESAS; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	44	49	-	MD 0.5 higher (0.68 lower to 1.68 higher)	MODERATE	CRITICAL
Symptom Improvement - Pain (follow-up 7 days; measured with: ESAS; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	44	49	-	MD 1.1 higher (0.16 lower to 2.36 higher)	LOW	CRITICAL
Symptom Improvement - Nausea and vomiting (follow-up mean 7 days; measured with: ESAS; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	44	49	-	MD 0.1 higher (1.05 lower to 1.25 higher)	MODERATE	CRITICAL
Symptom Improvement - Sedation/drowsiness (follow-up 7 days; measured with: ESAS; Better indicated by lower values)												
1	Randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	None	44	49	-	MD 0.6 lower (2.09 lower to 0.89 higher)	LOW	CRITICAL
Delirium - Nursing delirium screening scale (follow-up 7 days; measured with: NuDESC; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	44	49	-	MD 0 higher (1.02 lower to 1.02 higher)	MODERATE	IMPORTANT
Delirium - Memorial delirium scale (measured with: MDAS; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	44	49	-	MD 0.5 lower (2.37 lower to 1.37 higher)	MODERATE	IMPORTANT
Adverse events- Local - Pain at injection site (follow-up 2 days; measured with: NRS; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	27	22	-	MD 0.35 higher (1.19 lower to 1.89 higher)	LOW	IMPORTANT
Adverse events- Local - swelling at injection site (follow-up 2 days; measured with: NRS; Better indicated by lower values)												

1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	27	22	-	MD 0.59 lower (1.4 lower to 0.22 higher)	LOW	IMPORTANT
Biochemistry sodium- serum test (follow-up 7 days, better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	44	49	-	MD 0.01 lower (0.85 lower to 3.2 higher)	LOW	IMPORTANT
Biochemistry urea- serum test (follow-up 7 days, better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	44	49	-	The median change in urea in the control group was 2.0 (interquartile range -1-8). The median change in urea in the control group was -2.0 (interquartile range -7-3)	LOW	IMPORTANT
Biochemistry creatinine- serum test (follow-up 7 days, better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	44	49	-	The median change in creatinine in the control group was -0.1 (interquartile range -0.1-0.1). The median change in creatinine in the control group was -0.1 (interquartile range -0.2-0)	LOW	IMPORTANT

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 75: Clinical evidence profile: clinically assisted hydration versus usual care

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Assisted hydration	Usual care	Relative (95% CI)	Absolute		
Self-reported wellbeing (follow-up 14 days; measured with: VAS; Better indicated by lower values)												
1	Non-randomised trials	Very Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	20	6	-	MD -27.5 lower (-48.1 to 6.8 lower)	VERY LOW	CRITICAL
Symptom improvement - Anxiety (follow-up mean 14 days; measured with: VAS; Better indicated by lower values)												
1	Non-randomised trials	Very Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	20	6	-	MD 10.5 lower (39.33 lower to 18.33 higher)	VERY LOW	CRITICAL
Symptom improvement - Dyspnoea (follow-up 14 days; measured with: VAS; Better indicated by lower values)												
1	Non-randomised trials	Very Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	20	7	-	MD 8 higher (13.17 lower to 29.17 higher)	VERY LOW	CRITICAL
Symptom improvement - Pain (follow-up 14 days; measured with: VAS; Better indicated by lower values)												
1	Non-randomised trials	Very Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	20	8	-	MD 9.4 lower (29.41 lower to 10.61 higher)	VERY LOW	CRITICAL
Symptom improvement - Nausea and Vomiting (follow-up 14 days; measured with: VAS; Better indicated by lower values)												
1	Non-randomised trials	Very Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	20	8	-	MD 2.5 higher (26.44 lower to 31.44 higher)	VERY LOW	CRITICAL
Symptom improvement - Sedation/drowsiness (follow-up 14 days; measured with: VAS; Better indicated by lower values)												
1	Non-randomised trials	Very Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	20	7	-	MD 18.6 lower (43.11 lower to 5.91 higher)	VERY LOW	CRITICAL

Delirium (follow-up 3 weeks; assessed with: No. >3 on MDAS)												
1	Non-randomised trials	Very Serious[a]	No serious inconsistency	Serious indirectness[c]	Serious[b]	None	7/59 (11.9%)	13/167 (7.8%)	RR 1.52 (0.62 to 3.37)	40 more per 1000 (from 30 fewer to 184 more)	VERY LOW	IMPORTANT
								7.8%		41 more per 1000 (from 30 fewer to 185 more)		
Adverse events-fluid overload (follow-up 2 days; assessed with: No. of events)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	0/20 (0%)	0/22 (0%)	not pooled	not pooled	LOW	IMPORTANT
								0%		not pooled		
Adverse events- local (follow-up 2 days; assessed with: No. of events)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	1/20 (5%)	0/22 (0%)	RR 3.46 (0.13 to 89.95)	-	LOW	IMPORTANT
								0%		-		
Adverse events- pleural effusion (follow-up 21 days; assessed with pleural effusion scale)												
1	Non-randomised trials	Very Serious[a]	No serious inconsistency	Serious indirectness[c]	No serious imprecision	None	167	59	-	MD 0.05 higher (-0.13 lower to 0.23 higher)	VERY LOW	IMPORTANT
Adverse events- oedema (follow-up 21 days; assessed with oedema scale)												
1	Non-randomised trials	Very Serious[a]	No serious inconsistency	Serious indirectness[c]	Serious[b]	None	167	59	-	MD 0.9 higher (-0.91 lower to 2.71 higher)	VERY LOW	IMPORTANT
Hydration status (follow-up 21 days; assessed with ad hoc dehydration score)												
1	Non-randomised trials	Very Serious[a]	No serious inconsistency	Serious indirectness[c]	Serious[b]	None	167	59	-	MD 0.5 higher (0.05 lower to 0.96 higher)	VERY LOW	IMPORTANT
Biochemistry sodium- serum test (follow-up 2 days before death, better indicated by lower values)												
1	Non-	Very	No serious	No serious	Serious[b]	None	13	54	-	MD 9.5 higher (3.73	VERY LOW	IMPORTANT

	randomised trials	Serious[a]	inconsistency	indirectness						lower to 15.27 higher)		
Biochemistry urea/creatinine - serum test (follow-up 2 days before death, better indicated by lower values)-												
1	Non-randomised trials	Very Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	13	54	-	MD 0.5 higher (-7.67 lower to 8.67 higher)	VERY LOW	IMPORTANT
Biochemistry urea/creatinine - serum test (follow-up 7 days before death, better indicated by lower values)												
1	Non-randomised trials	Very Serious[a]	No serious inconsistency	Serious indirectness[c]	Serious[b]	None	167	59	-	MD 5.0 higher (-2.17 lower to 12.11 higher)	VERY LOW	IMPORTANT

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
(c) Downgraded by 1 increment because the study that contributed to this outcome had an intervention period of 3 weeks

J.5 Pharmacological Intervention

J.5.1 Pain management

Table 76: Clinical evidence profile: Diamorphine versus morphine

Quality assessment							No. of patients		Effect			
No. Of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Diamorphine	Morphine	Relative (95% CI)	Absolute	Quality	Importance
Pain (follow-up 2 days; range of scores: 0-100; Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	49	40	-	MD 6.41 higher (1.34 to 11.47 higher)	VERY LOW	CRITICAL
Nausea (follow-up 2 days; range of scores: 0-100; Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	49	40	-	MD 2.36 higher (1.04 lower to 5.77 higher)	VERY LOW	IMPORTANT
Night-time sleep quality (follow-up 2 days; range of scores: 0-100; Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	49	40	-	MD 7.77 lower (15.89 lower to 0.34 higher)	VERY LOW	IMPORTANT

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias or by 2 increments if the majority of the evidence was at very high risk of bias (observational studies start from low).

(b) Downgraded by 1 increment if the majority of the evidence was from studies with serious indirectness or by 2 increments if the majority of the evidence was from studies with very serious indirectness.

(c) *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.*

J.5.2 Breathlessness management

Table 77: Clinical evidence profile: Midazolam versus morphine

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Midazolam	Morphine	Relative (95% CI)	Absolute	Quality	Importance
Dyspnoea relief - 24 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	12/26 (46.2%)	20/29 (69%)	RR 0.67 (0.41 to 1.08)	228 fewer per 1000 (from 407 fewer to 55 more)	LOW	CRITICAL
Dyspnoea relief - 48 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	17/23 (73.9%)	21/24 (87.5%)	RR 0.84 (0.63 to 1.12)	140 fewer per 1000 (from 324 fewer to 105 more)	LOW	CRITICAL
Dyspnoea intensity - 24 hours (measured with: Borg scale; range of scores: 0-10; Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision[b]	None	33	35	Median (IQR) Midazolam: 4 (2-6.2); Morph: 3 (2-5.5)	median 1 higher	LOW	CRITICAL
Dyspnoea intensity - 48 hours (measured with: Borg scale; range of scores: 0-10; Better indicated by lower values)												
1	Randomised trials	Very serious[c]	No serious inconsistency	No serious indirectness	No serious imprecision[b]	None	33	35	Median (IQR) Midazolam: 2 (0-7); Morphine: 2 (0-4.7)	Median 0 lower	LOW	CRITICAL
Clinically relevant (grade 2 or above) adverse events at 48 hours – Nausea or vomiting (follow-up 48 hours)												
1	Randomised trials	serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	None	1/33 (3%)	4/35 (11.4%)	RR 0.27 (0.03 to 2.25)	83 fewer per 1000 (from 111 fewer to 143 more)	VERY LOW	IMPORTANT
Clinically relevant (grade 2 or above) adverse events at 48 hours - Somnolence (follow-up 48 hours)												
1	Randomised trials	serious[a]	No serious inconsistency	No serious indirectness	Very serious[e]	None	2/33 (6.1%)	6/35 (17.1%)	RR 0.35 (0.08 to 1.63)	111 fewer per 1000 (from 158 fewer to 108 more)	VERY LOW	IMPORTANT

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias or by 2 increments if the majority of the evidence was at very high risk of bias (observational studies start from low).
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
(c) Imprecision could not be assessed.

Table 78: Clinical evidence profile: Morphine plus midazolam versus midazolam

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Morphine + midazolam**	**Midazolam**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Dyspnoea relief - 24 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	23/25 (92%)	12/26 (46.2%)	RR 1.99 (1.3 to 3.07)	457 more per 1000 (from 138 more to 955 more)	MODERATE	CRITICAL
Dyspnoea relief - 48 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	22/23 (95.7%)	17/23 (73.9%)	RR 1.29 (1 to 1.67)	214 more per 1000 (from 0 more to 495 more)	LOW	CRITICAL
Dyspnoea intensity - 24 hours (measured with: Borg scale; range of scores: 0-10; Better indicated by lower values)												
1	Randomised trials	Very serious[c]	No serious inconsistency	No serious indirectness	No serious imprecision[c]	None	33	33	Median (IQR) M plus mid: 3 (2-5); mid: 4 (2-6.2)	median 1 lower	LOW	CRITICAL
Dyspnoea intensity - 48 hours (measured with: Borg scale; range of scores: 0-10; Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision[c]	None	33	33	Median (IQR) M plus mid: 2 (1-5); mid: 2 (0-7)	Median 0 lower	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Morphine + midazolam	Midazolam	Relative (95% CI)	Absolute		
Clinically relevant (grade 2 or above) adverse events at 48 hours - Nausea/vomiting												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	0/33 (0%)	1/33 (3%)	OR 0.14 (0 to 6.82)	26 fewer per 1000 (from 30 fewer to 145 more)	VERY LOW	IMPORTANT
Clinically relevant (grade 2 or above) adverse events at 48 hours - Somnolence												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	3/33 (9.1%)	2/33 (6.1%)	RR 1.5 (0.27 to 8.4)	30 more per 1000 (from 44 fewer to 448 more)	VERY LOW	IMPORTANT

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias or by 2 increments if the majority of the evidence was at very high risk of bias (observational studies start from low).
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
(c) Imprecision could not be assessed

Table 79: Clinical evidence profile: Morphine plus midazolam versus morphine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Morphine + midazolam	Morphine	Relative (95% CI)	Absolute		
Dyspnoea relief - 24 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	23/25 (92%)	20/29 (69%)	RR 1.33 (1.02 to 1.75)	228 more per 1000 (from 14 more to 517 more)	LOW	CRITICAL
Dyspnoea relief - 48 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	22/23 (95.7%)	21/24 (87.5%)	RR 1.09 (0.92 to 1.3)	79 more per 1000 (from 70 fewer to 262 more)	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Morphine + midazolam	Morphine	Relative (95% CI)	Absolute		
Dyspnoea intensity - 24 hours (measured with: Borg scale; range of scores: 0-10; Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision[c]	None	33	35	Median (IQR) M + mid: 3 (2-5); M: 3 (2-5.5)	median 0 lower	LOW	CRITICAL
Dyspnoea intensity - 48 hours (measured with: Borg scale; range of scores: 0-10; Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision[c]	None	33	35	Median (IQR) M + mid: 2 (1-5); M: 2 (0-4.7)	median 0 lower	LOW	CRITICAL
Clinically relevant (grade 2 or above) adverse events at 48 hours - Nausea/vomiting												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	0/33 (0%)	4/35 (11.4%)	OR 0.13 (0.02 to 0.97)	98 fewer per 1000 (from 3 fewer to 112 fewer)	LOW	IMPORTANT
Clinically relevant (grade 2 or above) adverse events at 48 hours - Somnolence												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	3/33 (9.1%)	6/35 (17.1%)	RR 0.53 (0.14 to 1.95)	81 fewer per 1000 (from 147 fewer to 163 more)	VERY LOW	IMPORTANT

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias or by 2 increments if the majority of the evidence was at very high risk of bias (observational studies start from low).

(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

(c) Imprecision could not be assessed

Table 80: Clinical evidence profile: Oxygen versus air

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Oxygen	Air	Relative (95% CI)	Absolute		
Dyspnoea on modified Borg scale (follow-up 15 minutes; range of scores: 0-10; Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	Serious[b]	No serious imprecision[c]	None	38	38	-	MD 0.2 lower (0 to 0 higher)	VERY LOW	CRITICAL
Dyspnoea on VAS (follow-up 15 minutes; range of scores: 0-100; Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	Serious[b]	No serious imprecision[c]	None	38	38	-	MD 3 lower (0 to 0 higher)	VERY LOW	CRITICAL
Dyspnoea on VAS: cardiopulmonary disease subgroup (follow-up 15 minutes; range of scores: 0-100; Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	Serious[b]	No serious imprecision[c]	None	16	16	-	MD 2 lower (0 to 0 higher)	VERY LOW	CRITICAL
Dyspnoea on VAS: non-cardiopulmonary disease subgroup (follow-up 15 minutes; range of scores: 0-100; Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	Serious[b]	No serious imprecision[c]	None	16	16	-	MD 6 lower (0 to 0 higher)	VERY LOW	CRITICAL
Adverse events (relating to study procedure)												
1	Randomised trials	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	0/38 (0%)	0/38 (0%)	not pooled	not pooled	LOW	IMPORTANT
								0%		not pooled		

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias or by 2 increments if the majority of the evidence was at very high risk of bias (observational studies start from low).

(b) Downgraded by 1 increment if the majority of the evidence was from studies with serious indirectness or by 2 increments if the majority of the evidence was from studies with very serious indirectness.

Table 81: Clinical evidence profile: Oxygen versus morphine or hydromorphone (NRS)

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Oxygen	Morphine or hydromorphone (NRS)	Relative (95% CI)	Absolute		
Dyspnoea at rest (follow-up 120 minutes after opioid application; Better indicated by lower values)												
1	Observational studies	Very serious[a]	No serious inconsistency	Very serious[b]	No serious imprecision	None	46	46	-	MD 4.31 higher (3.63 to 4.98 higher)	VERY LOW	CRITICAL

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias or by 2 increments if the majority of the evidence was at very high risk of bias (observational studies start from low).

(b) Downgraded by 1 increment if the majority of the evidence was from studies with serious indirectness or by 2 increments if the majority of the evidence was from studies with very serious indirectness.

Table 82: Clinical evidence profile: Morphine or hydromorphone versus room air (NRS)

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Morphine or hydromorphone	Room air (NRS)	Relative (95% CI)	Absolute		
Dyspnoea at rest (follow-up 120 minutes after opioid application; Better indicated by lower values)												
1	Observational studies	Very serious[a]	No serious inconsistency	Very serious[b]	No serious imprecision	None	46	46	-	MD 4.39 lower (5 to 3.78 lower)	VERY LOW	CRITICAL

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias or by 2 increments if the majority of the evidence was at very high risk of bias (observational studies start from low).

(b) Downgraded by 1 increment if the majority of the evidence was from studies with serious indirectness or by 2 increments if the majority of the evidence was from studies with very serious indirectness.

Table 83: Clinical evidence profile: Oxygen versus room air (NRS)

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Oxygen	Room air (NRS)	Relative (95% CI)	Absolute		
Dyspnoea at rest (follow-up 60 minutes; Better indicated by lower values)												
1	Observational studies	Very serious[a]	No serious inconsistency	Very serious[b]	No serious imprecision	None	46	46	-	MD 0.13 higher (0.96 lower to 0.70 higher)	VERY LOW	CRITICAL

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias or by 2 increments if the majority of the evidence was at very high risk of bias (observational studies start from low).

(b) Downgraded by 1 increment if the majority of the evidence was from studies with serious indirectness or by 2 increments if the majority of the evidence was from studies with very serious indirectness.

J.5.3 Nausea and vomiting

Table 84: Clinical evidence profile: octreotide versus hyoscine butylbromide

Quality assessment							Summary of Findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With control	With octreotide vs. hyoscine butylbromide 72 hours	Relative effect (95% CI)	Risk with Control	Risk difference with octreotide vs. hyoscine butylbromide 72 hours (95% CI)
Nausea at 72 hours (range of scores: 0-3; Better indicated by lower values)											
15 (1 study) 3 days	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	Undetected	VERY LOW[a,b,] due to risk of bias, imprecision	6	9	-	The mean nausea in the control groups was 1.6	The mean nausea in the intervention groups was 1.10 lower(1.45 to 0.75 lower)
17 (1 study)	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	Undetected	VERY LOW[a,b,] due to risk of bias,	Not possible to extract from paper.				

3 days						imprecision					
Vomiting at 72 hours (better indicated by lower values)											
15 (1 study) 3 days	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	Undetected	VERY LOW[a,b,] due to risk of bias, imprecision	6	9	-	The mean vomiting in the control groups was 1.6 points	The mean vomiting in the intervention groups was 1.40 lower (2.08 to 0.72 lower)
Sedation- Drowsiness at 72 hours (measured with: Measured on scale for drowsiness. Unclear who measured; range of scores: 0-3; Better indicated by lower values)											
15 (1 study) 3 days	Very serious[a]	No serious inconsistency	Serious	Very serious[b]	Undetected	VERY LOW[a,b,] due to risk of bias, imprecision	6	9	-	The mean sedation-drowsiness in the control groups was 1.6 points	The mean sedation-drowsiness in the intervention groups was 0.4 higher (0.05 lower to 0.85 higher)
17 (1 study) 3 days	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	LOW[a] due to risk of bias	Not possible to extract from paper.				
Vomiting (measured with: Number of episodes in 24 hours prior to death)											
53 (1 study) 1-61 days	Very serious[a]	No serious inconsistency	Serious[2]	Serious[b]	Undetected	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	22	31	-	The mean vomiting in the control groups was 0.59	The mean vomiting in the intervention groups was 0.04 lower (0.32 lower to 0.24 higher)
Nausea (range of scores: 1-3 and then multiplied by hours experienced; Better indicated by lower values)											
53 (1 study) 0-61 days	Very serious[a]	No serious inconsistency	Serious[c]	Serious[b]	Undetected	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	22	31	-	The mean nausea in the control groups was 0.5	The mean nausea in the intervention groups was 0.11 higher (0.25 lower to 0.47 higher)
Quality of life											
0 (0 studies)	No information on quality of life found in literature search.										
Adverse Symptoms: Dry mouth at 72 hours (range of scores: 0-3; Better indicated by lower values)											

15 (1 study) 3 days	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	Undetected	VERY LOW[a,b,] due to risk of bias, imprecision	6	9	-	The mean dry mouth rating in the control groups was 1.6	The mean dry mouth rating in the intervention groups was 0.1 higher (0.35 lower to 0.55 higher)
17 (1 study) 3 days	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	LOW[a] due to risk of bias	Not possible to extract from paper				

(a) The risk of bias should be based on what the majority of the evidence is saying for the particular outcome. Downgrade once if the majority of the evidence is from studies at high risk of bias. Downgrade twice if the majority of the evidence is from studies at very high risk of bias.

(b) Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

(c) The majority of the evidence included an indirect population (downgrade by 1 increment) or a very indirect population (downgrade by 2 increments).

J.5.4 Noisy Respiratory Secretions

Table 85: Clinical evidence profile: glycopyrronium bromide versus hyoscine hydrobromide

Quality assessment							No. of patients		Effect			
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Glycopyrronium bromide**	**Hyoscine hydrobromide**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Improvement in noise intensity (Likar 2008 added manually in the WORD document - could not be extracted from the graph)												
0	No evidence available					None	-	-	-	-		
Improvement in noise intensity initial vs. 1 hour												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	22/55 (40%)	59/103 (57.3%)	RR 0.7 (0.49 to 1.01)	172 fewer per 1000 (from 292 fewer to 6 more)	VERY LOW	CRITICAL
Improvement in noise intensity initial vs. final (median < 2 hours before death)												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	24/57 (42.1%)	46/103 (44.7%)	RR 0.94 (0.65 to 1.37)	27 fewer per 1000 (from 156 fewer to 165 more)	VERY LOW	CRITICAL
Secretions relieved at death (prospective audit)												
1	Observational studies	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	24/37 (64.9%)	20/37 (54.1%)	RR 1.2 (0.82 to 1.75)	108 more per 1000 (from 97 fewer to	VERY LOW	CRITICAL

										405 more)		
Response to drug (time from first observation until first observation of absent symptoms) - Immediate												
1	Observational studies	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	13/36 (36.1%)	11/36 (30.6%)	RR 1.18 (0.61 to 2.28)	55 more per 1000 (from 119 fewer to 391 more)	VERY LOW	CRITICAL
Response to drug (time from first observation until first observation of absent symptoms) - Late												
1	Observational studies	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	13/36 (36.1%)	10/36 (27.8%)	RR 1.3 (0.66 to 2.57)	83 more per 1000 (from 94 fewer to 436 more)	VERY LOW	CRITICAL
Response to drug (time from first observation until first observation of absent symptoms) - Transient												
1	Observational studies	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	10/36 (27.8%)	7/36 (19.4%)	RR 1.43 (0.61 to 3.34)	84 more per 1000 (from 76 fewer to 455 more)	VERY LOW	CRITICAL
Relatives' distress improved (prospective audit)												
1	Observational studies	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	22/25 (88%)	27/29 (93.1%)	RR 0.95 (0.79 to 1.13)	47 fewer per 1000 (from 196 fewer to 121 more)	VERY LOW	IMPORTANT
Length of survival (hours) (better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	6	7	-	MD 6.7 lower (21.12 lower to 7.72 higher)	MODERATE	IMPORTANT

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias (observational studies start from low).
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 86: Clinical evidence profile: hyoscine butylbromide versus hyoscine hydrobromide

Quality assessment							No. of patients		Effect			
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Hyoscine butylbromide**	**Hyoscine hydrobromide**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Improvement in noisy breathing (score of 0-1 defined as effective reduction) - At 4 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	46/85 (54.1%)	44/94 (46.8%)	RR 1.16 (0.86 to 1.55)	75 more per 1000 (from 66 fewer to	LOW	CRITICAL

										257 more)		
Improvement in noisy breathing (score of 0-1 defined as effective reduction) - At 12 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	35/68 (51.5%)	40/70 (57.1%)	RR 0.9 (0.66 to 1.22)	57 fewer per 1000 (from 194 fewer to 126 more)	LOW	CRITICAL
Improvement in noisy breathing (score of 0-1 defined as effective reduction) - At 24 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	28/47 (59.6%)	36/53 (67.9%)	RR 0.88 (0.65 to 1.18)	82 fewer per 1000 (from 238 fewer to 122 more)	LOW	CRITICAL
Secretions relieved at death (prospective audit)												
1	Observational studies	Very serious	No serious inconsistency	No serious indirectness	Serious[b]	None	24/37 (64.9%)	20/37 (54.1%)	RR 1.2 (0.82 to 1.75)	108 more per 1000 (from 97 fewer to 405 more)	VERY LOW	CRITICAL
Improvement in relatives' distress (prospective audit)												
1	Observational studies	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	24/27 (88.9%)	27/29 (93.1%)	RR 0.95 (0.81 to 1.13)	47 fewer per 1000 (from 177 fewer to 121 more)	VERY LOW	IMPORTANT
Worsening in level of consciousness - At 12 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	14/66 (21.2%)	31/68 (45.6%)	RR 0.47 (0.27 to 0.79)	242 fewer per 1000 (from 96 fewer to 333 fewer)	LOW	CRITICAL
Worsening in level of consciousness - At 24 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	11/45 (24.4%)	25/52 (48.1%)	RR 0.51 (0.28 to 0.91)	236 fewer per 1000 (from 43 fewer to 346 fewer)	LOW	CRITICAL

Improvement in confusion (for those with sufficient level of consciousness to assess) - At 12 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	4/12 (33.3%)	0/2 (0%)	Peto OR 4.56 (0.19 to 111.03)	333 more per 1000 (from 160 fewer to 830 more)[c]	VERY LOW	IMPORTANT
Improvement in confusion (for those with sufficient level of consciousness to assess) - At 24 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	1/9 (11.1%)	0/4 (0%)	Peto OR 4.24 (0.06 to 296.2)	111 more per 1000 (from 230 fewer to 450 more)[c]	VERY LOW	IMPORTANT

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias (observational studies start from low).
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
(c) When there are 0 events in either group the Peto OR was used and a risk difference was calculated.

Table 87: Clinical evidence profile: atropine versus hyoscine hydrobromide

Quality assessment							No. of patients		Effect			
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Atropine**	**Hyoscine hydrobromide**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Improvement in noisy breathing (score of 0-1 defined as effective reduction) - At 4 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	46/92 (50%)	44/94 (46.8%)	RR 1.07 (0.79 to 1.44)	33 more per 1000 (from 98 fewer to 206 more)	LOW	CRITICAL
Improvement in noisy breathing (score of 0-1 defined as effective reduction) - At 12 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	46/65 (70.8%)	40/70 (57.1%)	RR 1.24 (0.96 to 1.6)	137 more per 1000 (from 23 fewer to 343 more)	LOW	CRITICAL
Improvement in noisy breathing (score of 0-1 defined as effective reduction) - At 24 hours												
1	Randomised	Serious[a]	No serious	No serious	Serious[b]	None	41/54	36/53	RR 1.12	82 more per	LOW	CRITICAL

	trials		inconsistency	indirectness			(75.9%)	(67.9%)	(0.88 to 1.42)	1000 (from 82 fewer to 285 more)		
Worsening in level of consciousness - At 12 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	18/62 (29%)	31/68 (45.6%)	RR 0.64 (0.4 to 1.02)	164 fewer per 1000 (from 274 fewer to 9 more)	LOW	CRITICAL
Worsening in level of consciousness - At 24 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	19/51 (37.3%)	25/52 (48.1%)	RR 0.77 (0.49 to 1.22)	111 fewer per 1000 (from 245 fewer to 106 more)	LOW	CRITICAL
Improvement in confusion (for those with sufficient level of consciousness to assess) - At 12 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	1/5 (20%)	0/2 (0%)	Peto OR 4.06 (0.05 to 310.62)	200 more per 1000 (from 350 fewer to 750 more)[c]	VERY LOW	IMPORTANT
Improvement in confusion (for those with sufficient level of consciousness to assess) - At 24 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/6 (0%)	0/4 (0%)	Not pooled	Not pooled	MODERATE	IMPORTANT

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias (observational studies start from low).
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
(c) When there are 0 events in either group the Peto OR was used and a risk difference was calculated.

Table 88: Clinical evidence profile: atropine versus hyoscine butylbromide

Quality assessment							No. of patients		Effect			
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Atropine**	**Hyoscine butylbromide**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Improvement in noisy breathing (score of 0-1 defined as effective reduction) - At 4 hours												

1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[a]	None	46/92 (50%)	46/85 (54.1%)	RR 0.92 (0.7 to 1.23)	43 fewer per 1000 (from 162 fewer to 124 more)	LOW	CRITICAL
Improvement in noisy breathing (score of 0-1 defined as effective reduction) - At 12 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	46/65 (70.8%)	35/68 (51.5%)	RR 1.37 (1.04 to 1.82)	190 more per 1000 (from 21 more to 422 more)	LOW	CRITICAL
Improvement in noisy breathing (score of 0-1 defined as effective reduction) - At 24 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	41/54 (75.9%)	28/47 (59.6%)	RR 1.27 (0.96 to 1.69)	161 more per 1000 (from 24 fewer to 411 more)	LOW	CRITICAL
Worsening in level of consciousness - At 12 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	18/62 (29%)	31/68 (45.6%)	RR 0.64 (0.4 to 1.02)	164 fewer per 1000 (from 274 fewer to 9 more)	LOW	CRITICAL
Worsening in level of consciousness - At 24 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	19/51 (37.3%)	25/52 (48.1%)	RR 0.77 (0.49 to 1.22)	111 fewer per 1000 (from 245 fewer to 106 more)	LOW	CRITICAL
Improvement in confusion (for those with sufficient level of consciousness to assess) - At 12 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	1/5 (20%)	0/2 (0%)	Peto OR 4.06 (0.05 to 310.62)	200 more per 1000 (from 350 fewer to 750 more)[c]	VERY LOW	IMPORTANT
Improvement in confusion (for those with sufficient level of consciousness to assess) - At 24 hours												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/6 (0%)	0/4 (0%)	Not pooled	Not pooled	MODERATE	IMPORTANT

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias (observational studies start from low).
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

(c) When there are 0 events in either group the Peto OR was used and a risk difference was calculated.

Table 89: Clinical evidence profile: octreotide versus hyoscine hydrobromide

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Octreotide	Hyoscine hydrobromide	Relative (95% CI)	Absolute	Quality	Importance
Improvement in noisy breathing intensity (from 1 hour after first dose to 6 hours after second dose)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	2/5 (40%)	2/5 (40%)	RR 1 (0.22 to 4.56)	0 fewer per 1000 (from 312 fewer to 1000 more)	VERY LOW	CRITICAL

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias (observational studies start from low).
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 90: Clinical evidence profile: atropine versus placebo

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Atropine	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Improvement in noisy breathing (reduction of 1 point or more) - At 2 hours												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[a]	None	28/74 (37.8%)	26/63 (41.3%)	RR 0.92 (0.61 to 1.39)	33 fewer per 1000 (from 161 fewer to 161 more)	LOW	CRITICAL
Improvement in noisy breathing (reduction of 1 point or more) - At 4 hours												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	27/68 (39.7%)	31/60 (51.7%)	RR 0.77 (0.52 to 1.13)	119 fewer per 1000 (from 248 fewer to 67 more)	MODERATE	

(a) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 91: Clinical evidence profile: hyoscine hydrobromide versus placebo

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Hyoscine hydrobromide	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Improvement in noise intensity - from baseline up to 10 hours												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/15 (0%)	0/16 (0%)	-	-	LOW	CRITICAL
Restlessness												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	9/15 (60%)	6/16 (37.5%)	RR 1.6 (0.75 to 3.41)	225 more per 1000 (from 94 fewer to 904 more)	LOW	
Pain												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	13/15 (86.7%)	2/16 (12.5%)	RR 6.93 (1.87 to 25.73)	741 more per 1000 (from 109 more to 1000 more)	LOW	
Length of survival (minutes) (Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	15	16	-	MD 296 higher (51.81 lower to 643.81 higher)	VERY LOW	IMPORTANT

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias (observational studies start from low).
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 92: Clinical evidence profile: glycopyrronium bromide versus hyoscine butylbromide

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Glycopyrronium bromide**	**Hyoscine butylbromide**	**Relative (95% CI)**	**Absolute**		
Secretions relieved at death (prospective audit)												
1	Observational studies	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	24/37 (64.9%)	24/37 (64.9%)	RR 1 (0.72 to 1.4)	0 fewer per 1000 (from 182 fewer to 259 more)	VERY LOW	CRITICAL
Relatives' distress improved (prospective audit)												
1	Observational studies	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	22/25 (88%)	27/29 (93.1%)	RR 0.95 (0.79 to 1.13)	47 fewer per 1000 (from 196 fewer to 121 more)	VERY LOW	CRITICAL

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias (observational studies start from low).
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

J.6 Anticipatory Prescribing

None

Appendix K: Forest plots

K.1 Recognising Dying

K.1.1 Mortality

Figure 10: Prognostic indicators of mortality (within 7 days)

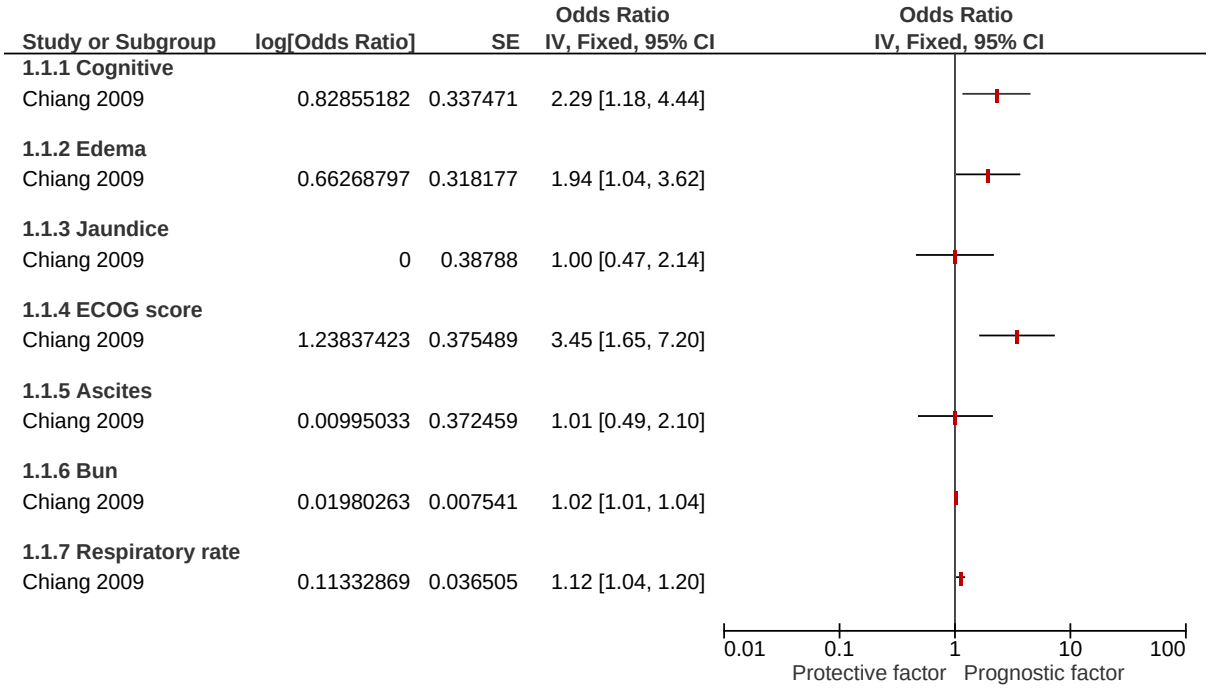
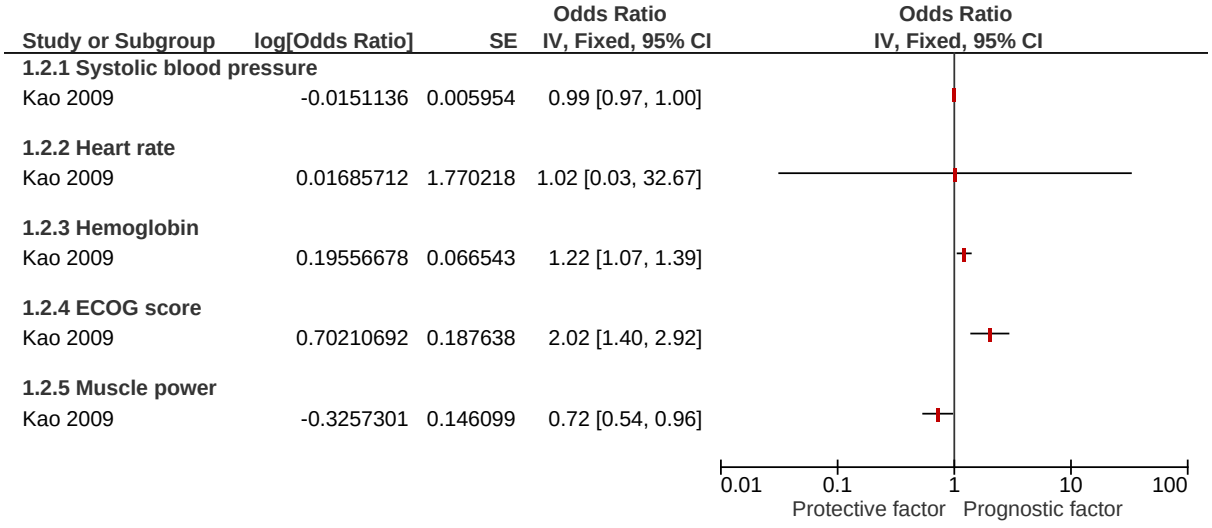
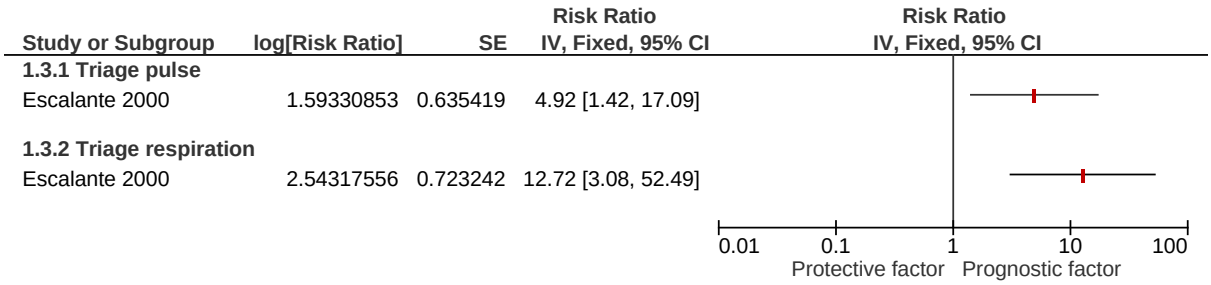


Figure 11: Prognostic indicators of mortality (within 7 days)



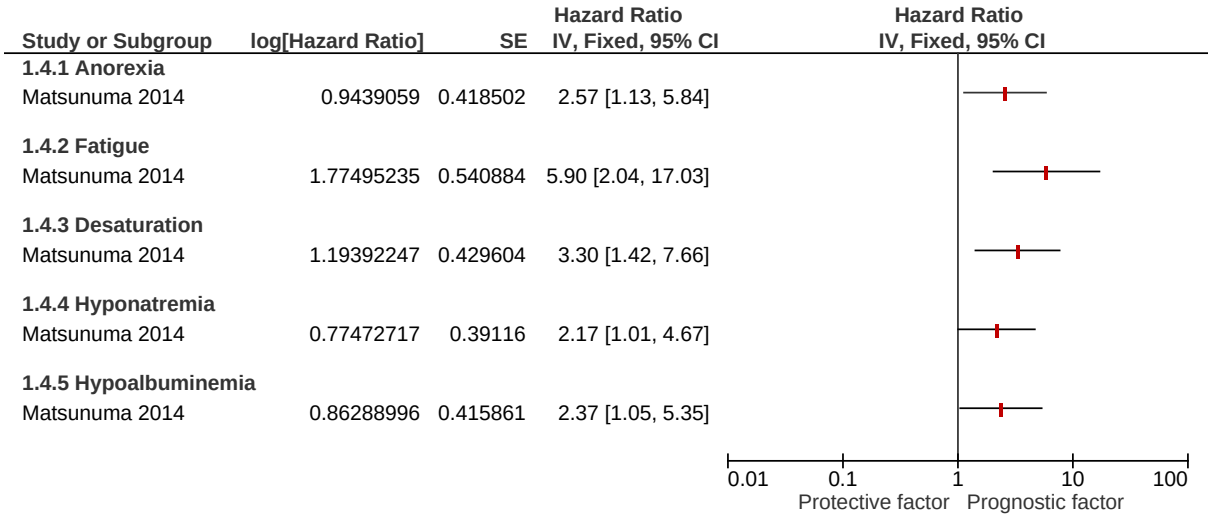
1

Figure 12: Prognostic indicators of mortality (within 2 weeks)



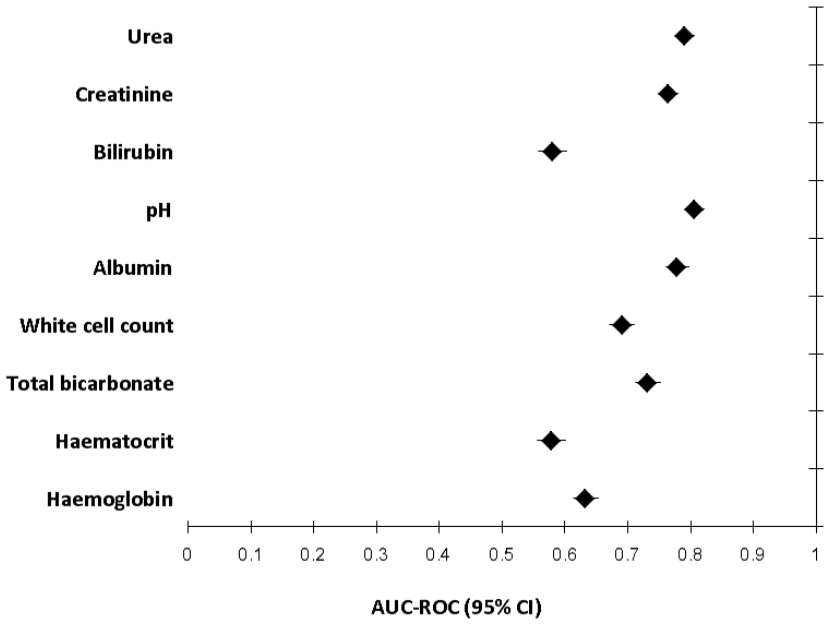
2

Figure 13: Prognostic indicators of mortality (within 2 weeks)



3

Figure 14: Diagnostic indicators of mortality (same day or the next)



K.2 Communications

None.

K.3 Shared Decision Making

None.

K.4 Assisted Hydration

K.4.1 Clinically assisted hydration versus placebo

Figure 15: Clinically assisted hydration versus placebo for quality of life (change in FACT G scale, range 0-108, high is good outcome)

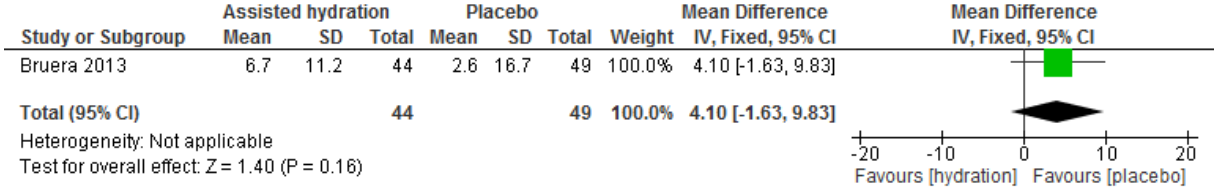
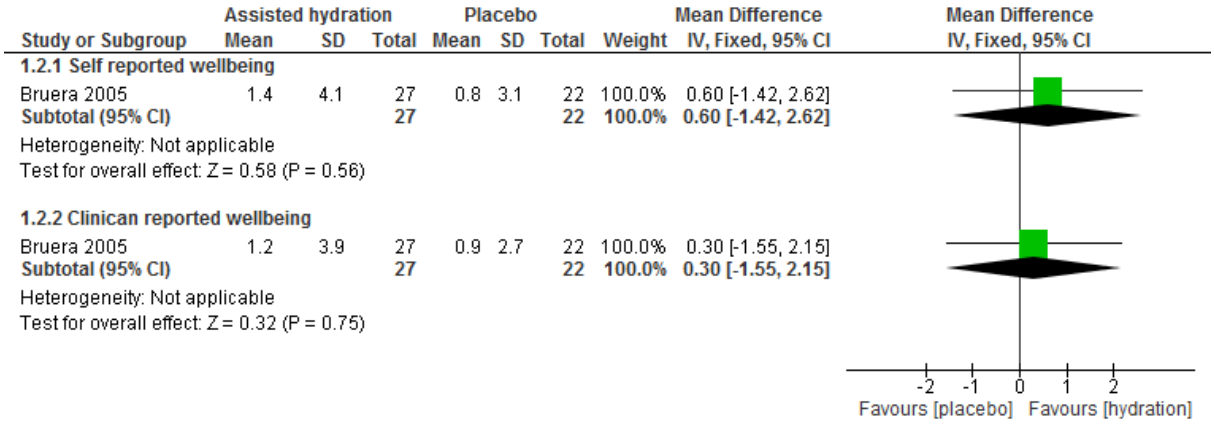
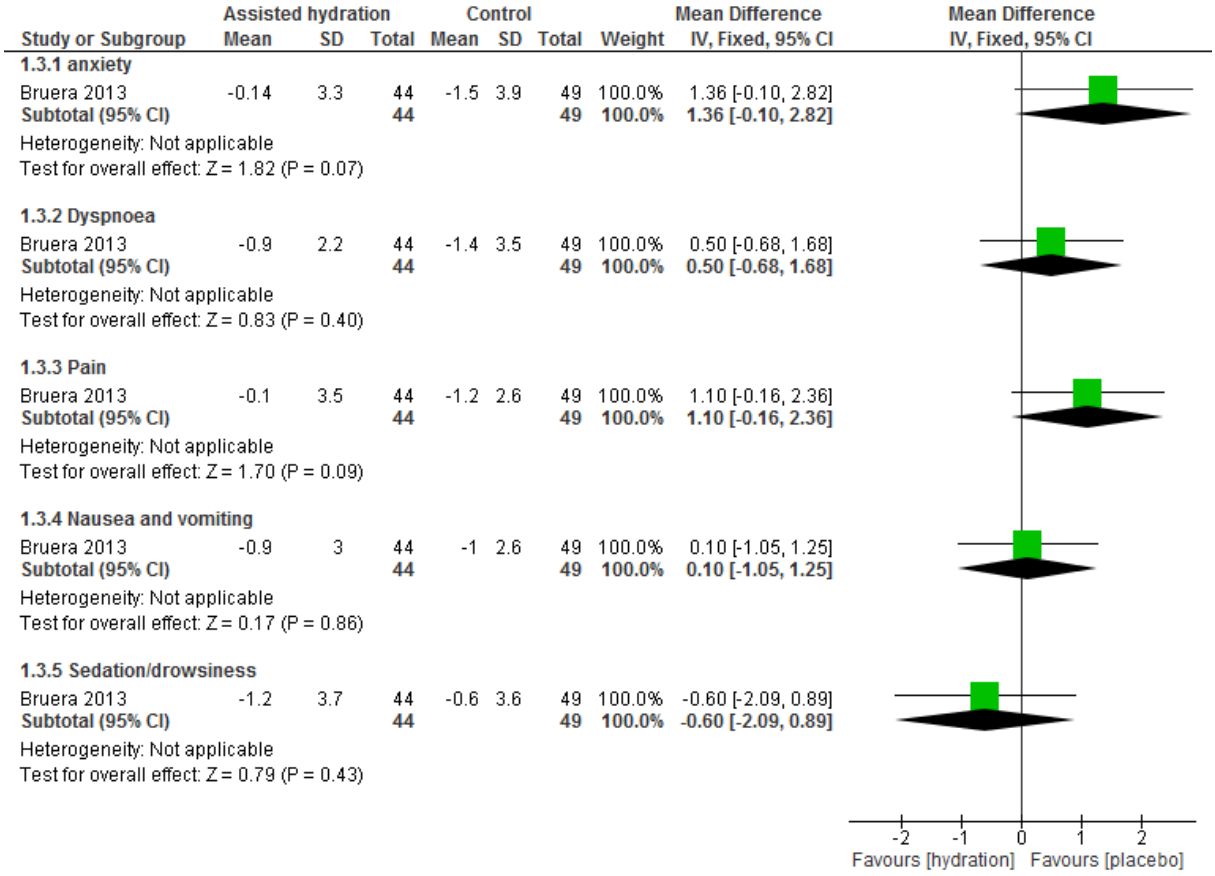


Figure 16: Clinically assisted hydration versus placebo for wellbeing (measured on 0-10 scale, high is good outcome)



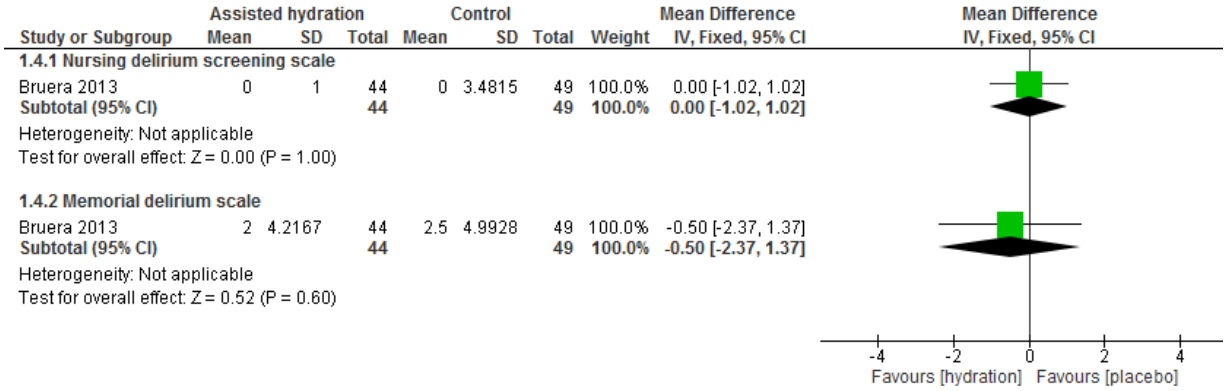
1

Figure 17: Clinically assisted hydration versus placebo for symptom relief (change in ESAS scale 0-10, high is poor outcome)



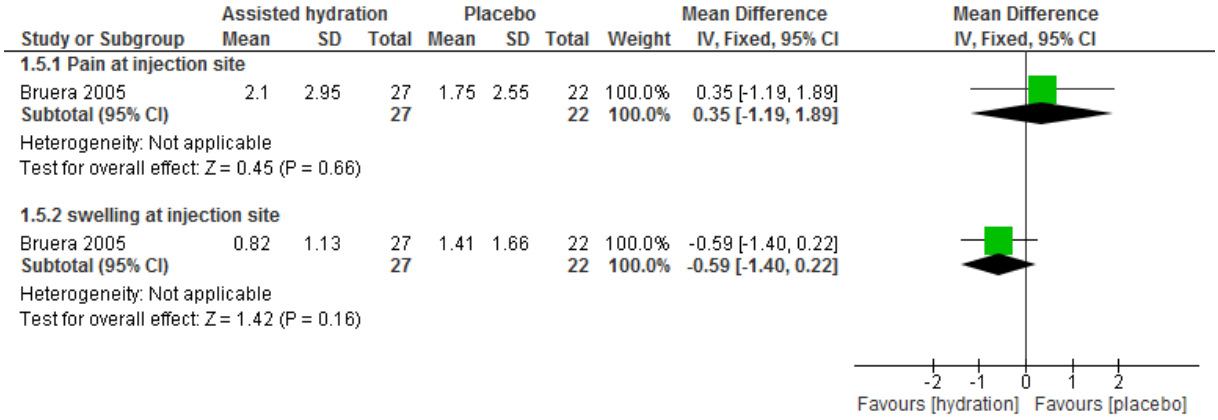
2

Figure 18: Clinically assisted hydration versus placebo for delirium (change in NUDESC scale 0-10 [high is poor outcome], change in MDAS scale 0-30 [high is poor outcome])



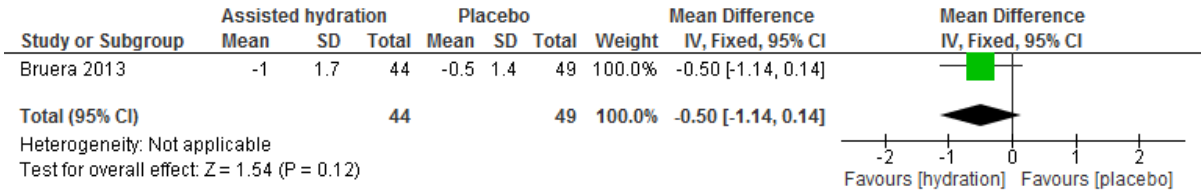
1

Figure 19: Clinically assisted hydration versus placebo for adverse local events (measured on 0-10 scale, high is a poor outcome)



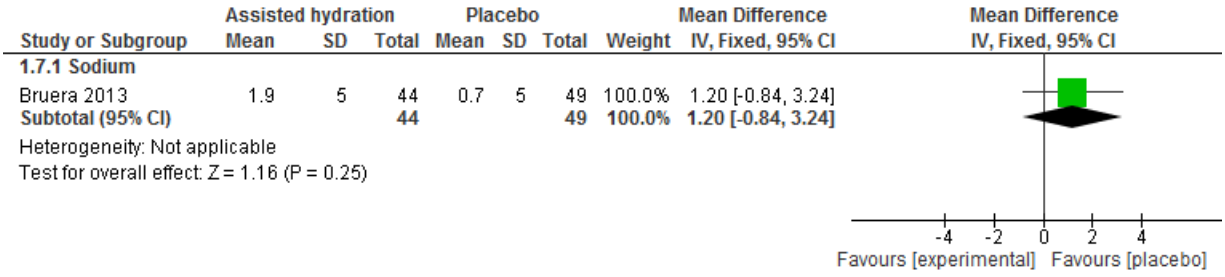
2

Figure 20: Clinically assisted hydration verses placebo for hydration status (change in dehydration scale 0-7, high is a poor outcome)



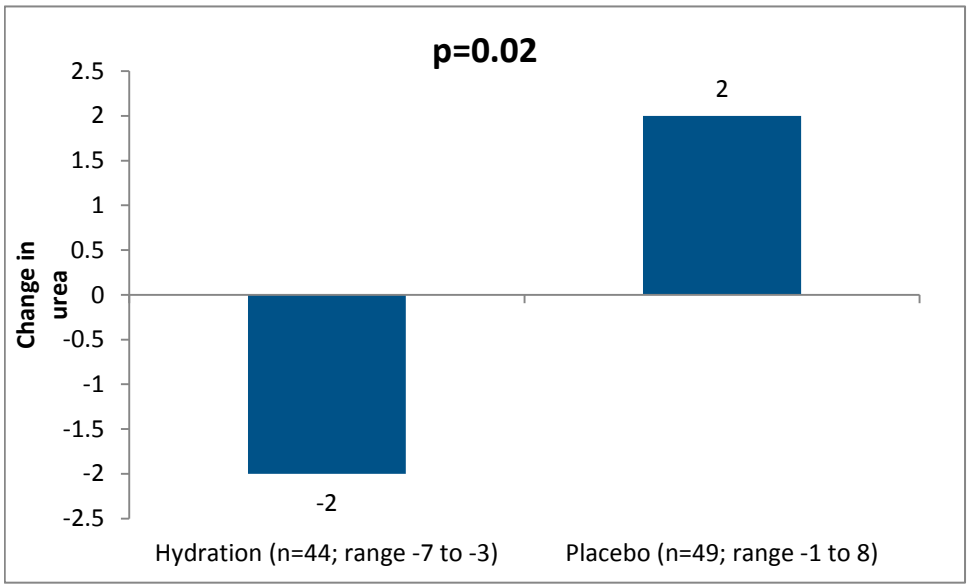
3

Figure 21: Clinically assisted hydration versus placebo for sodium (assumed measured in mEq/litre)



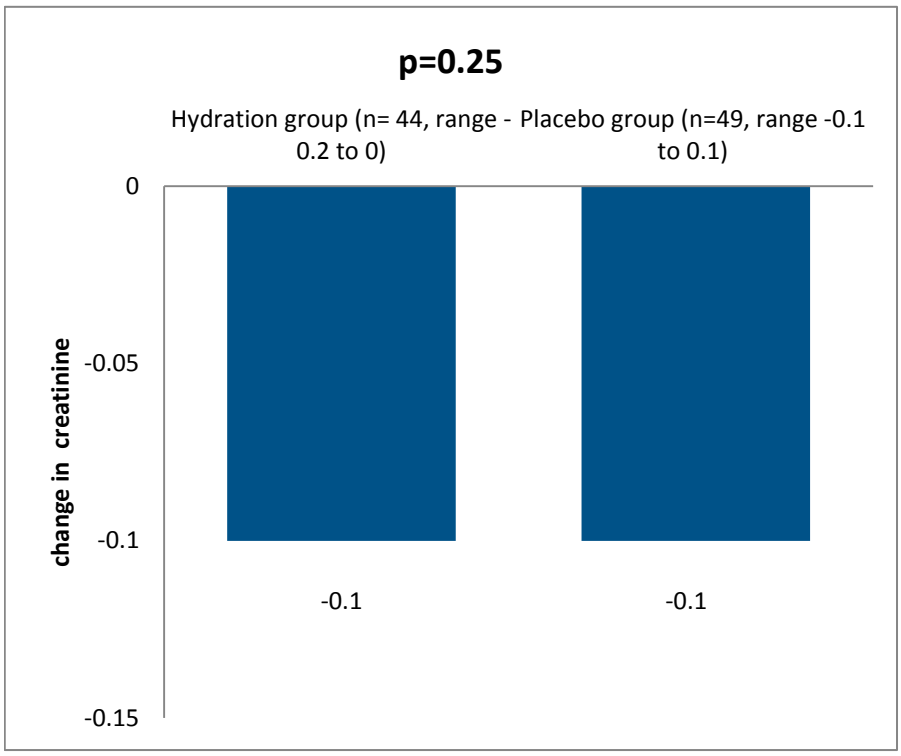
1

Figure 22: Clinically assisted hydration verses placebo for median change in urea (assumed measured in mg/dl)



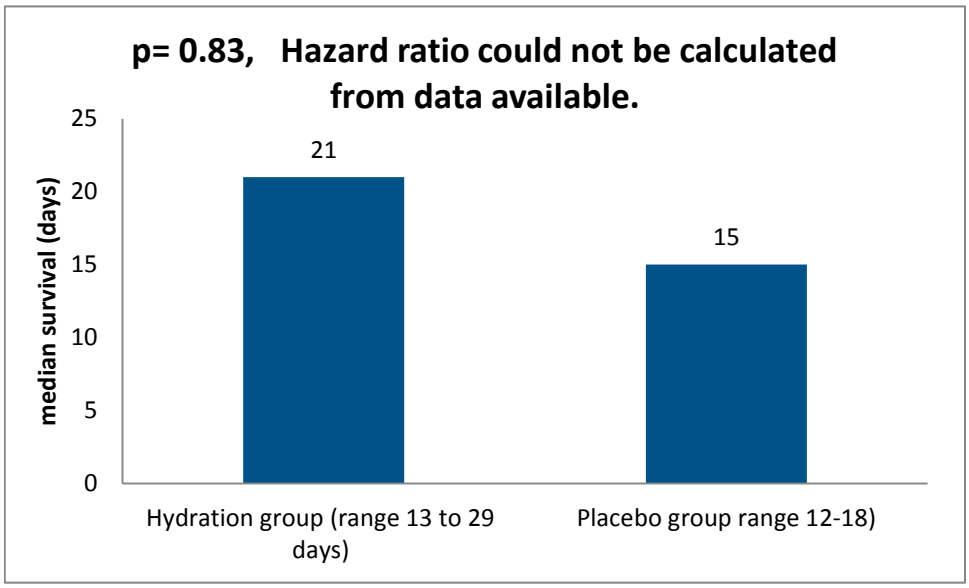
2

Figure 23: Clinically assisted hydration versus placebo for median change in creatinine (assumed measured in mg/dl)



1

Figure 24: Clinically assisted hydration verses placebo for change in survival (days, from entering study to death)



K.4.2 Clinically assisted hydration versus usual care

Figure 25: Clinically assisted hydration versus usual care for wellbeing (measured on VAS 0-100, high is poor outcome)

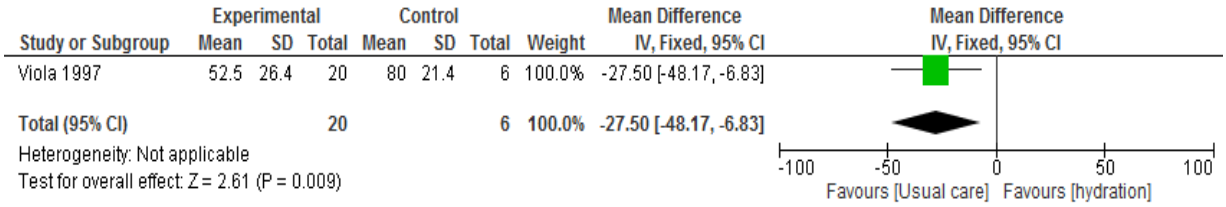


Figure 26: Clinically assisted hydration versus usual care for symptom relief (measured on VAS 0-100, high is poor outcome)

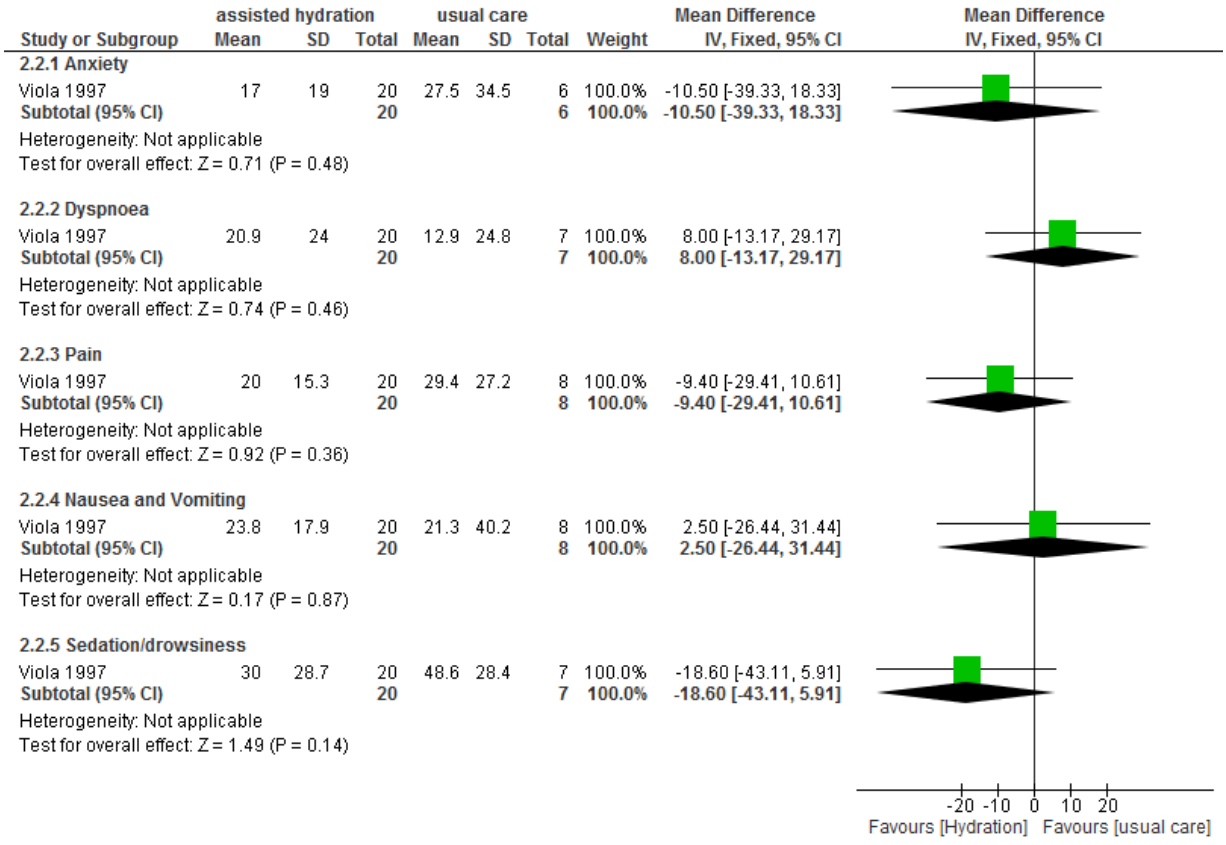
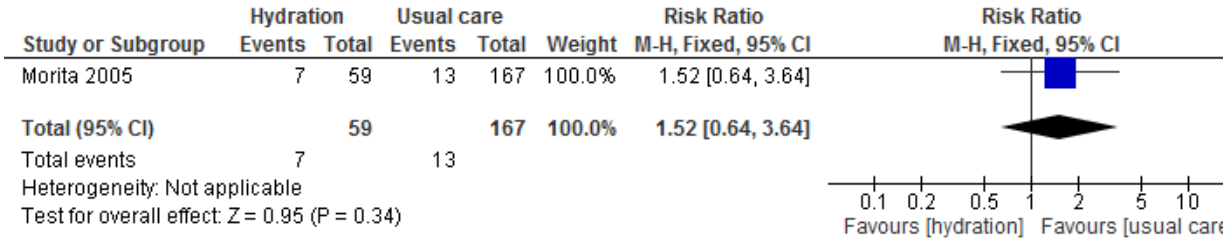
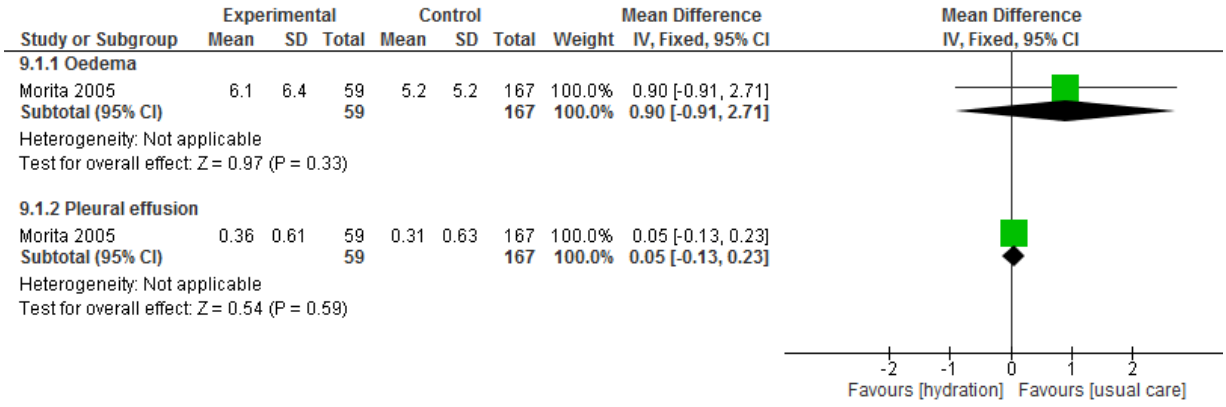


Figure 27: Clinically assisted hydration versus usual care for delirium (number of patients scoring over >2 on the psychomotor item on the MDAS)



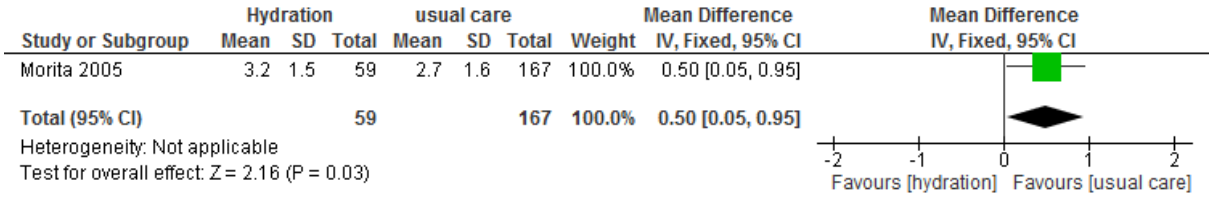
1

Figure 28: Clinically assisted hydration versus usual care for fluid overload adverse events (measured on oedema scale 0-21 [high is poor outcome], pleural effusion scale 0-2 [high is poor outcome])



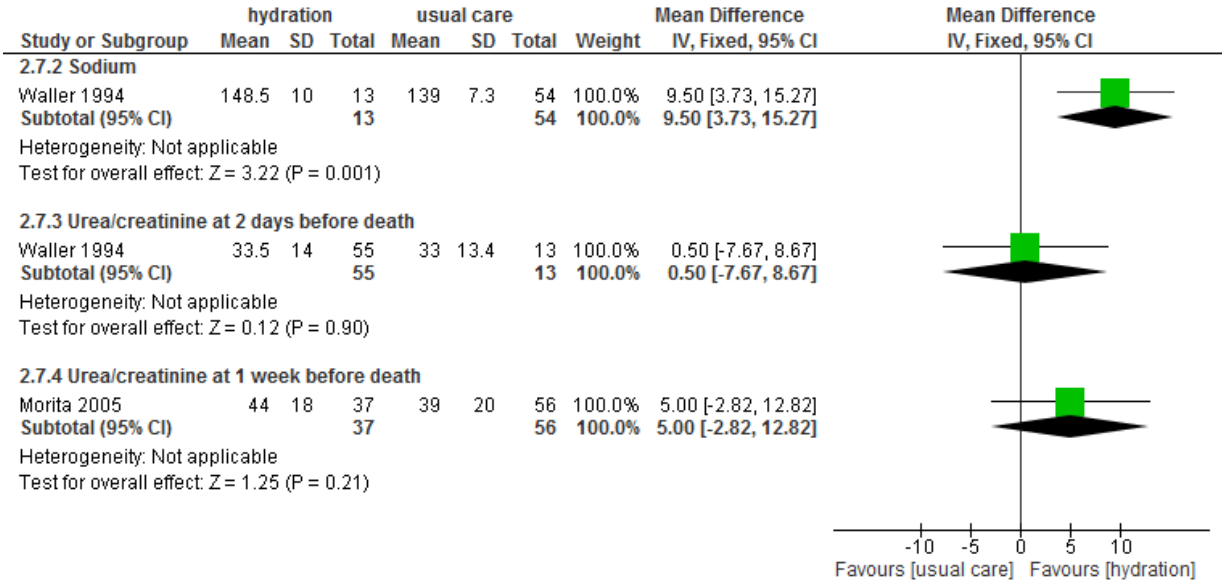
2

Figure 29: Clinically assisted hydration versus usual care for dehydration assessment (measured on ad hoc dehydration scale 0-5, high is poor outcome)



3

Figure 30: Clinically assisted hydration versus usual care for biochemistry (sodium measured in mEq/litre, urea/creatinine measured in mg/dl)



K.5 Pharmacological Intervention

K.5.1 Breathlessness management

K.5.1.1 Midazolam versus morphine

Figure 31: Dyspnoea relief

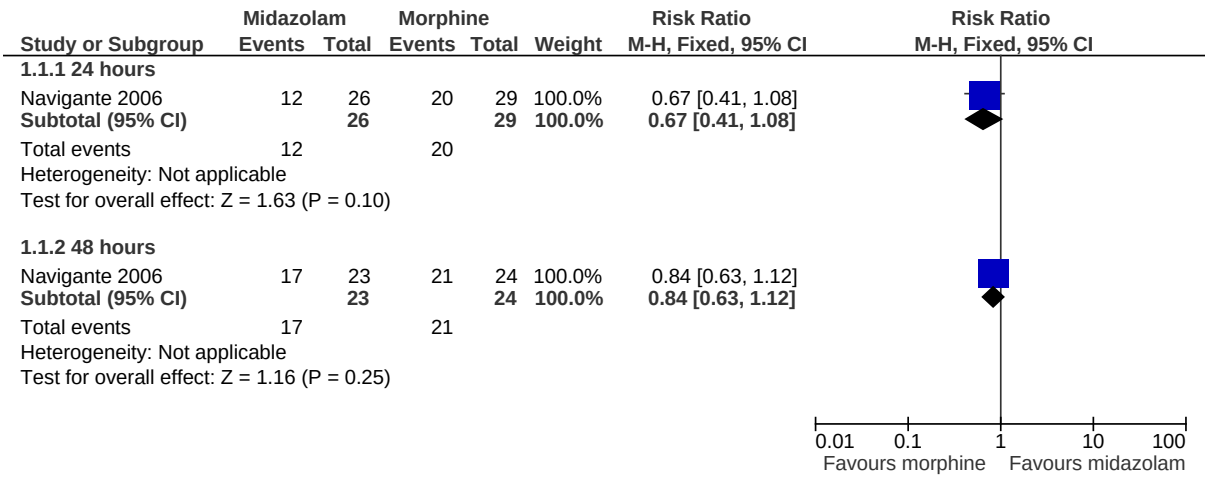
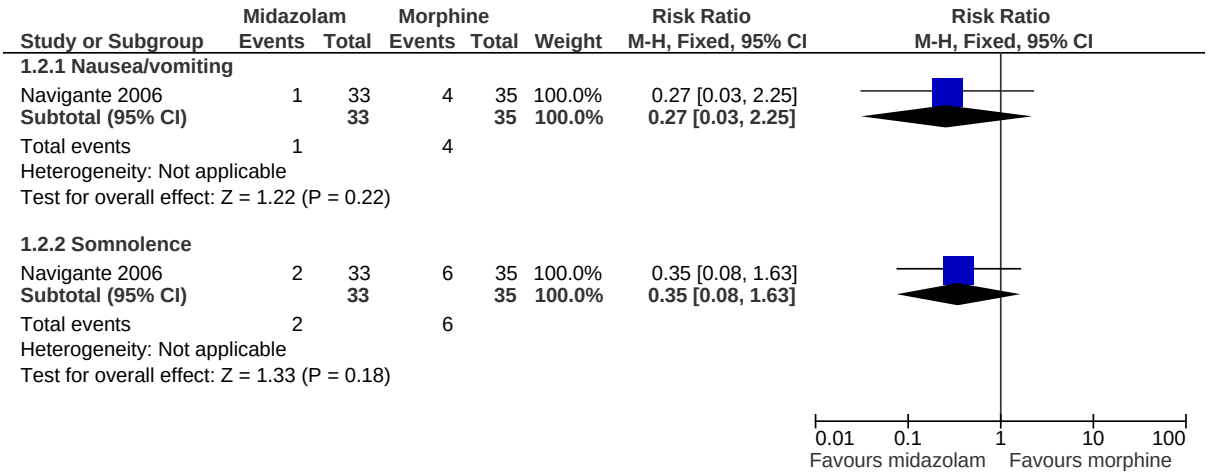


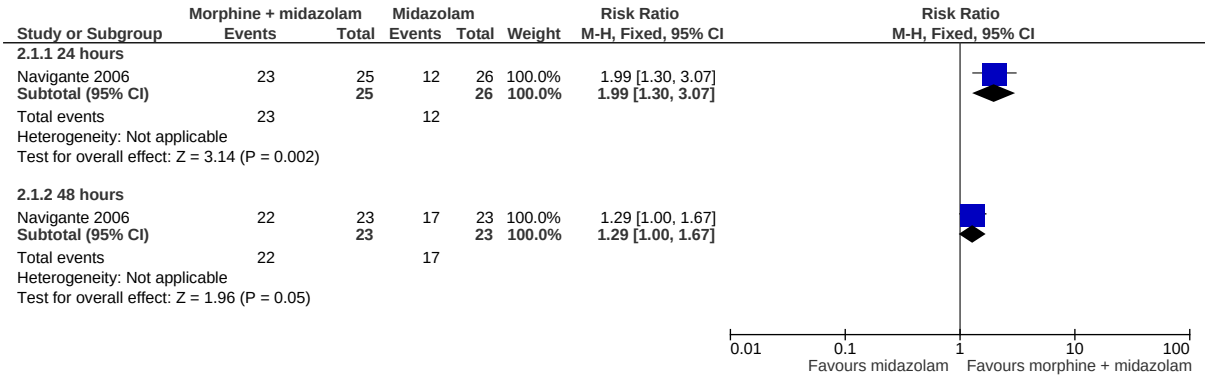
Figure 32: Clinically relevant (grade 2 or above) adverse events at 48 hours



1 **K.5.1.2 Morphine plus midazolam versus midazolam**

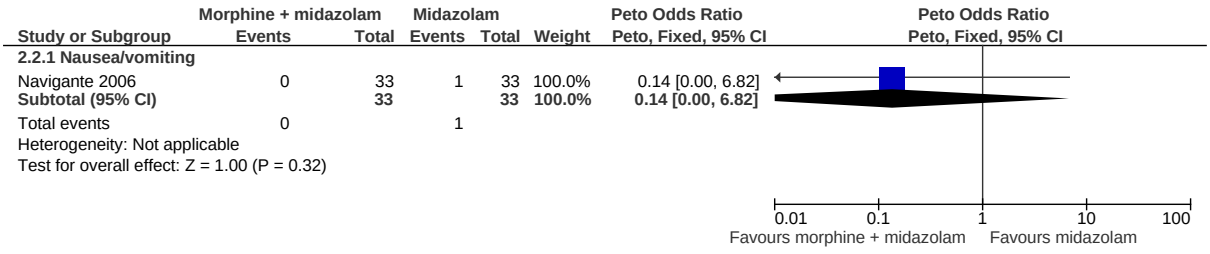
2

Figure 33: Dyspnoea relief



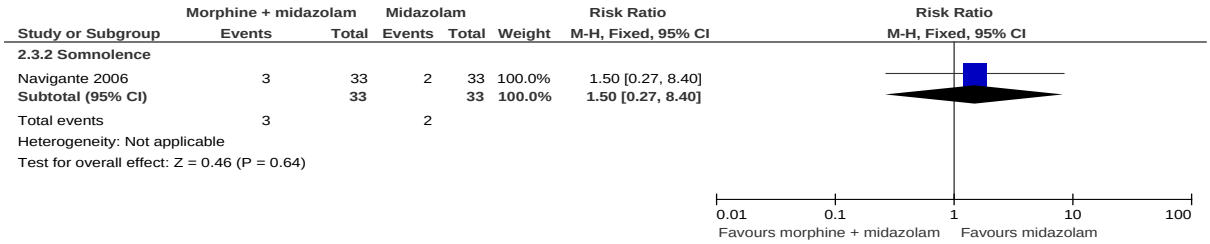
3

Figure 34: Clinically relevant (grade 2 or above) nausea or vomiting at 48 hours



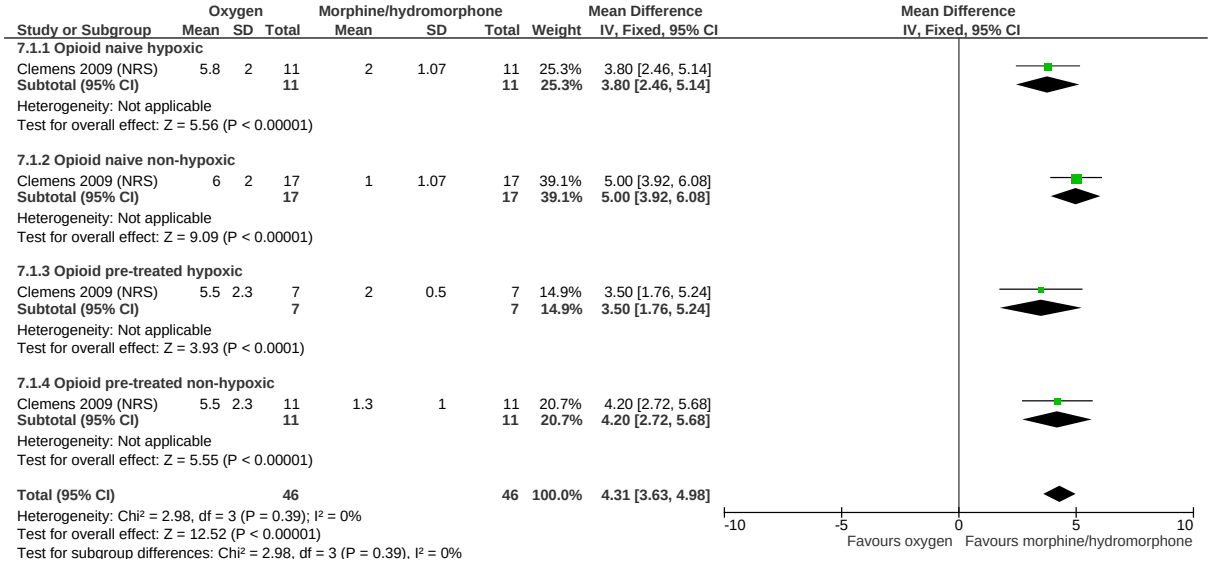
4

Figure 35: Clinically relevant (grade 2 or above) somnolence at 48 hours



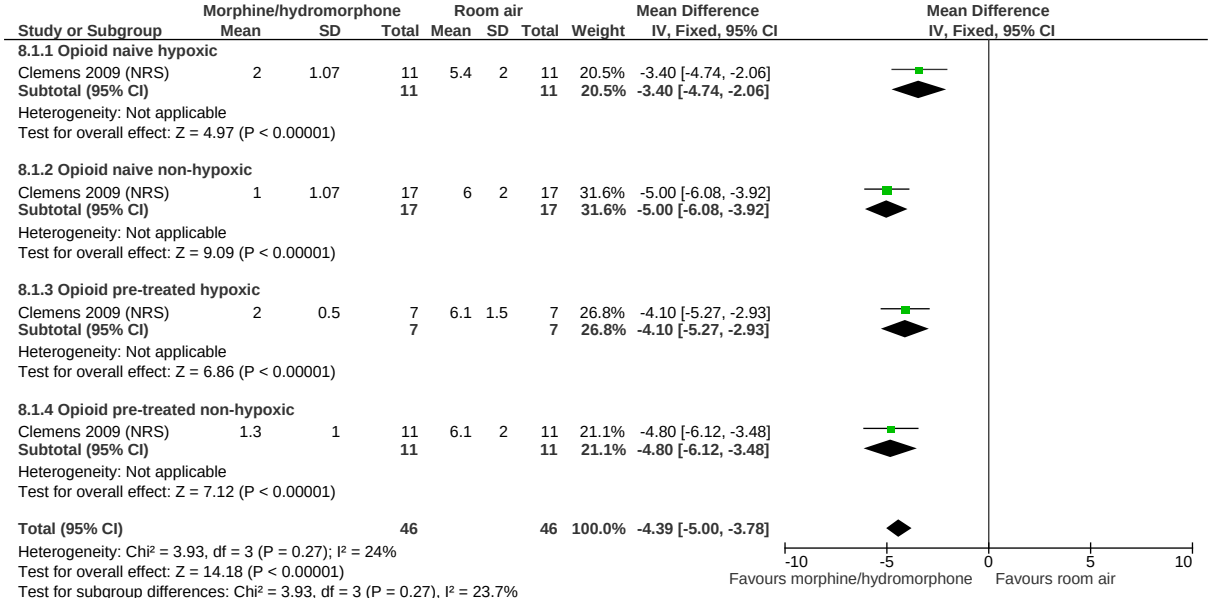
1 K.5.1.3 Oxygen versus morphine or hydromorphone (NRS)

Figure 36: Dyspnoea at rest; range 0 (absent) – 10 (worst possible)



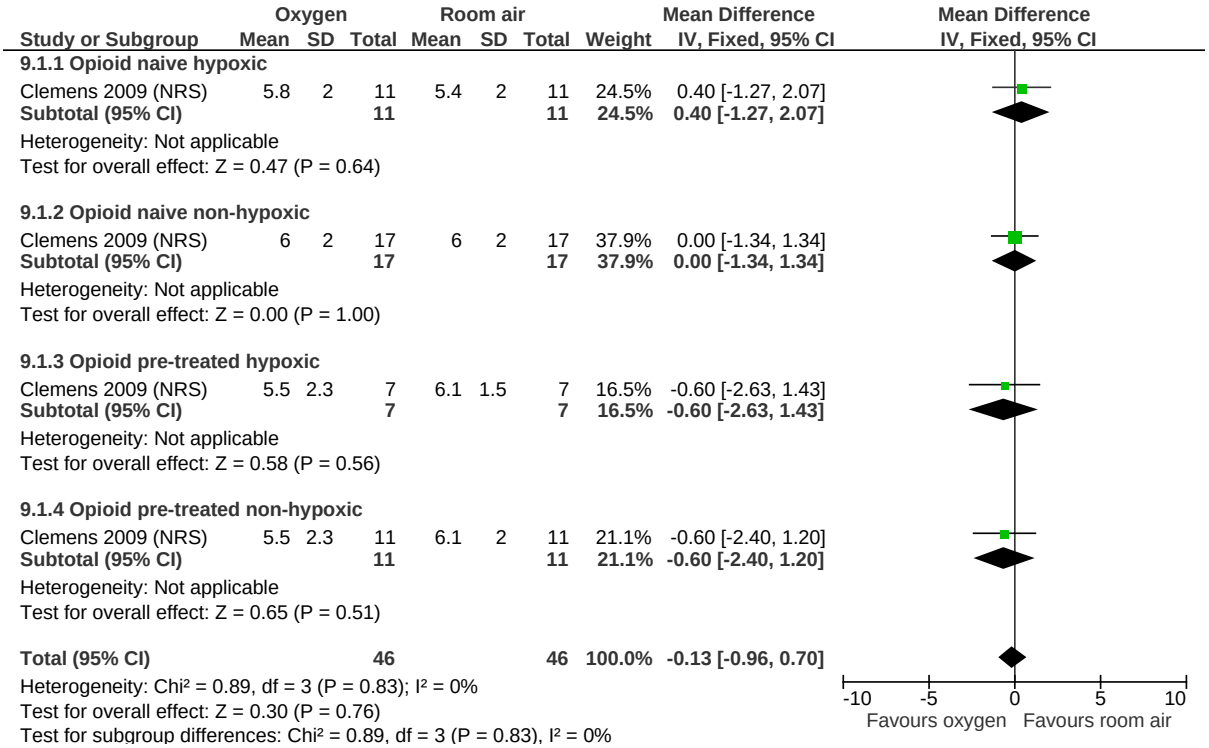
2 K.5.1.4 Morphine or hydromorphone versus room air (NRS)

Figure 37: Dyspnoea at rest; range 0 (absent – 10 (worst possible)



K.5.1.5 Oxygen versus room air (NRS)

Figure 38: Dyspnoea at rest; range 0 (absent) – 10 (worst possible)



K.5.2 Pain Management

K.5.2.1 Diamorphine versus morphine

Figure 39: Pain; range 0 (none) – 100 (most severe)

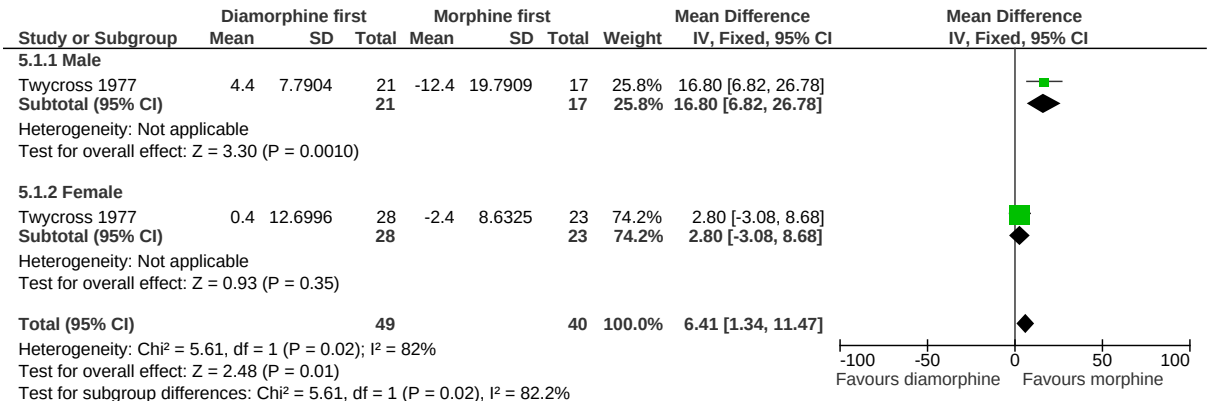
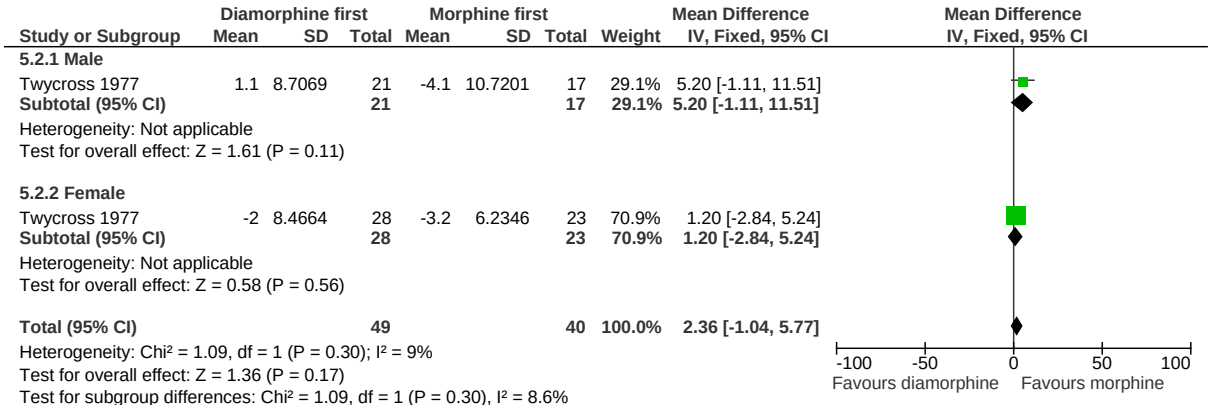
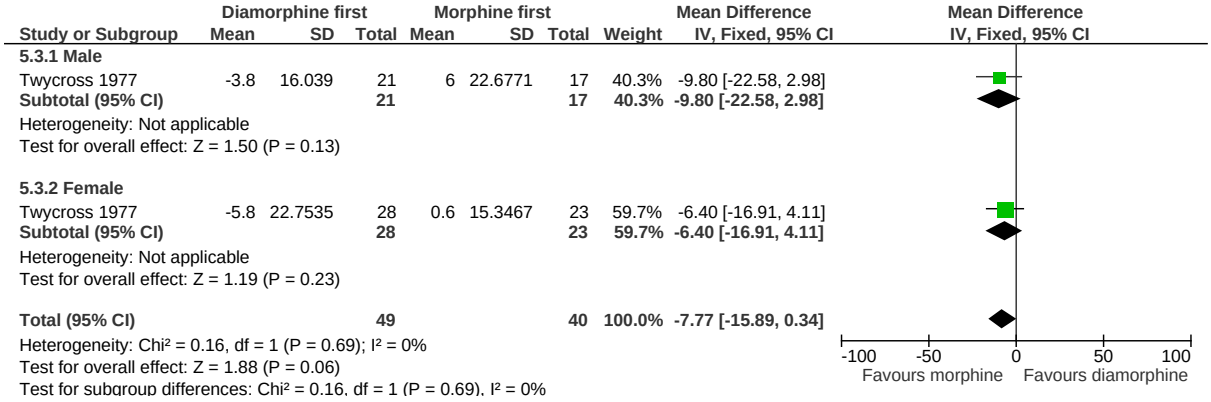


Figure 40: Nausea; range 0 (none) – 100 (most severe)



1

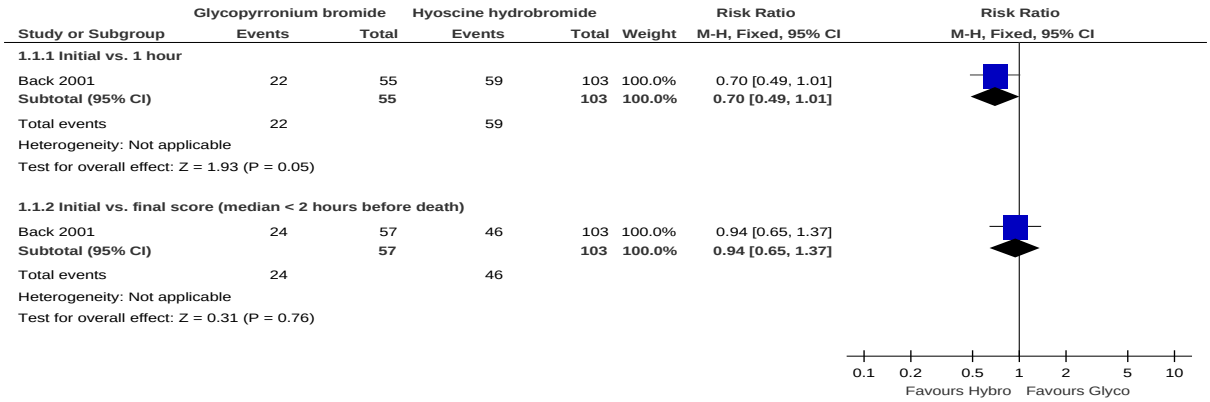
Figure 41: Night-time sleep quality; range 0 (none) – 100 (perfect night)



2 ## K.5.3 Noisy Respiratory Secretions

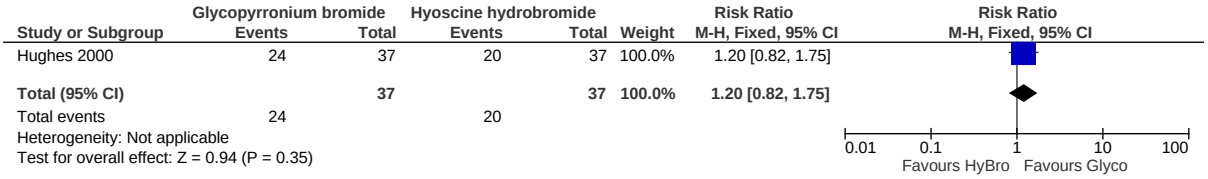
3 ### K.5.3.1 Glycopyrronium bromide versus hyoscine hydrobromide

Figure 42: Improvement in noise intensity: 'better' from baseline (scale same, better, worse – observational study)



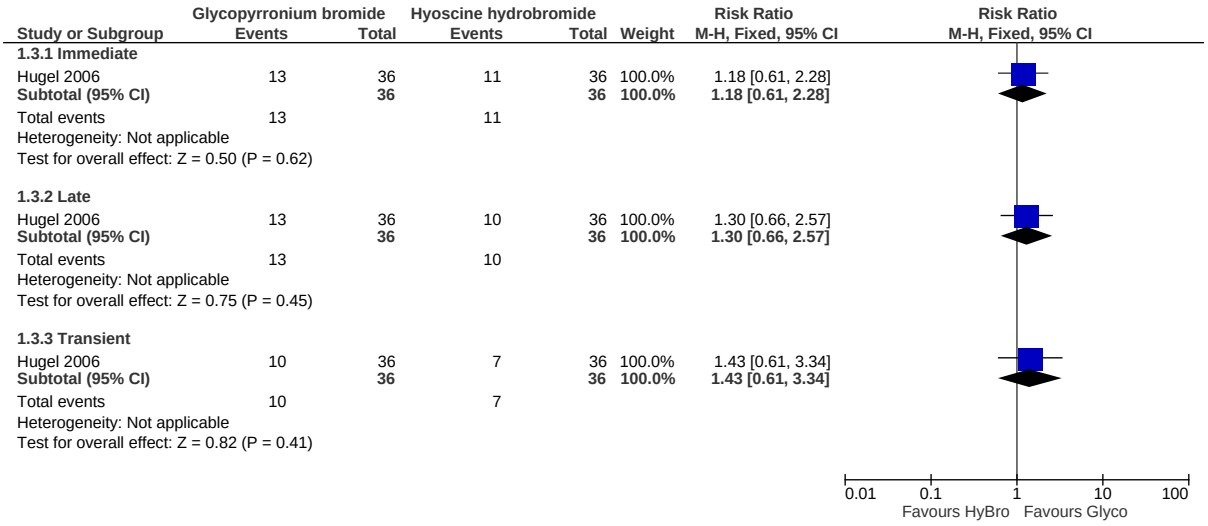
1

Figure 43: Secretions relieved at death ('absent' or 'much better' on a 6 point scale, - prospective audit)



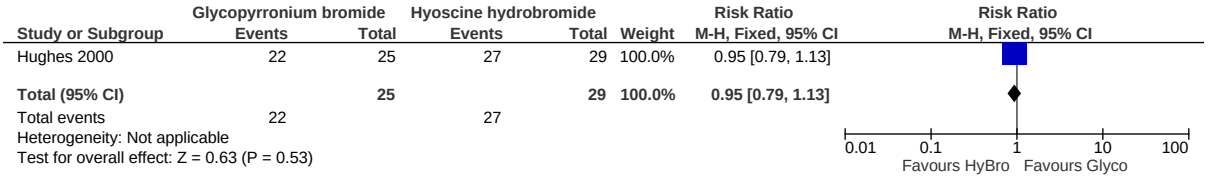
2

Figure 44: Response to drug (time from first observation until first observation of absent symptoms – observational study)



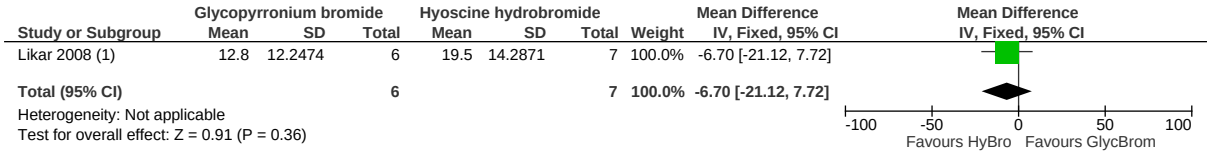
3

Figure 45: Improvement in relatives' distress ('absent' or 'much better' on a 6 point scale – prospective audit)



4

Figure 46: Length of survival (hours) – randomised controlled trial



Footnotes
(1) Other outcomes (such as noise intensity and restlessness) were also reported but can only be described narratively (non-significant)..

K.5.3.2 Hyoscine butylbromide versus hyoscine hydrobromide

Figure 47: Improvement in noisy breathing ('not audible' or 'only audible near the patient' on a 4 point scale defined as effective reduction) – RCT evidence

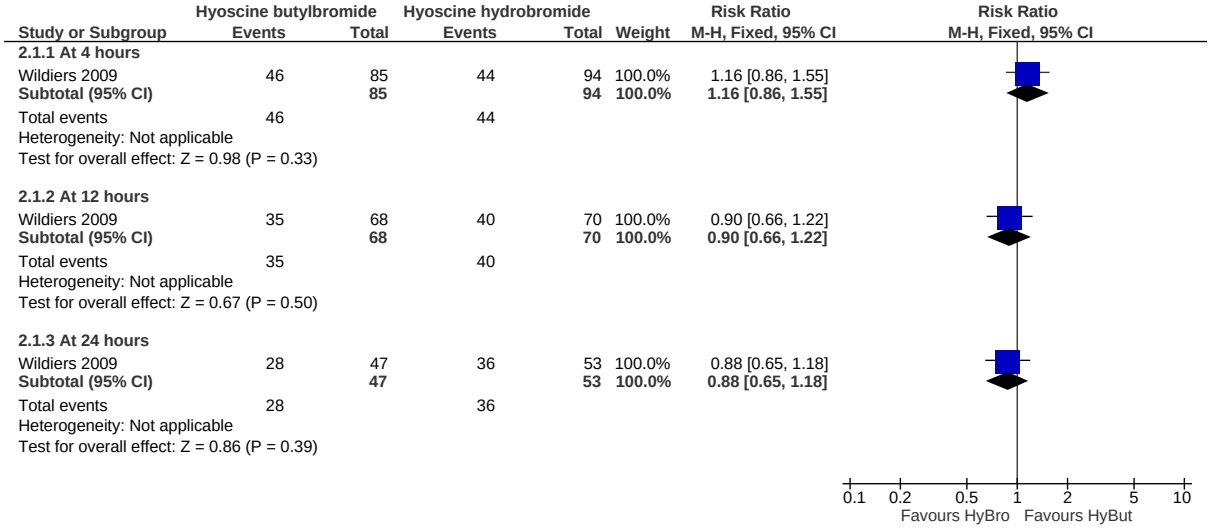


Figure 48: Secretions relieved at death ('absent' or 'much better' on a 6 point scale, - prospective audit)

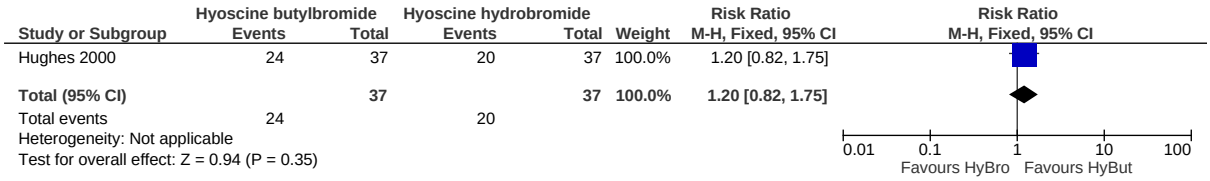


Figure 49: Improvement in relatives' distress ('absent' or 'much better' on a 6 point scale – prospective audit)

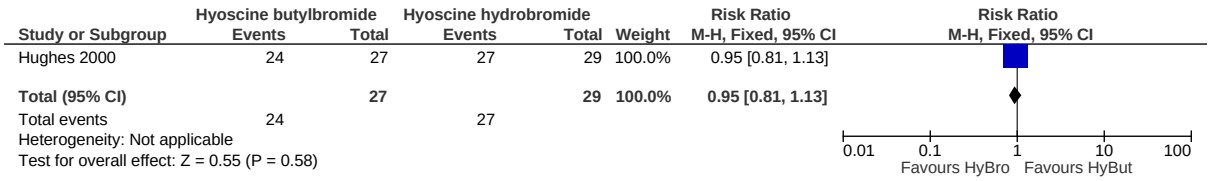


Figure 50: Worsening in level of consciousness (rating lower than 'alert' or 'somnolent') – RCT evidence

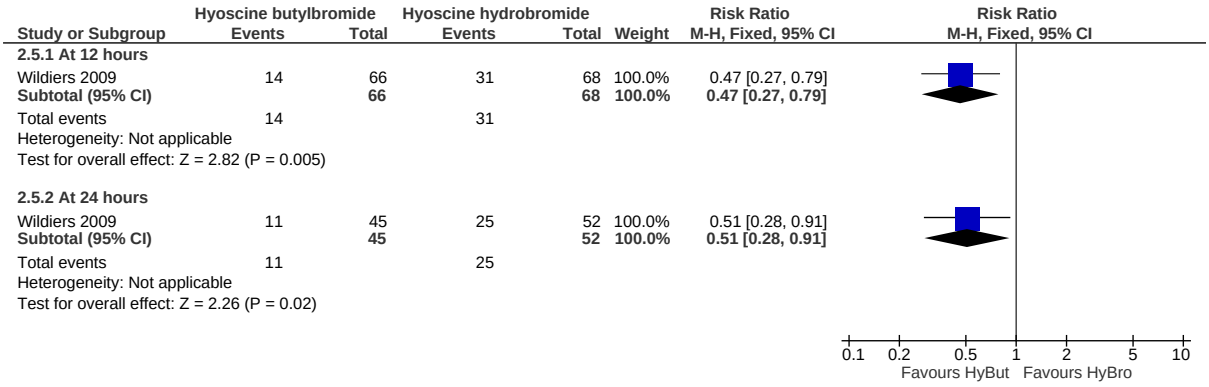
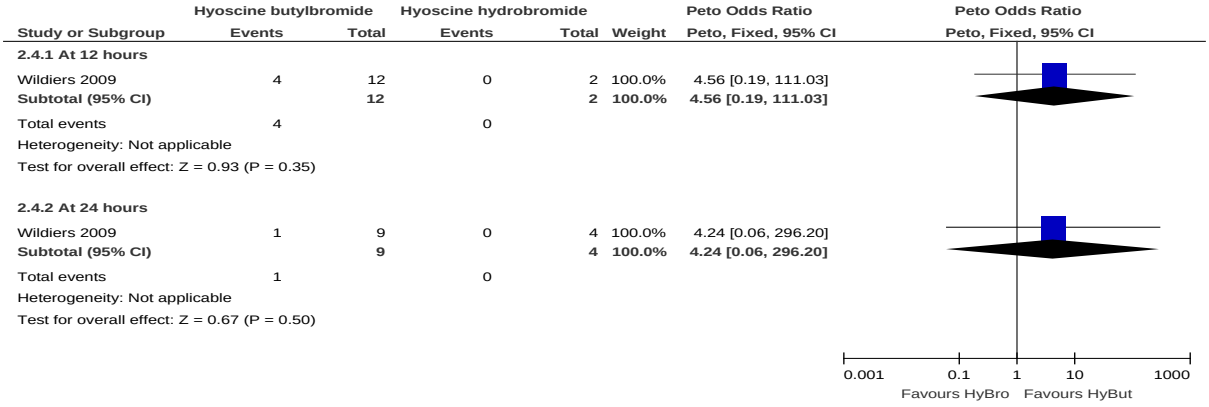


Figure 51: Improvement in confusion (for those with sufficient level of consciousness to assess) – RCT evidence



1 K.5.3.3 Atropine versus hyoscine hydrobromide

Figure 52: Improvement in noisy breathing ('not audible' or 'only audible near the patient' on a 4 point scale defined as effective reduction) – RCT evidence

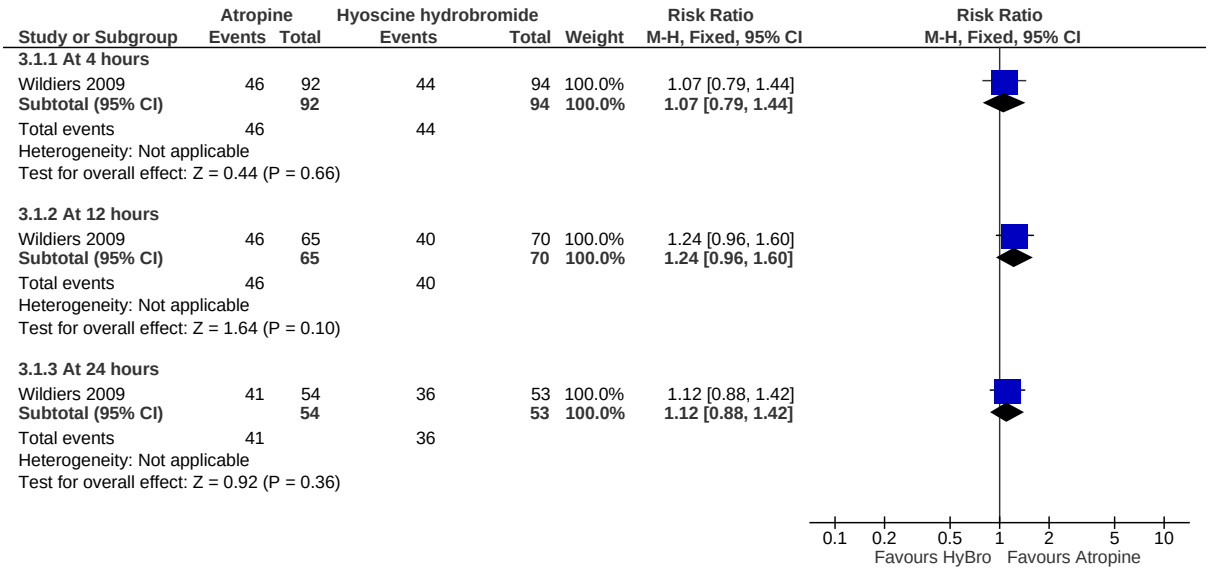


Figure 53: Worsening in level of consciousness (rating lower than 'alert' or 'somnolent') – RCT evidence

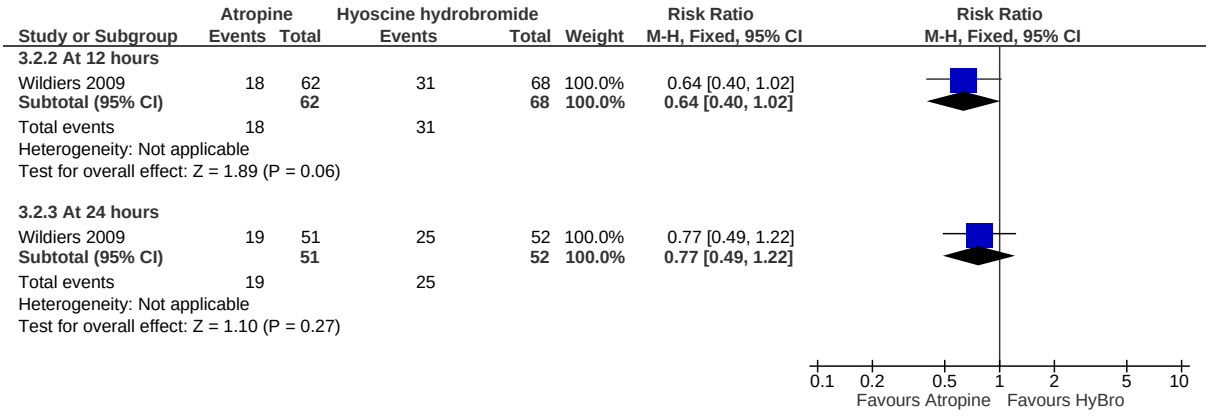
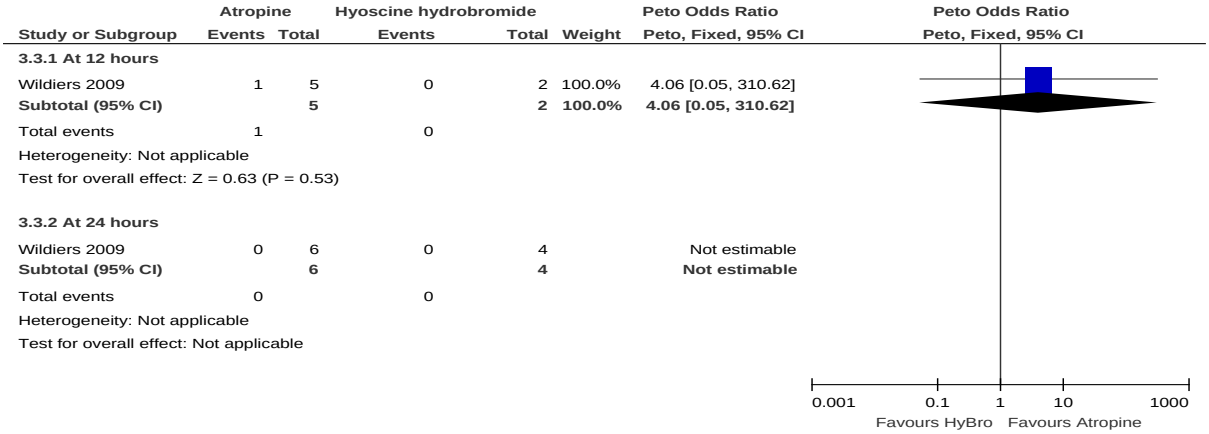


Figure 54: Improvement in confusion (for those with sufficient level of consciousness to assess) – RCT evidence



K.5.3.4 Atropine versus hyoscine butylbromide

Figure 55: Improvement in noisy breathing ('not audible' or 'only audible near the patient' on a 4 point scale defined as effective reduction) – RCT evidence

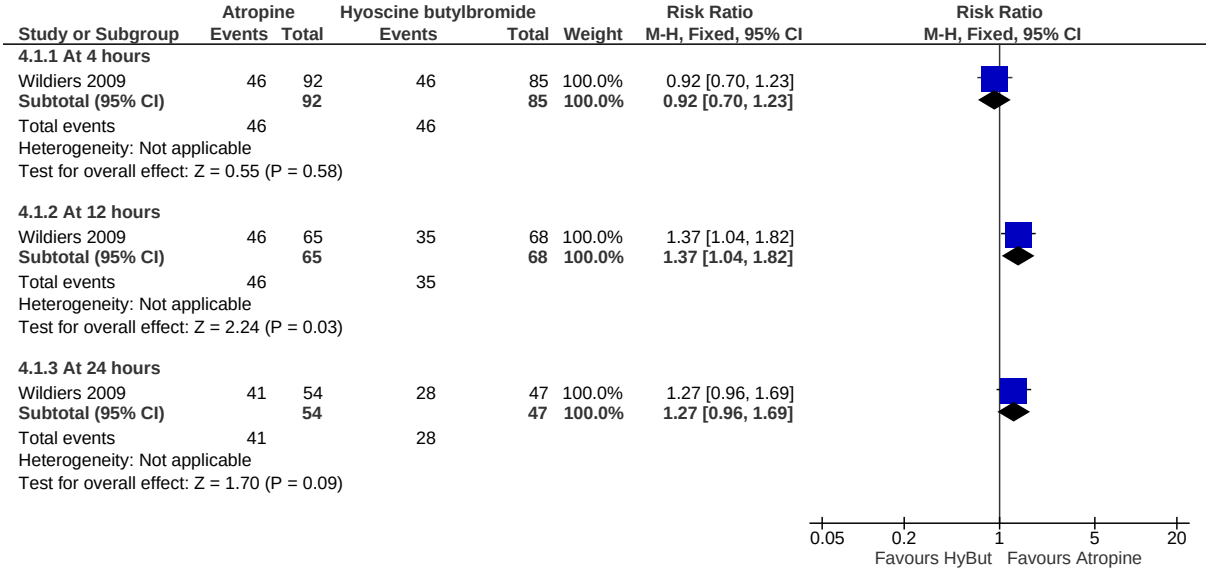


Figure 56: Worsening in level of consciousness (rating lower than 'alert' or 'somnolent' – RCT evidence

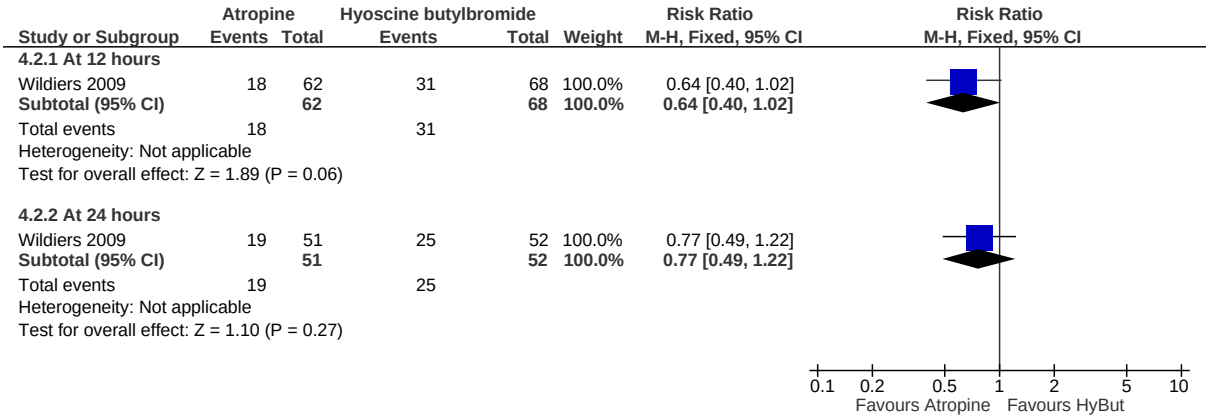
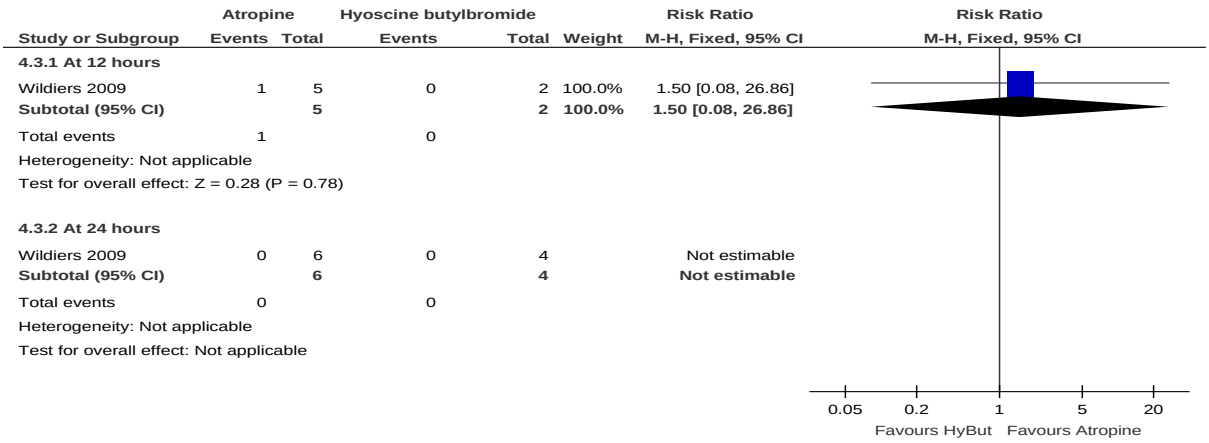


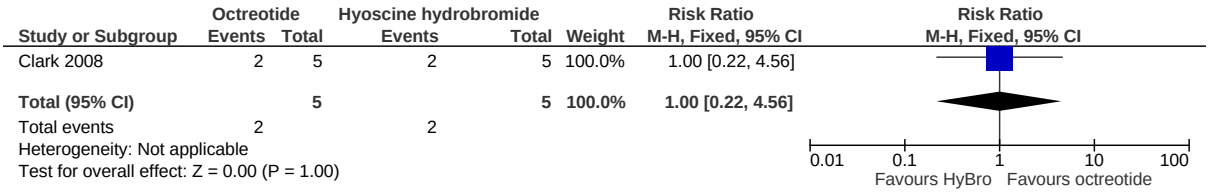
Figure 57: Improvement in confusion (for those who sufficient level of consciousness to assess) – RCT evidence



1 **K.5.3.5 Octreotide versus hyoscine hydrobromide**

2

Figure 58: Improvement in noisy breathing intensity (decrease on a five point scale) – pilot cross-over RCT evidence

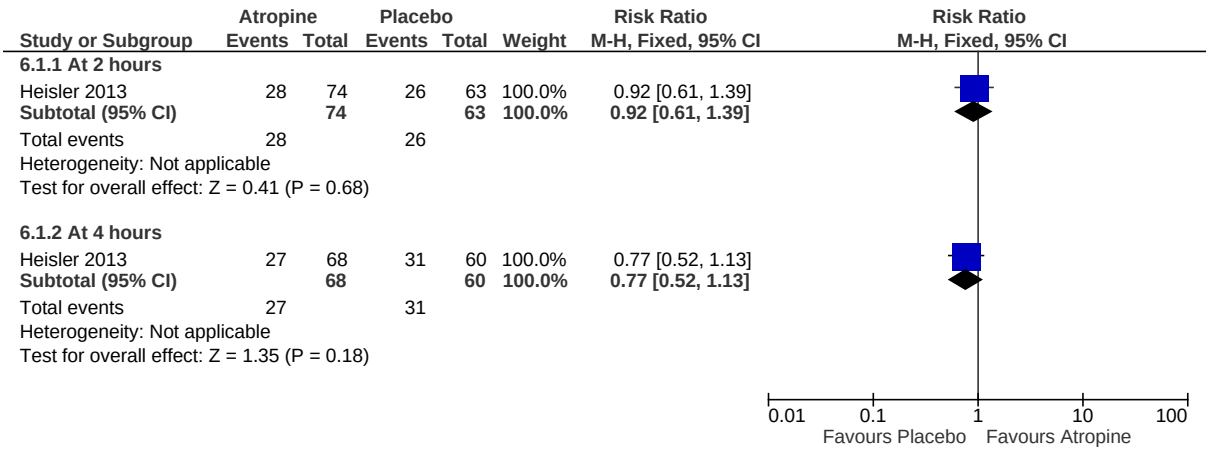


3

4 **K.5.3.6 Atropine versus placebo**

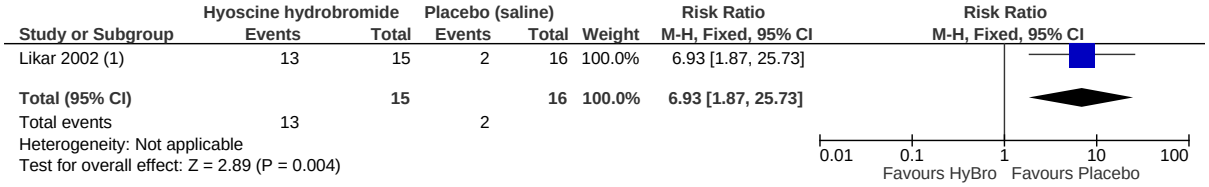
5

Figure 59: Improvement in noise intensity (at least 1 point score reduction on a 4 point scale ranging from 'inaudible' to 'clearly audible at about 20 feet') – RCT evidence



K.5.3.7 Hyoscine hydrobromide versus placebo

Figure 60: Increase in pain (3 point scale 'mild', 'moderate', 'severe') – RCT evidence



Footnotes
(1) Note. numbers only approximate the percentages provided in the study.

Figure 61: Increase in restlessness (3 point scale 'mild', 'moderate', 'severe') – RCT evidence

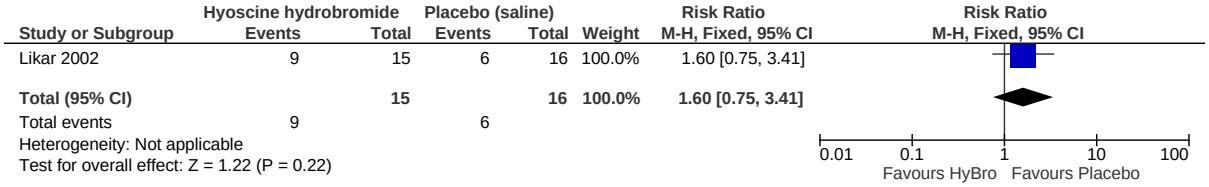
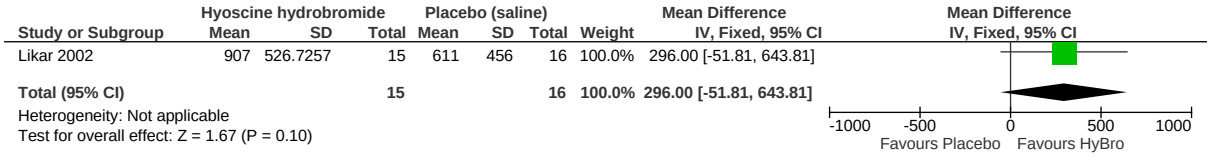


Figure 62: Length of survival (minutes) – RCT evidence



K.5.3.8 Glycopyrronium bromide versus hyoscine butylbromide

Figure 63: Secretions relieved at death ('absent' or 'much better' on a 6 point scale, - prospective audit)

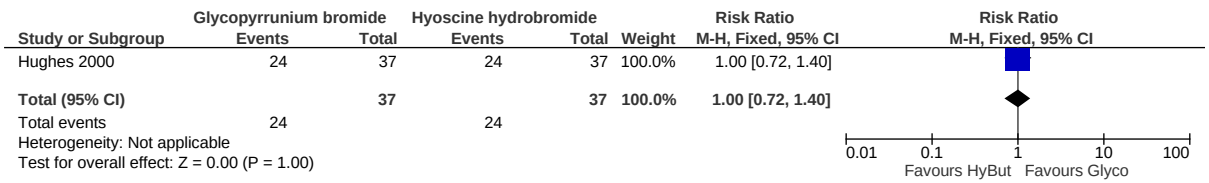
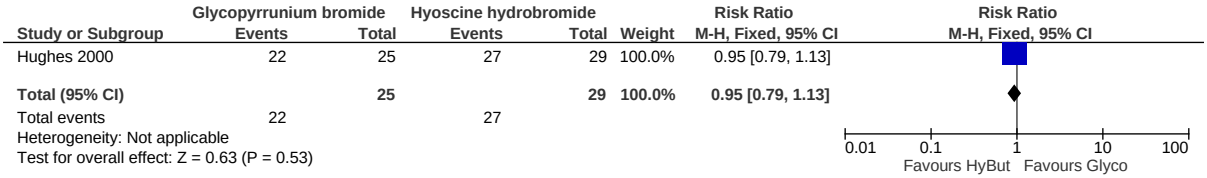


Figure 64: Improvement in relatives' distress ('absent' or 'much better' on a 6 point scale – prospective audit)



K.6 Anticipatory Prescribing

None.

Appendix L: Excluded clinical studies

L.1 Recognising Dying

Table 93: Studies excluded from the clinical review of Recognising dying

Reference	Reason for exclusion
Al 2010[18]	Incorrect study design, review
Alzahrani 2013[19]	Incorrect population, not last days of life.
Anon 2012a[3]	Incorrect study design, abstract
Asch 2005[30]	Incorrect study design, discussion/editorial
Barbera 2008[45]	Incorrect population, not last days of life.
Barrett 1997[46]	Incorrect population, not last days of life.
Bern-Klug 2006[54]	Incorrect population, not last days of life.
Campbell 2012[80]	Incorrect study design, non-systematic review
Casscells 2005[87]	Incorrect population, not last days of life.
Cheng 2009[92]	Incorrect study design, non-systematic review
Cobb 2000[108]	Incorrect population, not last days of life.
Conill 1997[111]	No relevant diagnostic or prognostic data: symptom prevalence
Cuervopinna 2009[118]	Incorrect population, not last days of life.
Currow 2010[121]	No relevant diagnostic or prognostic data: symptom prevalence
Downing 2011[138]	Incorrect study design, non-systematic review
Dunn 2002[140]	Incorrect study design, non-systematic review
Dunning 2012[141]	Incorrect study design, literature review
Ellershaw 1995[145]	No relevant diagnostic or prognostic data: symptom prevalence
Fainsinger 1991[154]	No relevant diagnostic or prognostic data: symptom prevalence
Fantoni 1996[155]	Incorrect population, not last days of life.
Feliu 2011[157]	Incorrect population, not last days of life.
Fordyce 2001[162]	Incorrect study design, discussion/editorial
Fortinsky 2014[163]	Incorrect study design, literature review
Fromme 2004[168]	No relevant diagnostic or prognostic data: symptom prevalence
Georges 2005a[174]	No relevant diagnostic or prognostic data: symptom prevalence
Gibbins 2009[175]	Incorrect study design, discussion/editorial
Gilbertsonwhite 2011[176]	Incorrect study design, non-systematic review
Gilman 2009[177]	Incorrect study design, non-systematic review
Glare 2008[179]	Incorrect study design, non-systematic review
Goebel 2009[182]	Incorrect population, not last days of life.
Gonzales 2011[184]	Incorrect study design, non-systematic review
Goodman 2010[185]	Incorrect study design, non-systematic review
Greer 2013[188]	Incorrect study design, literature review
Hendriks 2014[204]	No relevant diagnostic or prognostic data: symptom prevalence
Hirakawa 2006[210]	No relevant diagnostic or prognostic data: symptom prevalence
Hirakawa 2006a.[214]	No relevant diagnostic or prognostic data: symptom prevalence
Hirakawa 2006b[213]	No relevant diagnostic or prognostic data: symptom prevalence

Reference	Reason for exclusion
Hirakawa 2006c.[212]	No relevant diagnostic or prognostic data: symptom prevalence
Hirakawa 2006d.[211]	No relevant diagnostic or prognostic data: symptom prevalence
Huang 2014[225]	Incorrect population, not last days of life.
Hussain 2014[232]	Incorrect population, not last days of life.
Janssen 2008[240]	Incorrect study design, non-systematic review
Kehl 2013[255]	Incorrect study design, non-systematic review
Klinkenberg 2003[263]	No relevant diagnostic or prognostic data: symptom prevalence
Kompanje 2005[264]	Incorrect study design, case report
Kripp 2014[266]	Incorrect population, not last days of life.
Kutner 2001[269]	Incorrect population, not last days of life.
Kutner 2007[270]	Incorrect population, not last days of life.
Leak 2013[277]	No relevant diagnostic or prognostic data: symptom prevalence
Lee 2014a[281]	Incorrect population, not last days of life.
Levenson 2000[284]	Incorrect population, not last days of life.
Li 2008[285]	Incorrect population, not last days of life.
Lichter 1990[286]	No relevant diagnostic or prognostic data: symptom prevalence
Lindleydavis 1991[291]	Incorrect population, not last days of life.
Lindqvist 2008[293]	Incorrect population, not last days of life.
Liu 2013[294]	Incorrect population, not last days of life.
Lutz 2001[301]	No relevant diagnostic or prognostic data: symptom prevalence
Mastersoncreber 2013[309]	Incorrect population, not last days of life.
Mazzocato 2010[312]	No relevant diagnostic or prognostic data: symptom prevalence
Mccarthy 2000[313]	No relevant diagnostic or prognostic data: symptom prevalence
Mercadante 2000[317]	Incorrect population, not last days of life.
Morita 1998[328]	No relevant diagnostic or prognostic data: symptom prevalence
Morita 2003[330]	No relevant diagnostic or prognostic data: symptom prevalence
Moyer 2011[331]	Incorrect study design, non-systematic review
Munizterrera 2013[332]	Incorrect population, not last days of life.
Murphy 2010[333]	Incorrect population, not last days of life.
Murtagh 2010[334]	Incorrect population, not last days of life.
Nordgren 2003[351]	No relevant diagnostic or prognostic data: symptom prevalence
Olajide 2007[358,358]	Incorrect population, not last days of life.
Ostgathe 2008[361]	Incorrect study design, non-systematic review
Pace 2009[363]	No relevant diagnostic or prognostic data: symptom prevalence
Peppin 2003[366]	Incorrect study design, non-systematic review
Pinzon 2013[370]	No relevant diagnostic or prognostic data: symptom prevalence
Potter 2013[373]	Incorrect study design, non-systematic review
Price 2013b[374]	Incorrect population, not last days of life.
Radbruch 2008[379]	Incorrect study design, Guideline
Rashid i2011[384]	No relevant diagnostic or prognostic data: symptom prevalence
Richards 2011[390]	Incorrect population, not last days of life.
Ridley 2013[391]	Incorrect study design, non-systematic review
Roberts 1993[394]	No relevant outcomes on management of uncertainty, or recognising

Reference	Reason for exclusion
	dying.
Saini 2006[400]	Incorrect population, not last days of life.
Salpeter 2012a[402]	Incorrect study design, non-systematic review
Seah 2005[407]	No relevant diagnostic or prognostic data: symptom prevalence
Skaug 2007[415]	Incorrect population, not last days of life.
Solano 2006[418]	Incorrect population, not last days of life.
Solano 2006[418]	Incorrect study design, non-systematic review
Spoozak 2013[419]	No relevant diagnostic or prognostic data: symptom prevalence
Suh 2013[425]	Incorrect population, not last days of life.
Sullivan 2008[424]	No relevant outcomes on management of uncertainty, or recognising dying.
Trueman 2011[434]	Incorrect study design, Discussion/editorial
Tsai 2006[435]	No relevant diagnostic or prognostic data: symptom prevalence
Vandervoort 2013[446]	No relevant diagnostic or prognostic data: symptom prevalence
Veerbeek 2007[447]	No relevant diagnostic or prognostic data: symptom prevalence
Ventafridda 1990a[448]	No relevant diagnostic or prognostic data: symptom prevalence
Vitacca 2012[452]	No relevant diagnostic or prognostic data: symptom prevalence
Vongunten 2005[453]	Incorrect population, not last days of life.
Vongunten 2005[453]	Incorrect study design, non-systematic review
Walbert 2014[459]	Incorrect study design, non-systematic review
Yamanaka 2011[477]	Incorrect population, not last days of life.
Yanneo 2009[478]	Incorrect study design, non-systematic review
Yong 2009[481]	Incorrect population, not last days of life.
Zambroski 2005[484]	No relevant diagnostic or prognostic data: symptom prevalence

L.2 Communications

Table 94: Studies excluded from the clinical review of Communications

Reference	Reason for exclusion
Abarshi 2011[5]	Topic does not match protocol (discussion of prognosis before last weeks of life)
Abarshi 2011[4]	Topic does not match protocol (occurrence of communication)
Abdul-Razzak 2014[7]	Population does not match protocol (death not imminent)
Adamolekun 1998[11]	Indirect population (communication in a developing country)
Adelman 1994[14]	Population does not match protocol (death not imminent)
Anderson 2010[24]	Abstract only
Anderson 2013[26]	Topic does not match protocol (describing communication in end-of-life care conversations)
Apatira 2008[29]	Topic does not match protocol (balance of hope and truth)
Azoulay 2009[33]	Topic does not match protocol (conflicts in ITU)
Bachner 2014[36]	Full text unavailable
Bajwah 2013[41]	Population does not match protocol
Bakitas 2008[43]	Topic does not match protocol (quality of end of life care)

Reference	Reason for exclusion
Bailey[39]	Topic does not match protocol (opioid use)
Barry 2002[47]	Topic does not match protocol (barriers to preparedness for death)
Beckstrand 2008[49]	Topic does not match protocol (barriers and facilitators to end of life care)
Bekkema 2014[50]	Topic does not match protocol (barriers and facilitators to respecting autonomy)
Bern-Klug 2004[55]	Topic does not match protocol (quality of end of life care)
Biola 2007[56]	Topic does not match protocol (occurrence of communication)
Bradby 2013[61]	Population does not match protocol (death not imminent)
Broom 2014[65]	Full text unavailable
Bruera 2000[71]	Topic does not match protocol (perceived need for communication)
Butow 2014[78]	Abstract only
Cherlin 2005[93]	Topic does not match protocol (timing and content of discussion)
Clarke 2006[100]	Topic does not match protocol (conversations at end of life)
Clayton 2005[102]	Population does not match protocol (death not imminent)
Clayton 2005[103]	Population does not match protocol (death not imminent)
Clover 2004[107]	Topic does not match protocol (decision making techniques)
Conboy-Hill 1986[110]	Incorrect study design (descriptive not analytic)
Considine 2010[112]	Topic does not match protocol (managing dialectical tensions)
Crawford 2010[116]	Population does not match protocol (death not imminent)
Csikai 2006[117]	Population does not match protocol (death not imminent)
Curtis 2008[126]	Population does not match protocol (death not imminent)
Curtis 2004[122]	Topic does not match protocol (end-of-life planning)
Curtis 1999[124]	Incorrect study design (descriptive not analytic)
Curtis 2000[125]	Topic does not match protocol (end-of-life planning)
Curtis 1997[123]	Topic does not match protocol (palliative care)
El-Sahwi 2012[144]	Incorrect study design (descriptive not analytic)
Emanuel 2004[146]	Topic does not match protocol (effects of communication)
Endacott 2013[147]	Abstract only
Enguidanos 2014[148]	Incorrect study design (descriptive not analytic)
Evans 2009[150]	feelings about uncertainty in prognostic community
Evans 2014[151]	Incorrect study design (descriptive not analytic)
Evans 2012[152]	Population does not match protocol (death not imminent)
Exline 2012[153]	Topic does not match protocol (communication within families)
Friedrichsen 2000[166]	Incorrect study design (descriptive not analytic)
Gadoud 2013[170]	Abstract only
Granek 2013[186]	Topic does not match protocol (end-of-life planning)
Gutierrez 2012[192]	Incorrect study design (descriptive not analytic)
Hack 2010[193]	Incorrect study design (descriptive not analytic)
Hagerty 2004[194]	Topic does not match protocol (need for prognosis)
Hagerty 2005[195]	Population does not match protocol (death not imminent)
Hjelmfors 2013[216]	Abstract only
Hjelmfors 2013[217]	Abstract only
Hjelmfors 2014[219]	Topic does not match protocol (occurrence of communication)

Reference	Reason for exclusion
Hjelmfors 2014[218]	Population does not match protocol (death not imminent)
Hjorleifsdottir 2000[220]	Population does not match protocol (death not imminent)
Hofmann 1997[222]	Topic does not match protocol (care planning discussion)
Jackson 2012[237]	Population does not match protocol (death not imminent)
Janssen 2011[239]	Topic does not match protocol (care planning discussion)
Kai 1993[247]	Topic does not match protocol (care planning discussion)
Kaplowitz 2002[252]	Population does not match protocol (death not imminent)
Klindtworth 2012[262]	Abstract only
Kozar 2014[265]	Full text unavailable
Lawrence 2013[275]	Population does not match protocol (death not imminent)
Lofmark 2005[297]	Topic does not match protocol (occurrence of communication)
Marcus 2014[307]	Abstract only
Nedjat-Haiem 2011[346]	Abstract only
Norton 2013[353]	Incorrect study design (descriptive not analytic)
Norton 2000[352]	Topic does not match protocol (decision making)
Palmer 2012[364]	Abstract only
Puntillo 2006[377]	Incorrect study design (review)
Randhawa 2003[383]	Topic does not match protocol (general palliative care)
Reinke 2008[387]	Population does not match protocol (death not imminent)
Reinke 2010[388]	Incorrect study design (observational study describing practice)
Rhondali 2014[389]	Incorrect study design (observational study describing practice)
Roscoe 2013[397]	Topic does not match protocol (planning end of life care)
Stallworthy 2014[420]	Abstract only
Tang 2014[428]	Topic does not match protocol (planning end of life care)
Tomlinson 2012[433]	Topic does not match protocol (written information only)
Van Der Wal 2014[444]	Abstract only
Voorhees 2009[454]	Incorrect study design (observational study describing practice)
Vvedenskaya 2010[455]	Abstract only
Vvedenskaya 2012[456]	Abstract only
Vvedenskaya 2009[457]	Abstract only
Wadensten 2007[458]	Incorrect study design (observational study describing practice)
Walczak 2013[461]	Population does not match protocol (death not imminent)
Walczak 2010[460]	Population does not match protocol (death not imminent)
Waldrop 2012[462]	Topic does not match protocol (communication before death imminent)
Weinandy 1997[465]	Abstract only
Wenrich 2001[466]	Population does not match protocol (death not imminent)
Wilkinson 2014[469]	Population does not match protocol (death not imminent)
Witkamp 2010[473]	Abstract only
Yin 2007[480]	Topic does not match protocol (perceptions of communication)
You 2014[482]	Topic does not match protocol (importance of communication)
Young 2006[483]	Topic does not match protocol (discussion of use of narrative)

L.3 Shared Decision Making

Table 95: Studies excluded from the clinical review of Shared decision making

Reference	Reason for exclusion
Adams 2014[12]	Indirect population: healthcare professionals in the USA
Bach 2009 [35]	Indirect population: healthcare professionals in Canada
Grbich 2006 [187]	Indirect population: healthcare professionals in Australia
Hilden 2006 [206]	Indirect population: healthcare professionals in Finland
Hilden 2006 [207]	Indirect population healthcare professionals in Finland
Jensen 2013 [243]	Indirect population: healthcare professionals in Finland
Lee 2009 [280]	Indirect population: not in the last days of life.
Macdonald 2011 [302]	Indirect topic. The study focussed on an ethicist which does not apply to standard care in the UK. .
Oberle 2001 [357]	Indirect population: healthcare professionals in Canada
Ostertag 2008 [360]	Indirect population: healthcare professionals and family members in the USA
Radwany 2009 [381]	Indirect population: healthcare professionals in the USA
Reed 2011[386]	Non peer reviewed journal and poor quality, discussed with the Committee and excluded.
Ryan 2011 [399]	Indirect population: healthcare professionals in the Republic of Ireland
Samara 2013 [403]	Indirect population: healthcare professionals in Australia

L.4 Maintaining Hydration

Table 96: Studies excluded from the clinical review of clinically assisted hydration

Reference	Reason for exclusion
Boland 2013[57]	Systematic review that did not match protocol- included studies that were not controlled
Nwosu 2014[355]	Systematic review that did not match protocol- assessment of hydration status only
Fritzon 2013[167]	Retrospective study investigating people receiving fluids in the last day and week of life.

L.5 Pharmacological Intervention

Table 97: Studies excluded from the clinical reviews on anxiety, agitation, breathlessness, delirium and pain

Study	Exclusion reason
Abernethy 2003[9]	Not guideline condition
Abernethy 2010[10]	Not guideline condition
Abernethy 2011[8]	Not guideline condition
Ahmedzai 1997[16]	Not guideline condition
Ahmedzai 2004[17]	Not guideline condition
Allard 1999[20]	Incorrect interventions
Andersen 1988[23]	Incorrect interventions
Anderson 2004[25]	Systematic review is not relevant to review question or unclear PICO
Aurora 2012[32]	Systematic review is not relevant to review question or unclear PICO
Bach 2013[34]	Not guideline condition
Bailey 2014[40]	Incorrect interventions
Bajwah 2013[42]	Systematic review: quality assessment is inadequate. Systematic review is not relevant to review question or unclear PICO
Bandieri 2012[44]	Not guideline condition. Incorrect interventions
Bausewein 2013[48]	Systematic review is not relevant to review question or unclear PICO
Ben-Aharon 2008[51]	Systematic review is not relevant to review question or unclear PICO
Ben-Aharon 2012[52]	Systematic review is not relevant to review question or unclear PICO
Benitez-Rosario 2004[53]	Not guideline condition
Booth 2004[60]	Systematic review is not relevant to review question or unclear PICO
Breitbart 1996[63]	Not guideline condition
Brescia 1987[64]	Not guideline condition
Bruera 1985[72]	Not guideline condition
Bruera 1990[70]	Not guideline condition

Bruera 1992[74]	Not guideline condition
Bruera 1993[69]	Not guideline condition
Bruera 1993[67]	Not guideline condition
Bruera 2003[75]	Not guideline condition
Bush 2014[76]	Systematic review is not relevant to review question or unclear PICO
Cadth 2014[79]	Systematic review: methods are not adequate or unclear
Campbell 2013[81]	Not review population
Candy 2012[83]	Systematic review is not relevant to review question or unclear PICO
Candy 2012[84]	Not guideline condition
Chan 2013[89]	Not guideline condition
Charles 2008[91]	Not guideline condition
Chew 2011[94]	Not guideline condition
Clemens 2011[104]	Not guideline condition
Clemens 2011[105]	Not guideline condition. Incorrect study design
Coyne 2002[114]	Not guideline condition
Cranston 2008[115]	Systematic review: withdrawn from publication
Currow 2009[119]	Not guideline condition
Dale 2011[127]	Systematic review is not relevant to review question or unclear PICO
Danoff 2013[128]	Systematic review: methods are not adequate or unclear
Daud 2007[130]	Systematic review: methods are not adequate or unclear
Dietz 2013[134]	Systematic review: quality assessment is inadequate
Douglas 2009[137]	Systematic review: quality assessment is inadequate
Dudgeon 2007[139]	Not guideline condition
Eaton 1999[142]	Not guideline condition
Flume 2002[161]	Systematic review: methods are not adequate or unclear

Frank 1997[165]	Systematic review is not relevant to review question or unclear PICO
Gamborg 2013[171]	Not guideline condition. Incorrect interventions
Ganzini 2007[172]	Incorrect study design
Generali 2004[173]	Systematic review: methods are not adequate or unclear
Girard 2010[178]	Not guideline condition
Gomutbutra 2013[183]	Not guideline condition
Grosset 2005[190]	Not guideline condition
Hardy 1998[197]	Not guideline condition. Not review population
Harlow 2011[198]	Not guideline condition
Harris 2003[201]	Not guideline condition
Harris 2014[200]	Not guideline condition
Hinkka 2001[208]	Inappropriate comparison
Hochgerner 2009[221]	Systematic review: quality assessment is inadequate
Hui 2013[229]	Not guideline condition
Hunt 1999[230]	Not guideline condition
Husic 2011[231]	Not guideline condition
Imanaka 2013[233]	Not guideline condition
Israel 2010[234]	Not guideline condition
Jackson 2004[238]	Not guideline condition
Jennings 2001 [241]	Systematic review is not relevant to review question or unclear PICO
Jennings 2003[242]	Systematic review: methods are not adequate or unclear
Johnson 2013[245]	Not guideline condition
Kallet 2007[248]	Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate
Kamboj 2005[250]	Not guideline condition

Kamboj 2014[249]	Not guideline condition
Keeley 2009[254]	Systematic review is not relevant to review question or unclear PICO
Kehl 2004[256]	Systematic review is not relevant to review question or unclear PICO
Kestenbaum 2014[258]	Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate
King 2011[259]	Systematic review is not relevant to review question or unclear PICO
King 2011[260]	Systematic review is not relevant to review question or unclear PICO
Kurita 2011[268]	Systematic review is not relevant to review question or unclear PICO
Lauretti 1999[272]	Not guideline condition
Leblanc 2014[278]	Not guideline condition
Lebon 2009[279]	Systematic review: literature search not sufficiently rigorous. Systematic review: study designs inappropriate
Legge 2006[282]	Systematic review: methods are not adequate or unclear
Lennernas 2010[283]	Not guideline condition
Lorenz 2008[299]	Systematic review: quality assessment is inadequate
Sayed 2014[404]	Not guideline condition
Maltoni 2012[304]	Palliative sedation
Marinangeli 2004[308]	Not guideline condition
Mazzocato 1999[311]	Not guideline condition
Mcnamara 2002[315]	Not guideline condition
Mercadante 1998[316]	Not guideline condition
Mercadante 2002 [319]	Not guideline condition
Mercadante 2004[320]	Not guideline condition
Mercadante 2007[322]	Not guideline condition
Mercadante 2012[318]	Not guideline condition
Mercadante 2013[321]	Not guideline condition

Miller 2014[323]	Not review population
Moore 1994[325]	Not guideline condition
Morgan 1994[326]	Incorrect study design
Morita 2005[329]	Not guideline condition
Mystakidou 2004[338]	Not guideline condition
Mystakidou 2005[336]	Not guideline condition
Naing 2013[339]	Systematic review is not relevant to review question or unclear PICO
Naqvi 2009[340]	Systematic review: methods are not adequate or unclear
Nava 2013[343]	Not guideline condition
Navigante 2003[344]	Not in English language
Nicholson 2007[349]	Systematic review is not relevant to review question or unclear PICO
Oxberry 2009[362]	Systematic review: methods are not adequate or unclear
Parlow 2005[365]	Not guideline condition
Peterson 1996[368]	Not guideline condition
Philip 2006[369]	Not guideline condition
Plonk 2005[371]	Incorrect study design
Popiela 1989[372]	Not guideline condition
Raffa 2012[382]	Systematic review: methods are not adequate or unclear
Rauck 2009[385]	Not guideline condition
Ripamonti 1999[392]	Systematic review: methods are not adequate or unclear
Ripamonti 2000[393]	Incorrect interventions
Rodrigues 2004[395]	Not guideline condition
Rodriguez 2007[396]	Not guideline condition
Salas 2012[401]	Not guideline condition
Schultheis 2005[405]	Incorrect study design

Sim 2014[411]	Systematic review: literature search not sufficiently rigorous
Simon 2010[413]	Not guideline condition
Simon 2012[412]	Not English language
Sittl 2003[414]	Not guideline condition
Smith 2002[416]	Not guideline condition
Stiefel 2004[422]	Systematic review: methods are not adequate or unclear. Systematic review is not relevant to review question or unclear PICO
Thomas 2009[430]	Not guideline condition
Tse 2012[436]	Incorrect interventions
Twycross 1985[440]	Not guideline condition
Uronis 2008[443]	Systematic review: methods are not adequate or unclear
Uronis 2008[442]	Not guideline condition. Systematic review is not relevant to review question or unclear PICO
Viola 2008[451]	Systematic review is not relevant to review question or unclear PICO
Wang 2012[464]	Systematic review is not relevant to review question or unclear PICO. Systematic review: quality assessment is inadequate
Wiffen 2014[467]	Not guideline condition
Williams 2011[471]	Systematic review: methods are not adequate or unclear
Wootton 2004[474]	Systematic review is not relevant to review question or unclear PICO
Wyne 2011[475]	Systematic review is not relevant to review question or unclear PICO
Xu 1997[476]	Not guideline condition
Yates 2013[479]	Systematic review: methods are not adequate or unclear
Zeppetella 2000[485]	Not guideline condition
Zeppetella 2001[486]	Not guideline condition
Zeppetella 2010[487]	Not guideline condition
Zerzan 2010[488]	Incorrect study design

L.5.1 Nausea and Vomiting

Author	Exclusion reason
Bruera 2000[66]	Incorrect population, not in the last days of life.
Clark 2013[98]	Cochrane review- protocol only.
Corli 1995[113]	Incorrect population, not in the last days of life.
Currow – unpublished data[120]	Incorrect population, not in the last days of life.
Darvil 2013[129]	Systematic review, did not match our protocol. Found no studies of levomepromazine in the last days of life.
Davis 2002[131]	Narrative review
Davis 2010	Systematic review, different PICO question: not limited to the last days of life.
Dean 2001[132]	Narrative review
Dietz 2013[134]	Systematic review- did not match our population, included studies focused on chemotherapy/radiotherapy induced nausea.
Dorman 2010[136]	Systematic review, did not match our protocol.
Eisenchlas 2005[143]	Incorrect population, not in the last days of life. Open label prospective study design.
Feuer 1999[158]	Systematic review, different PICO question: not limited to the last days of life. Included unpublished data but limited data presented and none relevant to this PICO.
Fowell 2004[164]	Study design description only.
Glare 2004[181]	Systematic review- Incorrect population, not in the last days of life.
Glare 2008[179]	Narrative review
Glare 2011[180]	Narrative review
Hardy 1998[197]	Incorrect population, not in the last days of life.
Hardy 2002[196]	Incorrect population, not in the last days of life.
Harris 2010[199]	Narrative review
Heegaard 2014[202]	Conference abstract- Systematic review, limited write up available.
Herndon 2002[205]	Narrative review
Laugsand 2011[271]	Systematic review, different PICO question: opioid-induced nausea only, not limited to the last days of life and included interventions not included in our protocol, such as reducing dose of opioid.
Laval 2000[273]	Incorrect population, not in the last days of life.
Laval 2012[274]	Incorrect population, not in the last days of life
Magee 2014[303]	Conference abstract- Systematic review, limited write-up available.
Mangili 2005[305]	Incorrect population, not in the last days of life.
McLean 2013[314]	Systematic review- did not match our population, included studies focused on post-operative nausea.
Mystakidou 1998[335]	Incorrect population, not in the last days of life.
Mystakidou 2010[337]	Incorrect population- patients receiving chemotherapy/radiotherapy.
O'Neill 1999[356]	Opinion piece.
Perkins 2009[367]	Systematic review, did not match our protocol. Found no studies of haloperidol in the last days of life.
Prommer 2012[375]	Literature review. Found no controlled studies of haloperidol in the last days of life.
Prommer 2012[376]	Literature review.
Tatum 2009[429]	Systematic review- summarised another Cochrane whose protocol did not

Author	Exclusion reason
	match.
Tuca 2009[437]	Incorrect population, not in the last days of life.
Tygat 2009	Systematic review, did not match our protocol. Found no studies of hyoscine butylbromide used for nausea in the last days of life.

L.5.2 Noisy Respiratory Secretions

Table 98: Studies excluded from the clinical review of Noisy respiratory secretions

Study	Exclusion reason
Ahamed 2011[15]	Not the protocol condition: breathlessness rather than respiratory secretion
Bailey 2014[40]	Intervention does not match the protocol - staff training
Campbell 2013[82]	Comparison does not match the protocol - people with death rattle compared with people without death rattle
Chapman 2011[90]	Narrative review
Clark 2009[99]	Narrative review
Clary 2009[101]	Background (general pharmacological management at the end of life)
Furst 2012[169]	Background (general pharmacological management at the end of life)
Hipp 2009[209]	Narrative review
Hirsch 2013[215]	Qualitative (focus group) study
Kintzel 2009[261]	Systematic review without quality assessment
Lindqvist 2013[292]	Background (Delphi consensus on drugs needed for dying people)
Lokker 2014[298]	Systematic review (cross-checked for references)
Lundquist 2011[300]	Related to communication about dying
Manthous 2013[306]	Commentary
Nunn 2014[354]	Background (symptom management)
Radbruch 2012[378]	Background (pharmaceutical management of dying people)
Sheehan 2011[409]	Prognostic study for noisy respiratory secretions (factors predictive or protective)
Shimizu 2014[410]	Survey study
Smucker 2010[417]	Commentary (related to long term care)
Twomey 2013[438]	Narrative review

L.6 Anticipatory Prescribing

Table 99: Studies excluded from the clinical review of Anticipatory prescribing

Reference	Reason for exclusion
Amass 2005 [22]	Opinion piece
Anon 2011[2]	Opinion piece
Anon 2008[1]	Opinion piece
Anquinet 2015[27]	Indirect topic of questioning: related to terminal sedation in home settings

Reference	Reason for exclusion
Bailey 2005[38]	Indirect intervention where anticipatory prescribing in a hospital setting was 1 component of a multiprofessional intervention
Butler 2013 [77]	Narrative review
Finucane 2014[160]	Descriptive date indirect to context of access.
Griggs 2010[189]	Indirect topic of questioning: related to nursing staffs beliefs of a 'good death'
Jack 2013[235]	Indirect topic of questioning: evaluation of hospice at home service
Lawton 2012 [276]	Non controlled intervention.
Oliver 2010 [359]	Indirect topic of questioning: comfort care packs not consisting of pharmacological interventions in the terminally ill
Radly 1998[380]	Opinion piece
Scott-Ation 2009 [406]	Not qualitative research
Stone 2013[423]	Indirect context.

Appendix M: Excluded economic studies

M.1 Recognising Dying

None

M.2 Communications

None

M.3 Shared Decision Making

None

M.4 Assisted Hydration

None

M.5 Pharmacological Intervention

Table 100 - Excluded economic studies

Reference	Reason for exclusion
Back 2001[37]	This study was assessed as partially applicable with very serious limitations. This study was included in the clinical review conducted for this guideline, but the economic data were limited (only drug costs were reported) and old, therefore with limited applicability. The quality of the clinical evidence was also assessed as very low.

M.6 Anticipatory Prescribing

None

1

2 # Appendix N: Unit Costs

Drug	Preparation	Units/ pack	Cost/ pack	Cost/ unit(a)	Usual 24 hour dose	Cost/ day	Source(b)
Alfentanil	1 mg/2 ml solution for injection ampoules	10	£3.50	£0.35	0.5-no max	£0.35	eMIT[109]
Atropine	600 micrograms/ 1 ml solution for injection ampoules	10	£11.70	£1.17	0.4mg	£1.17	NHS Drug Tariff, December 2014[347]
Buprenorphine	10 micrograms/hour transdermal patches	4	£31.56	£7.89	Changed every 7 days	£1.12	NHS Drug Tariff, March 2015[348]
Buprenorphine	200 microgram sublingual tablets sugar free	50	£5.04	£0.10	800-1200mcg	£0.80 - £1.20	NHS Drug Tariff, March 2015[348]
Clonazepam	1mg/ml injection ampoules	1	£6.00	£6.00	1-8mg (depending on indication)	£6.00 - £48.00	Palliative Care Formulary (PCF5)[441]
Clonazepam	2 mg tablets	100	£8.97	£0.09	0.5mg	£0.09	NHS Drug Tariff, March 2015[348]
Cyclizine	50 mg tablets	100	£11.26	£0.11	150 mg	£0.33	NHS Drug Tariff, December 2014[347]
Cyclizine	50 mg/1 ml solution for injection ampoules	5	£8.65	£1.73	150mg	£5.19	NHS Drug Tariff, December 2014[347]
Dexamethasone	2mg/5ml oral solution sugar free	150ml	£42.30	£0.28	4mg	£2.82	NHS Drug Tariff, March 2015[348]
Dexamethasone	4mg/ml ampoules for injection	NA	NA	£1.99	2-16mg	£1.98 - £7.96	BNF 2015[246]
Dexamethasone	2 mg tablets	50	£49.45	£0.99	4mg	£1.98	NHS Drug Tariff, December 2014[347]
Dexamethasone	500 micrograms tablets	28	£60.50	£2.16	4mg	£17.28	NHS Drug Tariff, December 2014[347]
Diamorphine	10 mg powder for solution for injection ampoules	5	£14.05	£2.81	5 - no max dose	£2.81	NHS Drug Tariff, March 2015[348]
Diazepam	5 mg/2.5 ml rectal solution	5	£7.35	£1.47	5-30mg	£1.47 -	NHS Drug Tariff, March 2015[348]

Drug	Preparation	Units/ pack	Cost/ pack	Cost/ unit(a)	Usual 24 hour dose	Cost/ day	Source(b)
	tube					£8.82	
Diclofenac	100mg suppositories	10	£3.03	£0.30	100 mg	£0.30	NHS Drug Tariff, March 2015[348]
Diclofenac	75 mg/3 ml solution for injection ampoules	10	£8.26	£0.83	100 – 150 mg	£0.83 - £1.66	NHS Drug Tariff, March 2015[348]
Domperidone	10 mg tablets	30	£2.06	£0.07	30mg	£0.21	NHS Drug Tariff, December 2014[347]
Domperidone	10 mg tablets	100	£6.87	£0.07	30mg	£0.21	NHS Drug Tariff, December 2014[347]
Domperidone	5 mg/5 ml oral suspension 200 ml	200	£13.32	£0.07	30mg	£2.00	NHS Drug Tariff, December 2014[347]
Fentanyl	100 microgram buccal tablets sugar free	28	£139.42	£4.99	Variable 100-800mcg	£4.99 - £39.92	NHS Drug Tariff, March 2015[348]
Fentanyl	25 micrograms/ hour transdermal patches	5	£18.00	£3.60	1 patch every 3 days	£1.20	NHS Drug Tariff, March 2015[348]
Fosaprepitant	150 mg per vial powder for reconstitution (vial)	1	£47.42	£47.42	150mg	£47.42	BNF December 2014[246]
Furosemide	10mg/ml ampoules for injection	NA	NA	£0.50 per 2ml ampoules	40-160mg	£1.00 - £4.00	Palliative Care Formulary (PCF5)[441]
Glycopyrronium bromide	0.2 mg/mL solution for injection ampoules	3ml	£1.50	£0.50	0.6 mg	£1.50	BNF December 2014[246]
Granisetron	3.1mg/24 hours patches	1	£56.00	£56.00	1 patch for 5 days	£11.20	BNF December 2014[246]
Granisetron hydrochloride	1mg/mL solution for injection ampoules	3	£2.40	£0.80	9 mg	£7.20	BNF December 2014[246]
Haloperidol	5 mg/1 ml solution for injection ampoules	5	£1.82	£0.36	1.5mg	£0.36	NHS Drug Tariff, March 2015[348]
Haloperidol	500microgram capsules	30	£1.18	£0.04	1.5mg	£0.12	NHS Drug Tariff, March 2015[348]
Haloperidol	1.5 mg tablets	28	£2.50	£0.09	1.5mg	£0.09	NHS Drug Tariff, December 2014[347]

Drug	Preparation	Units/ pack	Cost/ pack	Cost/ unit(a)	Usual 24 hour dose	Cost/ day	Source(b)
Haloperidol	5 mg/5 ml oral solution	100	£6.41	£0.06	1.5mg	£0.09	NHS Drug Tariff, December 2014[347]
Hydromorphone	10mg/ml ampoules for injection	NA	NA	£9.00	2mg – no max	£9.00	Palliative Care Formulary (PCF5)[441]
Hyoscine butylbromide	20 mg/1 ml solution for injection ampoules	10	£2.92	£0.29	60mg	£0.87	NHS Drug Tariff, December 2014[347]
Hyoscine hydrobromide	400 micrograms/ 1 ml solution for injection ampoules	10	£30.51	3.05	0.4mg	£3.05	NHS Drug Tariff, December 2014[347]
Ketorolac	30 mg/1 ml solution for injection ampoules	6	£3.99	£0.67	60-90mg	£1.34 - £2.01	eMIT[109]
Levomepromazine	25 mg/1 ml solution for injection ampoules	10	£20.13	£2.01	6mg	£2.01	NHS Drug Tariff, March 2015[348]
Lorazepam	1 mg tablets sublingual	28	£2.52	£0.09	0.5-4mg	£0.09 - £0.36	NHS Drug Tariff, March 2015[348]
Metoclopramide	10 mg tablets	28	£0.97	£0.03	30mg	£0.09	NHS Drug Tariff, December 2014[347]
Metoclopramide	10 mg/2 ml solution for injection ampoules	10	£3.15	£0.32	30mg	£1.92	NHS Drug Tariff, December 2014[347]
Metoclopramide	5 mg/5 ml oral solution 150 ml	150	£19.60	£0.13	30mg	£3.90	NHS Drug Tariff, December 2014[347]
Midazolam	10 mg/2 ml solution for injection ampoules	10	£1.60	£0.16	10-60mg (but can be higher)	£0.16	eMIT[109]
Midazolam	2.5 mg/0.5 ml oromucosal solution pre-filled oral syringes	4	£82.00	£20.50	10-30mg	£82.00 - £230.00	NHS Drug Tariff, March 2015[348]
Morphine sulfate	10 mg/1 ml solution for injection ampoules	10	£9.36	£0.09	10mg – no max dose	£0.09	NHS Drug Tariff, March 2015[348]
Morphine sulfate	10mg/5ml oral solution	300ml	£5.45	£5.45	10mg – no max dose	£0.09	NHS Drug Tariff, March 2015[348]

Drug	Preparation	Units/ pack	Cost/ pack	Cost/ unit(a)	Usual 24 hour dose	Cost/ day	Source(b)
Octreotide	500 micrograms/ 1 ml solution for injection ampoules	5	£135.47	£27.09	0.25mg	£54.18	NHS Drug Tariff, December 2014[347]
Olanzapine	2.5 mg orodispersible tablets	28	£1.12	£0.04	2.5-10mg	£0.04 - £0.16	NHS Drug Tariff, March 2015[348]
Olanzapine	10 mg orodispersible tablets	28	£3.43	£0.12	2.5-10mg	£0.12	NHS Drug Tariff, December 2014[347]
Olanzapine	5 mg orodispersible tablets	28	£2.73	£0.10	2.5-10mg	£0.10	NHS Drug Tariff, December 2014[347]
Olanzapine	5 mg orodispersible tablets	28	£3.66	£0.13	2.5-10mg	£0.13	NHS Drug Tariff, December 2014[347]
Ondansetron	8 mg 0rodispersible tablets	10	£80.26	£8.03	8mg	£8.03	NHS Drug Tariff, December 2014[347]
Oxycodone	10 mg/1ml solution for injection ampoules	5	£8.00	£1.60	5-no max dose	£1.60	NHS Drug Tariff, March 2015[348]
Oxycodone	10 mg/ml oral solution sugar free	120ml	£46.63	£0.39	10- no max dose	£0.39 - maximum dose given	NHS Drug Tariff, March 2015[348]
Oxycodone	50mg/1ml solution for injection ampoules	5	£70.01	£14.01	5-no max dose	£14.01 - maximum dose given	NHS Drug Tariff, March 2015[348]
Palonosetron	0.05 mg/ml solution for injection ampoules	5	£55.89	£11.18	0.25mg	£55.90	BNF December 2014[246]
Prochlorperazine	12.5 mg/1 ml solution for injection ampoules	10	£5.23	£0.52	2.5mg	£0.52	NHS Drug Tariff, December 2014[347]
Prochlorperazine	3 mg tablets	28	£1.03	£0.04	6mg	£0.08	NHS Drug Tariff, December 2014[347]
Prochlorperazine	5 mg/5 ml oral solution	100	£3.34	£0.03	5mg	£0.15	NHS Drug Tariff, December 2014[347]

(a) Cost per unit for oral solutions is presented as £ per ml.

(b) Cost sources are given as they were when presented to the Committee.

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Appendix O: Research recommendations

O.1 Recognising dying

O.1.1 Research question

What can multiprofessional teams do to reduce the impact of uncertainty of recognising when a person is entering the last days of life on clinical care, shared decision-making and communication with the dying person and those important to them?

O.1.2 Why this is important

It may be difficult to determine when the dying person is entering the last few days or weeks of life. Predicting the end of life is often inaccurate, and current prognostic tools and models are limited. Some level of uncertainty in recognising when a person is entering the last days of life is likely and is often a challenge to planning care. However, it is crucial to minimise this uncertainty to ensure that it does not prevent key discussions between the healthcare professional and the dying person and those important to them.

It is therefore important to identify how the uncertainty of recognising when a person is entering the last days of life influences information sharing, advanced care planning and the behaviour of healthcare professionals. A mixed-methods approach (quantitative and qualitative evidence) is proposed that aims to explore how different multidisciplinary team interventions can reduce the impact of uncertainty on clinical care, shared decision-making and communication, specifically on engaging the dying person and those important to them in end of life care discussions. Multidisciplinary team interventions include any different methods of giving feedback, initiating end of life discussions, record keeping or updating care plans, compared with usual care. Outcomes of interest include quality of life, patient or carer satisfaction, changes to clinical care and identification and/or achievement of patient wishes such as preferred place of death. In addition the barriers and facilitators for the healthcare professionals to manage this uncertainty to best support the dying person and those important to them should be explored.

Appendix table

PICO question	Mixed methods approach (quantitative and qualitative evidence). Quantitative: P: Patients with any condition identified as potentially being in the last weeks of life and in any setting (hospital, hospice or usual residence). I: Different multidisciplinary team interventions aiming to reduce impact of uncertainty around recognizing dying on clinical care, shared decision making or communication (any different methods of giving feedback, initiating end of life discussions, record keeping or updating care plans). C: Usual care/current practice) O: Quality of life/patient or carer satisfaction/changes to clinical care.

	/identification and achievement of a person's goals or wishes. Qualitative: Interviews or focus groups with healthcare staff, the dying person or those important to them to explore barriers and facilitators to reducing the impact of uncertainty around recognizing death on good clinical care, shared decision making and communication.
Importance to patients or the population	Healthcare professional can have difficulty in breaking bad news and initiating discussions around end of life care and may find they want to delay any such discussions if they are uncertain over when a person is actually nearing death. There is a fear of doing harm by initiating conversation too early or inappropriately and the person or those important to them loosing hope when they may recover. Conversely for patients and families they may wish for time to prepare including, time to enable families to visit, preparation of financial or legal documents, preparation of loved ones (for example, communication with children), or time to achieve transfer to preferred place of care.
Relevance to NICE guidance	Uncertainty around when a person is entering the last days of life was a key finding throughout the guideline and impact several questions as highlighted in the current evidence section.
Relevance to the NHS	Improving how uncertainty in prognostication of death can be addressed to increase communication at end-of-life is death with would have a positive impact on healthcare and patient experience.
National priorities	Relevant to national priorities, as discussed in the review of the Liverpool Care Pathway: More Care less pathway, One Chance to Get it Right.
Current evidence base	The review on recognizing dying showed that there are no definitive signs or symptoms to determine when a person is entering the last days of life. Uncertainty around recognizing death was a reoccurring theme within the qualitative review on communication and shared decision making.
Study design	Mixed methods approach (quantitative and qualitative review question). Quantitative question would be best addressed through and RCT and the qualitative through structured interviews or focus groups. Power calculations should be conducted to establish the required sample size of the trial. It is important that the study is adequately powered to detect a clinically important effect size.
Economic considerations	Achievement of preferred place of care/death, reduction in un-necessary hospital admissions and change in use of out of hours services due to earlier planning.
Feasibility	The Committee recognise the difficulty in undertaking research in this

	group raised by the sensitive time point of study, however small number, but RCT evidence has been identified and included within the guideline so research is possible in this population. It would be necessary to be cognizant when undertaking recruitment of these patients of the need for a sensitive approach.
Equalities	Research would cover all disease groups and all people over 18 years rather than focussing on cancer like the majority of clinical evidence that is available in the last days of life.
Other comments	None.

O.2 Agitation and Delirium:

O.2.1 Research question

What is the best way to control delirium, with or without agitation, in the dying person, without causing undue sedation and without shortening life?

Why this is important

People who are entering the last days of life may develop sepsis, dehydration and various biochemical disorders which may lead to the development of delirium. This is characterised by altering levels of consciousness, confusion and possibly hallucinations.

Many of the drugs used to control delirium are classed as sedatives. It can be difficult for inexperienced clinicians to reduce delirium without causing undue sedation. An inappropriately large dose of sedative medication may also compromise respiration. A perceived risk of over-sedation is that the dying person's life may be shortened because of the sedation itself.

Specialists in palliative care are knowledgeable about which drugs to use and in which combinations, and know how to use the correct routes and frequency to achieve reduction in delirium, and of any accompanying agitation, without over-sedating the dying person. However most people who are dying are not under the direct care of such specialists, although they may be called in for advice out-of-hours if the person becomes agitated and this has resource implications for specialist palliative care services.

The research should study how key drugs in UK palliative care practice (such as benzodiazepines and antipsychotics) can be applied in a range of settings in order to reduce delirium and agitation without causing undue sedation or inadvertently shortening life. This is proposed to be conducted as multi-arm, multi-stage interventions using escalating doses over 12-hours as clinically indicated.

Appendix Table

PICO question	Population: Adults who are considered to be in the last days of life and who exhibit signs of delirium according to a validated delirium scale. Intervention: Multi-arm, multi-stage interventions at escalating doses taken from 1 of 3 classes – A) Benzodiazepine - lorazepam; midazolam; clonazepam; diazepam; B) Classical anti-psychotic - haloperidol; levomepromazine; C) Atypical anti-psychotics - olanzapine; risperidone. Comparison: In a multi-arm, multi-stage design participants are first randomised to 1 drug out of multiple options, in this case from class A, B or C. It may be possible to use a placebo, provided that open label rescue medication is always available. However, because of the widely different dosing of the different medications, it is unlikely that blinding will be feasible in such a setting. People who fail to respond within 12 hours to the first randomized drug are allocated to a drug from 1 of the other 2 classes. Within each class, dose can be escalated over 12 hours by the clinician as indicated by clinical response. If there is no response after 3 allocations in 36 hours, the person is withdrawn from the study

	and treated empirically by the clinician. Outcomes: A) Cognitive level – cognitive functioning and delirium scales validated for this population B) Sedation – Glasgow Coma Scale C) Presence and severity of hallucinations D) Activity level – wrist or ankle-worn actimeter E) Social interactions F) Survival from entry to study.
Importance to patients or the population	At present there is no guideline or consensus about which class of drug to use first-line and which drugs within each class are optimal in the care of dying people. Given that delirium and possibly agitation are so prevalent at the end of life, it would have a major impact on the quality of care for a large number of people and also on their families and others important to them. As the LCP review found the public perceives that over-sedation may lead to earlier death in some cases, it is important for research to verify or refute this perception.
Relevance to NICE guidance	The NICE guideline found no good evidence about the pharmacological control of delirium and agitation in people in the last days of life. The Committee has made consensus-based recommendations on the use of benzodiazepines and anti-psychotics. The literature review did not uncover evidence on the drugs most commonly used in UK clinical practice and on the newer atypical antipsychotics which may have advantages for some people. This was thought to be a very important question in view of the concerns expressed about over-sedation of dying people in the LCP review. Gaining new evidence about the classes and specific drugs that are best for controlling delirium in dying people, without causing undue sedation and risking an earlier death, would be of great importance to UK clinical care.
Relevance to the NHS	Most people die in acute hospitals or in settings where specialist palliative care staff are not readily available round the clock. The Committee has recommended calling a specialist if the dying person does not respond to first-line treatment. In fact being called in to deal with agitated people is 1 of the commonest reasons for out of hours visits by on-call specialist staff. This research would enable non-specialist staff to be more confident about the use of drugs to control delirium and agitation and thus this could reduce the need for calling in specialists. Knowing that the best drugs are being used without risking an earlier death would not only have a beneficial impact on patient care and the experience of families, but also would make clinical staff more comfortable with this aspect of care.
National priorities	None identified.

Current evidence base	The evidence review undertaken as part of this guideline identified no studies investigating the management of delirium or agitation in the last days of life.
Study design	A multi-arm, multi stage randomised controlled trial design is complex but has advantages when there are many therapeutic options. If only 1 drug was to be compared with placebo, or 2 drugs were compared against each other (possibly with placebo) then this would only achieve new information about those drugs. Several other studies would be needed sequentially to evaluate the other drugs, which potentially could take many years. In some clinical areas, such as oncology, a multi-arm multi-stage design is used to speed up clinical testing of multiple new agents, either against placebo or against each other (for example, MATRIX trial in lung cancer; reference Prof Max Parmar of MRC). Clearly a multi-arm, multi-stage design needs careful planning and relatively large numbers of subjects, depending on the effect size of the improvement to be obtained. By testing a single person potentially with 3 drugs in 36 hours, the testing of such agents can be speeded up. It is important that the study is adequately powered to detect a clinically important effect size. Sophisticated power calculations should be conducted to establish the required sample size of the trial. Because of the complex design, it is most likely that such a trial would be best conducted in centres which are used to clinical trial research, such as acute hospitals and oncology departments – rather than smaller independent hospices.
Economic considerations	A significant proportion of people dying from various conditions experience a period of delirium and agitation and this is likely to increase as the number of people with dementia rises. The proposed research will have significant cost benefit as it could reduce the proportion of people who may have to transfer to specialist settings for care at the end of life; and it could reduce the number of times that specialists may be called in to deal with agitated people out of hours.
Feasibility	There are many candidate drugs for the relief of delirium and control of agitation and all of them are, to varying extents, being used in different settings in the UK. To test each drug sequentially or to compare them in pairs would take a prohibitive number of years and a lot of NHS research costs. The proposed multi-arm multi-stage design would still take some time but it would deliver multiple drug comparisons within that timescale. NHS research costs would also be reduced. The main ethical issue for this trial would be obtaining consent. There are 2 solutions: first, to pre-consent people who are approaching end of life and who still have full capacity, in the event that they may develop delirium later one; second, to obtain consent (assent) from a person nominated to be important to the dying person, at the time that they becomes delirious. Both types of consent could theoretically co-exist in the same study.

	Technically the study is more difficult to design and implement and therefore it will be better conducted in a smaller number of units with clinical trials experience.
Equalities	The research recommendation has no overall impact on excluded groups. By including people with dementia in the proposed clinical trial, it is possible that people with that condition who are dying in settings where trials are not feasible, may still have this important clinical question addressed.
Other comments	This is an appropriate subject for funding by NIHR through its RfPB or better, HTA routes.

O.3 Noisy respiratory secretions

O.3.1 Research question

In people considered to be in the last few hours and days of life, are antisecretory anti-muscarinic drugs (used alongside nursing interventions, such as repositioning and oropharyngeal suction) better at reducing noisy respiratory secretions and patient, family and carer distress without causing unwanted side effects, than nursing interventions alone?

O.3.2 Why this is important

It is common for people to experience noisy respiratory secretions at the end of life and the so called 'death rattle' is a predictor of death. The noise can cause considerable distress for people important to the dying person, both at the time and possibly after death, because of concerns that the person may have drowned or suffocated to death. Clinicians may administer subcutaneous anti-muscarinic agents in an attempt to 'dry up' secretions and relieve any distress primarily to people important to the person despite a lack of evidence of any beneficial effect to the patient or improvement in distress levels.

The evidence for the efficacy of pharmacological interventions in managing respiratory secretions is of low quality, and it is not clear if any one drug is more effective than another or if drugs are more effective than non-pharmacological approaches such as repositioning or oropharyngeal suction. Most studies involved low numbers of patients and were primarily based on cancer patients in hospices and so may not reflect the larger numbers of patients dying with non-malignant diseases in hospitals and in community care.

Anti-muscarinic agents may have undesired side effects, such as dry mouth, blurred vision or urinary retention, as well as a cost implication, and it is therefore hard to justify their continued use given the limited evidence base.

A randomised controlled trial is proposed comparing antisecretory anti-muscarinic drugs and nursing care to nursing care alone. Nursing interventions include repositioning, mouth care and education and reassurance for those important to the dying person. Outcomes of interest are subjective and objective measures of reduction in noise level, reduction in distress to the dying person or those important to them and adverse effects.

Appendix Table

PICO question	Population: Adults over 18 years with both cancer and non-cancer diagnoses considered to be in the last 72 hours of life with noisy respiratory secretions in both community (own home, residential or nursing home, hospice) and hospital settings. Intervention: Randomised to receive subcutaneous injection of glycopyrronium 0.2mg (repeated after 4-8 hours if necessary, max 1.2g in 24 hours) or hyoscine butylbromide 20mg (repeated after 4-8 hours if necessary, max 120mg in 24 hours) or atropine 0.4mg sublinual or subcut (repeated after 4-8 hours if necessary, max dose 2g in 24 hours) or placebo injection of 1ml subcutaneous normal saline.

	Comparison: Repositioning (and judicious oropharyngeal suction if appropriate) as required, good mouth care and education and reassurance for professional carers and family members (standard information sheet). Outcomes: a) subjective reduction in noise level by both professional carer and family member on standardized scale such as Death Rattle Intensity Scale or Victoria Respiratory Congestion Scale, b) objective measure of noise intensity using a noise recorder by professional carer in a subgroup of people in hospital, c) self-rated subjective reduction in distress of patient and family member by family member, d) subjective reduction in distress of both patient and family member by professional carer, f) patient conscious level, e) adverse effects of medication including dry mouth, sedation, confusion, g) post death questionnaire.
Importance to patients or the population	If new evidence shows no benefit in giving antisecretory drugs then people will avoid being given unnecessary medications and injections with potentially harmful side effects, for example, dry mouth, urinary retention and focus can shift to non-pharmacological interventions and explanation and reassurance.
Relevance to NICE guidance	This research recommendation is directly relevant to the chapter in this guidance on the pharmacological management of respiratory secretions in the last few days of life and is needed in order to provide any robust evidence based guidance to change or corroborate current practice.
Relevance to the NHS	The practice of prescribing antimuscarinic antisecretory drugs for noisy respiratory secretions at the end of life is has become routine despite any clear evidence of benefit so a robust study would allow evidence based clinical guidance to be drawn up and would be a driver for education in this area.
National priorities	Improved end of life care is a national priority area and the need for evidence based guidance and better education arose out of the findings of the Neuberger Report. Poor symptom control was also 1 of the 6 key themes outlined in the recent Parliamentary and Health Service Ombudsman's report (Dying Without Dignity).
Current evidence base	A small number of studies have attempted to answer this question but the study numbers have been small and they have primarily been based in cancer populations within a hospice setting. The Committee also felt that there were flaws in the methodology, for example doses of drugs not reflecting common clinical practice, inadequate washout periods, retrospective analysis, wide variation in outcomes with lack of objective measures and inconsistencies in scoring noise levels, lack of measure of family or patient distress as important outcomes.
Study design	A large multi-centre multi-arm randomised, double blind placebo controlled trial with an intention to treat analysis (drop out after

	24 hours if no improvement). "Power calculations should be conducted to establish the required sample size of the trial. It is important that the study is adequately powered to detect a clinically important effect size."
Economic considerations	Unless we obtain the answer to this research question, many people will continue to receive medications without benefit (a waste of resources) and potential harm leading to carer distress (requiring increased psychological support and bereavement counselling, higher rates of sick leave) which will have a cost implication).
Feasibility	The Committee felt that it was feasible to carry out this study, although commented that given the large number of arms involved this would need to be a multicentre design. Although people are likely to need to give advanced consent to participate in the study and may not meet the inclusion criteria, this was not felt to be a barrier to research. The treatment of respiratory secretions is largely based on treating carer or family member distress as the person is rarely disturbed by the sound. This use of drugs to ally relatives' distress fits uncomfortably with many health care professionals. Atropine is not commonly used in the UK but there is evidence of its benefit in the sublingual form in 1 US study. A sublingual drug has advantages in that it does not require a trained nurse to administer it so could easily be used in the community setting.
Equalities	It is important that we also study the effect of these drugs in the non-cancer population and in the hospital setting as current studies were not based in these people yet we know most people die in hospital and from non-malignant conditions.
Other comments	The Committee felt it important to note that the "death rattle" is specific to the last few hours to days of life and although there is more evidence (albeit of poor quality) for this area of the guideline than other areas such as management of pain, there is evidence from other areas outside of the end of life that could be used to help guide practice in those areas.

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O.4 Anticipatory Prescribing

O.4.1 Research Question:

What is the clinical and cost effectiveness of anticipatory prescribing for patients dying in their usual place of residence, on patient and carer reported symptoms at end of life?

O.4.2 Why this is important

Anticipatory prescribing can provide access to essential medicines for symptom control at the end of life. Current best practice when it is recognised that someone is entering the final days of life recommends that medicines to manage pain, breathlessness, nausea and vomiting, and agitation are prescribed with authorisation for administration if clinically indicated when it is recognised that someone is entering the final days of life. Although their use is relatively widespread, there remains a need to investigate the clinical and cost effectiveness of this approach. Studies undertaken to date have been small-scale audit-type projects evaluating the use of anticipatory prescriptions and qualitative studies exploring the barriers to uptake.

Uncertainty remains as to the impact of anticipatory prescribing on outcomes such as preferred place of death and symptom control, and also uncertainty as to what should be prescribed.

A cluster randomised controlled trial (randomised by GP practice) is proposed to compare interventions of anticipatory prescribing ('just in case' boxes) with a generic list of medicines or anticipatory prescribing individualised to the patient's expected symptoms, compared with reactive prescribing at the bedside after symptoms have occurred. Outcomes of interest include patient and carer symptom ratings, patient-rated quality of life and healthcare use.

Appendix Table

PICO question	P = Patients with any condition identified as potentially being in the last weeks of life and dying in their usual residence. I = • Anticipatory prescribing (Just in case boxes) with a generic list of medications • Anticipatory prescribing individualised to the person's expected symptoms. C = Reactive prescribing at the bed side after symptoms have occurred. O = Patient symptom ratings VAS, patient rated quality of life (EQ5D), carer satisfaction ratings VAS, healthcare utilisation: the number of prescribing undertaken in the final days of life, healthcare utilisation: hospital admissions in the last days of life.
Importance to patients or the population	Symptom control in the last days of life remains a challenge as highlighted in numerous recent reports. Anticipatory prescribing for symptoms that are likely to occur in the last days of life could help

	address this. However, there are numerous concerns from clinicians (as evidenced in the qualitative evidence report in this guideline) regarding prescribing these. Addressing uncertainties regarding anticipatory prescribing's effectiveness has the potential to improve the quality of life for patients and carers and reduce morbidity.
Relevance to NICE guidance	The topic of anticipatory prescribing was specifically included within the scope of the current last days of life guidance. There was no identified quantitative evidence on which to base recommendations on effectiveness.
Relevance to the NHS	Addressing this topic would potentially be of economic value in terms of reducing admissions in the final days due to poor symptom control. There are also clear implications for service delivery with scope to develop a uniform approach rather than current situation of numerous local or regional schemes.
National priorities	Anticipatory prescribing is highlighted in One chance to get it right. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/323188/One_chance_to_get_it_right.pdf
Current evidence base	There were no identified quantitative studies in the evidence review undertaken in this guideline.
Study design	A cluster randomised controlled trial would be the most appropriate study design. Different GP practices would be randomised to the 2 intervention arms or the comparison arm. Power calculations should be conducted to establish the required sample size of the trial. It is important that the study is adequately powered to detect a clinically important effect size.
Economic considerations	Providing anticipatory prescribing means incurring costs up front but with the potential to generate cost savings downstream by preventing unplanned healthcare admissions such as GP or hospital visits. However, if a lot of the medication remains unused then this represents a waste of NHS resources. Likewise as medication is more readily available it may be used more willingly in situations where it does not improve health outcomes which could be detrimental to health outcomes from the associated side effects but also generate wasted NHS resources. Quantifying these costs will help identify whether anticipatory prescribing is cost saving or if it at least generates higher outcomes at a cost-effective price. Therefore the outcomes from this research would justify the cost of research taking into account the size of the population this intervention affects.
Feasibility	The Committee recognise the difficulty in undertaking research in this group raised by the sensitive time point of study, but they noted that in other evidence reviews such as assisted hydration randomised trials were possible to undertake in this cohort of people. It would be necessary to be cognisant when undertaking recruitment of these participants of the need for a sensitive approach.
Equalities	Research would cover all disease groups and all people over 18 years rather than focussing on cancer like the majority of clinical evidence

	that is available in the last days of life.
Other comments	

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Appendix P: NICE technical team

Name	Role
Christine Carson	Guideline Lead
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Steven Barnes	Technical Lead
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