National Clinical Guideline Centre

FINAL

# Care of dying adults in the last days of life

## Care of dying adults in the last days of life

*Clinical guideline NG31*

*Methods, evidence and recommendations*

*16 December 2015*

*Final*

*Commissioned by the National Institute for Health and Care Excellence*

**Funding**
National Institute for Health and Care Excellence

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## Acknowledgements

The development of this guideline was greatly assisted by the following people:

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| Jill Cobb | NCGC, Information Scientist |
| Pamela Young | NIHR Evaluation Trials and Studies Coordinating Centre (NETSCC), Scientific adviser (Identification) |

# 1 Guideline summary

## 1.1 Full list of recommendations

This guideline applies to all adults who are potentially entering the last days of their lives in any setting that is covered by NHS services. It includes those who may be dying from chronic diseases, for example, cancer, heart or lung disease or dementia; and it also includes people who have deteriorated after an event such as a stroke, subarachnoid haemorrhage or myocardial infarction.

**Recognising when a person may be in the last days of life.**

1. If it is thought that a person may be entering the last days of life, gather and document information on:
    - the person's physiological, psychological, social and spiritual needs
    - current clinical signs and symptoms
    - medical history and the clinical context, including underlying diagnoses
    - the person's goals and wishes
    - the views of those important to the person about future care.
2. Assess for changes in signs and symptoms in the person and review any investigation results that have already been reported that may suggest a person is entering the last days of life. These changes include the following:
    - signs such as agitation, Cheyne–Stokes breathing, deterioration in level of consciousness, mottled skin, noisy respiratory secretions and progressive weight loss
    - symptoms such as increasing fatigue and loss of appetite
    - functional observations such as changes in communication, deteriorating mobility or performance status, or social withdrawal.
3. Be aware that improvement in signs and symptoms or functional observations could indicate that the person may be stabilising or recovering.
4. Avoid undertaking investigations that are unlikely to affect care in the last few days of life unless there is a clinical need to do so, for example, when a blood count could guide the use of platelet transfusion to avoid catastrophic bleeding.
5. Use the knowledge gained from the assessments and other information gathered from the multiprofessional team, the person and those important to them, to help determine whether the person is nearing death, deteriorating, stable or improving.
6. Monitor for further changes in the person at least every 24 hours and update the person's care plan.
7. Seek advice from colleagues with more experience of providing end of life care when there is a high level of uncertainty (for example, ambiguous or conflicting clinical signs or symptoms)about whether a person is entering the last days of life, may be stabilising or if there is potential for even temporary recovery.

**Communication**

8. Establish the communication needs and expectations of people who may be entering their last days of life, taking into account:
    - if they would like a person important to them to be present when making decisions about their care
    - their current level of understanding that they may be nearing death
    - their cognitive status and if they have any specific speech, language or other communication needs
    - how much information they would like to have about their prognosis
    - any cultural, religious, social or spiritual needs or preferences.
9. Identify the most appropriate available multiprofessional team member to explain the dying person's prognosis. Base this decision on the professional's:
    - competence and confidence
    - rapport with the person.
10. Discuss the dying person's prognosis with them (unless they do not wish to be informed) as soon as it is recognised that they may be entering the last days of life and include those important to them in the discussion if the dying person wishes.
11. Provide the dying person, and those important to them, with:
    - accurate information about their prognosis (unless they do not wish to be informed), explaining any uncertainty and how this will be managed, but avoiding false optimism
    - an opportunity to talk about any fears and anxieties, and to ask questions about their care in the last days of life
    - information about how to contact members of their care team
    - opportunities for further discussion with a member of their care team.
12. Explore with the dying person and those important to them:
    - whether the dying person has an advance statement or has stated preferences about their care in the last days of life (including any anticipatory prescribing decisions or an advance decision to refuse treatment or details of any legal lasting power of attorney for health and welfare)
    - whether the dying person has understood and can retain the information given about their prognosis.
13. Discuss the dying person's prognosis with other members of the multiprofessional care team, and ensure that this is documented in the dying person's record of care.

**Shared decision making**

14. Establish the level of involvement that the dying person wishes to have and is able to have in shared decision-making, and ensure that honesty and transparency are used when discussing the development and implementation of their care plan.
15. As part of any shared decision-making process take into account:

- whether the dying person has an advance statement or an advance decision to refuse treatment in place, or has provided details of any legal lasting power of attorney for health and welfare
- the person's current goals and wishes
- whether the dying person has any cultural, religious, social or spiritual preferences.

16. Identify a named lead healthcare professional, who is responsible for encouraging shared decision-making in the person's last days of life. The named healthcare professional should:
    - give information about how they can be contacted and contact details for relevant out-of-hours services to the dying person and those important to them
    - ensure that any agreed changes to the care plan are understood by the dying person, those important to them, and those involved in the dying person's care.

Providing individualised care

17. Establish as early as possible the resources needed for the dying person (for example, the delivery of meals, equipment, care at night, volunteer support or assistance from an organisation) and their availability.
18. In discussion with the dying person, those important to them and the multiprofessional team, create an individualised care plan. The plan should include the dying person's:
    - personal goals and wishes
    - preferred care setting
    - current and anticipated care needs including:

    -preferences for symptom management

    -needs for care after death, if any are specified

    - resource needs.
19. Record individualised care plan discussions and decisions in the dying person's record of care and share the care plan with the dying person, those important to them and all members of the multiprofessional care team.
20. Continue to explore the understanding and wishes of the dying person and those important to them, and update the care plan as needed. Recognise that the dying person's ability and desire to be involved in making decisions about their care may change as their condition deteriorates or as they accept their prognosis.
21. While it is normally possible and desirable to meet the wishes of a dying person, when this is not possible explain the reason why to the dying person and those important to them.
22. Ensure that shared decision-making can be supported by experienced staff at all times. Seek further specialist advice if additional support is needed.

**Maintaining hydration**

23. Support the dying person to drink if they wish to and are able to. Check for any difficulties, such as swallowing problems or risk of aspiration. Discuss the

risks and benefits of continuing to drink, with the dying person, and those involved in the dying person's care.

24. Offer frequent care of the mouth and lips to the dying person, and include the management of dry mouth in their care plan, if needed. Offer the person the following, as needed:
    - help with cleaning their teeth or dentures, if they would like
    - frequent sips of fluid.
25. Encourage people important to the dying person to help with mouth and lip care or giving drinks, if they wish to. Provide any necessary aids and give them advice on giving drinks safely.
26. Assess, preferably daily, the dying person's hydration status, and review the possible need for starting clinically assisted hydration, respecting the person's wishes and preferences.
27. Discuss the risks and benefits of clinically assisted hydration with the dying person and those important to them. Advise them that, for someone who is in the last days of life:
    - clinically assisted hydration may relieve distressing symptoms or signs related to dehydration, but may cause other problems (see recommendation 31)
    - it is uncertain if giving clinically assisted hydration will prolong life or extend the dying process
    - it is uncertain if not giving clinically assisted hydration will hasten death.
28. Ensure that any concerns raised by the dying person or those important to them are addressed before starting clinically assisted hydration.
29. When considering clinically assisted hydration for a dying person, use an individualised approach and take into account:
    - whether they have expressed a preference for or against clinically assisted hydration, or have any cultural, spiritual or religious beliefs that might affect this documented in an advance statement or an advance decision to refuse treatment
    - their level of consciousness
    - any swallowing difficulties
    - their level of thirst
    - the risk of pulmonary oedema
    - whether even temporary recovery is possible.
30. Consider a therapeutic trial of clinically assisted hydration if the person has distressing symptoms or signs that could be associated with dehydration, such as thirst or delirium, and oral hydration is inadequate.
31. For people being started on clinically assisted hydration:
    - Monitor at least every 12 hours for changes in the symptoms or signs of dehydration, and for any evidence of benefit or harm.
    - Continue with clinically assisted hydration if there are signs of clinical benefit.

- Reduce or stop clinically assisted hydration if there are signs of possible harm to the dying person, such as fluid overload, or if they no longer want it.

32. For people already dependent on clinically assisted hydration (enteral or parenteral) before the last days of life:
    - Review the risks and benefits of continuing clinically assisted hydration with the person and those important to them.
    - Consider whether to continue, reduce or stop clinically assisted hydration as the person nears death.

**Pharmacological interventions**

**Managing pain**

33. Consider non-pharmacological management of pain in a person in the last days of life.
34. Be aware that not all people in the last days of life experience pain. If pain is identified, manage it promptly and effectively, and treat any reversible causes of pain, such as urinary retention.
35. Assess the dying person's level of pain and assess for all possible causes when making prescribing decisions for managing pain.
36. Follow the principles of pain management used at other times when caring for people in the last days of life, for example, matching the medicine to the severity of pain and, when possible, using the dying person's preferences for how it is given.
37. For a person who is unable to effectively explain that they are in pain, for example someone with dementia or learning disabilities, use a validated behavioural pain assessment to inform their pain management.

**Managing breathlessness**

38. Identify and treat reversible causes of breathlessness in the dying person, for example pulmonary oedema or pleural effusion.
39. Consider non-pharmacological management of breathlessness in a person in the last days of life. Do not routinely start oxygen to manage breathlessness. Only offer oxygen therapy to people known or clinically suspected to have symptomatic hypoxaemia.
40. Consider managing breathlessness with:
    - an opioid[a] or
    - a benzodiazepine[a] or
    - a combination of an opioid[a] and benzodiazepine[a].

**Managing nausea and vomiting**

41. Assess for likely causes of nausea or vomiting in the dying person. These may include:
    - certain medicines that can cause or contribute to nausea and vomiting

[a] At the time of publication (December 2015), this medication did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

- recent chemotherapy or radiotherapy
- psychological causes
- biochemical causes, for example hypercalcaemia
- raised intracranial pressure
- gastrointestinal motility disorder
- ileus or bowel obstruction.

42. Discuss the options for treating nausea and vomiting with the dying person and those important to them.
43. Consider non-pharmacological methods for treating nausea and vomiting in a person in the last days of life.
44. When choosing medicines to manage nausea or vomiting in a person in the last days of life, take into account:
    - the likely cause and if it is reversible
    - the side effects, including sedative effects, of the medicine
    - other symptoms the person has
    - the desired balancing of effects when managing other symptoms
    - compatibility and drug interactions with other medicines the person is taking.
45. For people in the last days of life with obstructive bowel disorders who have nausea or vomiting, consider:
    - hyoscine butylbromide[b] as the first-line pharmacological treatment
    - octreotide[b] if the symptoms do not improve within 24 hours of starting treatment with hyoscine butylbromide[b].

**Managing anxiety, delirium and agitation**

46. Explore the possible causes of anxiety or delirium, with or without agitation, with the dying person and those important to them. Be aware that agitation in isolation is sometimes associated with other unrelieved symptoms or bodily needs for example, unrelieved pain or a full bladder or rectum.
47. Consider non-pharmacological management of agitation, anxiety and delirium in a person in the last days of life.
48. Treat any reversible causes of agitation, anxiety or delirium, for example, psychological causes or certain metabolic disorders (for example renal failure or hyponatraemia).
49. Consider a trial of a benzodiazepine to manage anxiety or agitation.
50. Consider a trial of an antipsychotic medicine to manage delirium or agitation.
51. Seek specialist advice if the diagnosis of agitation or delirium is uncertain, if the agitation or delirium does not respond to antipsychotic treatment or if treatment causes unwanted sedation.

**Managing noisy respiratory secretions**

[b] At the time of publication (December 2015), this medication did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

52. Assess for the likely causes of noisy respiratory secretions in people in the last days of life. Establish whether the noise has an impact on the dying person or those important to them. Reassure them that, although the noise can be distressing, it is unlikely to cause discomfort. Be prepared to talk about any fears or concerns they may have.

53. Consider non-pharmacological measures to manage noisy respiratory or pharyngeal secretions, to reduce any distress in people at the end of life.

54. Consider a trial of medicine to treat noisy respiratory secretions if they are causing distress to the dying person. Tailor treatment to the dying person's individual needs or circumstances, using 1 of the following drugs:

- atropine[c] or
- glycopyrronium bromide[c] or
- hyoscine butylbromide[c] or
- hyoscine hydrobromide[c].

55. When giving medicine for noisy respiratory secretions:

- Monitor for improvements, preferably every 4 hours, but at least every 12 hours.
- Monitor regularly for side effects, particularly delirium, agitation or excessive sedation when using atropine or hyoscine hydrobromide.
- Treat side effects, such as dry mouth, delirium or sedation (see recommendations 24, 66 and 46).

56. Consider changing or stopping medicines if noisy respiratory secretions continue and are still causing distress after 12 hours (medicines may take up to 12 hours to become effective).

57. Consider changing or stopping medicines if unacceptable side effects, such as dry mouth, urinary retention, delirium, agitation and unwanted levels of sedation, persist.

**General pharmacological considerations**

58. When it is recognised that a person may be entering the last days of life, review their current medicines and, after discussion and agreement with the dying person and those important to them (as appropriate), stop any previously prescribed medicines that are not providing symptomatic benefit or that may cause harm.

59. When involving the dying person and those important to them in making decisions about symptom control in the last days of life:

- Use the dying person's individualised care plan to help decide which medicines are clinically appropriate.
- Discuss the benefits and harms of any medicines offered.

60. When considering medicines for symptom control, take into account:

- the likely cause of the symptom

[c] At the time of publication (December 2015), this medication did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

- the dying person's preferences alongside the benefits and harms of the medicine
- any individual or cultural views that might affect their choice
- any other medicines being taken to manage symptoms
- any risks of the medicine that could affect prescribing decisions, for example prescribing cyclizine to manage nausea and vomiting may exacerbate heart failure.

61. Decide on the most effective route for administering medicines in the last days of life tailored to the dying person's condition, their ability to swallow safely and their preferences.

62. Consider prescribing different routes of administering medicine if the dying person is unable to take or tolerate oral medicines. Avoid giving intramuscular injections and give either subcutaneous or intravenous injections.

63. Consider using a syringe pump to deliver medicines for continuous symptom control if more than 2 or 3 doses of any 'as required' medicines have been given within 24 hours.

64. For people starting treatment who have not previously been given medicines for symptom management, start with the lowest effective dose and titrate as clinically indicated.

65. Regularly reassess, at least daily, the dying person's symptoms during treatment to inform appropriate titration of medicine.

66. Seek specialist palliative care advice if the dying person's symptoms do not improve promptly with treatment or if there are undesirable side effects, such as unwanted sedation.

**Anticipatory prescribing**

67. Use an individualised approach to prescribing anticipatory medicines for people who are likely to need symptom control in the last days of life. Specify the indications for use and the dosage of any medicines prescribed.

68. Assess what medicines the person might need to manage symptoms likely to occur during their last days of life (such as agitation, anxiety, breathlessness, nausea and vomiting, noisy respiratory secretions and pain). Discuss any prescribing needs with the dying person, those important to them and the multiprofessional team.

69. Ensure that suitable anticipatory medicines and routes are prescribed as early as possible. Review these medicines as the dying person's needs change.

70. When deciding which anticipatory medicines to offer take into account:

- the likelihood of specific symptoms occurring
- the benefits and harms of prescribing or administering medicines
- the benefits and harms of not prescribing or administering medicines
- the possible risk of the person suddenly deteriorating (for example, catastrophic haemorrhage or seizures) for which urgent symptom control may be needed
- the place of care and the time it would take to obtain medicines.

71. Before anticipatory medicines are administered, review the dying person's individual symptoms and adjust the individualised care plan and prescriptions as necessary.

72. If anticipatory medicines are administered:

- Monitor for benefits and any side effects at least daily, and give feedback to the lead healthcare professional.
- Adjust the individualised care plan and prescription as necessary.

## 1.2 Key research recommendation

1. **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?**

   - 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.

2. **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.

3. **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?**

- 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.

4. **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?**

- 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.

# 2 Introduction

Death is inevitable with many illnesses, but its predictability and the healthcare needs of dying people vary widely because of numerous underlying conditions, the symptoms associated with them, the speed of deterioration and the wishes of the person and those important to them. British society places a high value on the individual's choices and these are especially relevant at the end of life. There is a notable tradition of good end of life care, as demonstrated by the British hospice movement, which is respected worldwide.

However, without an evidence-based approach to the care of dying people, there is a danger of placing tradition and familiar policies before meeting the needs of individuals and families. The Liverpool Care Pathway (LCP) for the Care of the Dying Adult, and its numerous local derivatives were widely adopted in the NHS as well as in UK hospices until 2014. Although it was designed to bring values of 'good' end of life care from the hospice movement to mainstream hospitals and elsewhere, the LCP met with increasingly loud opposition from the public, professionals and the media. There were 3 main areas of concern:

- recognising that a person was dying was not always supported by an experienced clinician and not reliably reviewed, even if the person may have had potential to improve
- the dying person may have been unduly sedated as a result of injudiciously prescribed symptom control medicines
- the perception that hydration and some essential medicines may have been withheld or withdrawn, resulting in a negative effect on the dying person.

These were not necessarily a direct consequence of following the LCP, but often happened because of poor or indiscriminate implementation and a lack of staff training and supervision.

The Government's independent review of the LCP led by Neuberger (More Care Less Pathway, 2013)[30] considered these and other shortcomings and called for its withdrawal and replacement with an evidence-based and individualised care plan approach. The Leadership Alliance, which was set up following the Neuberger report, detailed the changes that needed to be made to improve end of life care, within 5 broad principles (One Chance To Get It Right, 2014).[56] A parallel set of shortcomings in the Mid-Staffordshire hospital led to another scathing independent report,[36] which highlighted several examples of poor care, particularly in the care of the elderly, leading to lack of dignity and respect for dying people and those important to them.

The need for this guideline has arisen from the recent history encapsulated above. It provides an evidence-based set of recommendations for the clinical care of the dying adult, throughout the NHS. It is focused on the care needed when a person is judged by the multiprofessional clinical team to be within a few days of death. This is different from other important contemporaneous NHS initiatives – also labelled 'end of life care' – which are aimed at improving care for those in the last year or so of a chronic condition.

It aims to provide guidance to health and care professionals to enable them to better recognise when a person is dying, and how to communicate and share decisions respectfully with the dying person and those important to them. Additionally, guidance is provided on how best to manage difficult symptoms in order to maintain comfort and dignity without causing unacceptable side-effects.

It is aimed at all health and care professionals who might be involved in the care of a person who is dying in any NHS setting. It is specifically targeted towards non-specialists (those working in primary care or in care homes) and to those working in a wide range of medical specialties in which people may die, but who do not have specialist level training in end of life care. For those dying at home or in prison it is likely that care will be provided at end of life by NHS providers and so

recommendations contained in this guideline apply. It will also be of value to provide a baseline for establishing standards of care in settings which specialise in the care of dying people, such as non-NHS palliative care units and hospices.

The process and timescale of dying varies widely, mostly because of the underlying diseases responsible, but also the person's robustness or frailty. Some people can remain ambulant and largely self-caring, and continue to take oral medication as well as drink and eat right up to the point of dying. Others may die suddenly or unexpectedly following unintentional trauma. Some may never experience any of the symptoms addressed in the guideline. Others, such as those with progressive neurological disorders following stroke or with dementia, may spend several weeks or months in a gradual decline. Although the recommendations cover those who are thought to be entering the last few days of life, it is acknowledged that for the latter group, many of the principles of communication, shared decision-making and of pharmacological care can be initiated long before that time.

It is acknowledged that, for some people who are entering the last days of life, mental capacity to understand what is being communicated with them and their ability to engage in shared decision-making may be limited. This could be from a temporary or fluctuating state, for example, delirium associated with infection or a biochemical upset. For others it could be a permanent loss of capacity from dementia or other similar conditions. The guideline complements, but does not replace the clinician's duties with respect to ensuring compliance with the Mental Capacity Act.[4] It also makes clear the duties of the multiprofessional team regarding communication and shared decision making involving those important to the dying person as appropriate.

The specific ordering of symptoms within chapters does not reflect the absolute prevalence or importance of these issues; nor do they represent the strength of the evidence base for them. Rather, they represent the Committee's view of the most distressing, to possibly the least distressing symptoms or signs for the dying person. Thus the last in this series – noisy respiratory secretions – are usually not at all distressing for the dying person, who is probably unresponsive by this stage, but may be upsetting for those important to them and even to healthcare staff caring for them.

This guideline applies to dying people aged 18 or older. It is acknowledged that a parallel guideline is being developed by NICE to cover the end of life care for infants, children and young people.

This guideline covers recognising dying, communication and shared decision-making and only the clinical aspects of symptom management. We have not made recommendations about how services should be configured to deliver these aspects of care. An update of the 2004 guidance on Supportive and Palliative Care for Adults with Cancer will be started in 2016, and this will not only cover the service delivery aspects of the current guideline, but will also extend beyond the cancer focus.

# 3 Development of the guideline

## 3.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of healthcare. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patients and health professionals.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health.
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guideline Centre (NCGC).
- The NCGC establishes a Guideline Committee.
- A draft guideline is produced after the Committee assesses the available evidence and makes recommendations.
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the ‘full guideline’ contains all the recommendations, plus details of the methods used and the underpinning evidence
- the ‘NICE guideline’ lists the recommendations
- ‘information for the public’ is written using suitable language for people without specialist medical knowledge
- NICE Pathways brings together all connected NICE guidance.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk.

## 3.2 Remit

National Health Service England (NHSE) asked NICE ‘to develop a guideline on the care of the dying adult’. NICE, in discussion with the NHSE agreed that the remit could be covered by two guidelines. The service delivery aspect of the guideline will be covered by improving supportive and palliative care (update). They commissioned the NCGC to produce the guideline.

## 3.3 Who developed this guideline?

A multiprofessional Guideline Committee comprising health professionals and researchers as well as lay members developed this guideline (see the list of Guideline Committee members and the acknowledgements).

The National Institute for Health and Care Excellence (NICE) funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The Committee was convened by the NCGC and chaired by Sam Ahmedzai in accordance with guidance from NICE.

The Committee met every 5 – 6 weeks during the development of the guideline. At the start of the guideline development process all Committee members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry, in accordance with the NICE guidelines manual 2012.[78] At all subsequent Committee meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the Committee.

### 3.3.1 What this guideline covers

The population covered by this guideline includes adults (aged 18 years and over) in whom death is expected within a few days. Key clinical issues covered include:

- 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 person may be improving and recovering, as well as how uncertainties regarding both situations are managed and communicated.
- Shared decision-making with the person and carers about clinical care in the last days of life.
- Anticipatory prescribing in the last days of life.
- Clinical effectiveness of clinically assisted hydration.
- Pharmacological management of pain, anxiety, breathlessness, terminal agitation, nausea, vomiting and respiratory secretions.

For further details please refer to the scope in Appendix A and the review questions in sections: 5 to 10.

### 3.3.2 What this guideline does not cover

Populations not covered in this guideline include infants, children and young people aged under 18 years and any young people over the age of 18 years who are cared for by paediatric services.

Clinical areas not included are:

- Service delivery (for example out-of-hours availability of staff or how services are structured).
- Palliative care or end of life care before the last few days or hours of life.
- Care after death (care of the body, certification and bereavement).

- Case notes review for recognition of dying.
- The usefulness of laboratory and other biological evidence.
- Multi-professional team structure.
- Clinically assisted nutrition.

### 3.3.3 Relationships between the guideline and other NICE guidance

**Published guidance: general**

- Medicines adherence (2009) NICE guideline CG76

**Published guidance: other**

- Bladder cancer. NICE guideline. NICE clinical guideline NG2. (2015).
- Medicines Optimisation. NICE clinical guideline NG5. (2015)
- Multiple sclerosis. NICE clinical guideline 186. (2014).
- 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).
- Delirium. NICE clinical guideline 103 (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).

**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).

**Under development**

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

- Transition between inpatient hospital settings and community or care home settings for adults with social care needs. Social Care guideline. Publication expected November 2015.
- Motor neurone disease. NICE guideline. Publication expected February 2016.
- Transition from children's to adults' services. NICE guideline. Publication expected February 2016.
- Major trauma. NICE 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 guideline. Publication expected November 2016.
- End of life care for infants, children and young people. Publication date to be confirmed.

# 4 Methods

This chapter sets out in detail the methods used to review the evidence and to generate the recommendations that are presented in subsequent chapters. This guidance was developed in accordance with the methods outlined in the NICE guidelines manual, 2014 versions.[79] The Committee recruitment and management of conflicts of interest were handled in accordance with the methods outlined in the NICE guidelines manual 2012.[78]

## 4.1 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews; in a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy; and using population, presence or absence of factors under investigation (for example, prognostic factors) and outcomes for prognostic reviews.

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the Committee. The review questions were drafted by the NCGC technical team and refined and validated by the Committee. The questions were based on the key clinical areas identified in the scope (Appendix A).

As part of the scope a total of 11 questions were identified. During protocol development with the Committee, recognising dying was divided to include both a quantitative and a qualitative component which were then integrated into a framework.[106]

The Committee also decided that pharmacological symptom management of pain, anxiety, breathlessness, agitation and delirium should be combined into 1 question. The rationale for this was that there was likely to be an overlap in the medications and in symptom outcome reporting.

The Committee decided to include both qualitative and quantitative evidence for the topic of anticipatory prescribing (comparing to prescribing at the bedside). The quantitative focus was added to the review topic to identify evidence of data that could inform the associated costs of anticipatory prescribing which would not be possible from qualitative data.

This led to a total of 10 review questions.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

**Table 1: Review questions, question types and outcomes**

| Chapter | Type of review | Review questions | Outcomes |
|---|---|---|---|
| Chapter 5 | Mixed qualitative and quantitative (prognostic / diagnostic) review – combined into an integrative review with an | 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? | Critical outcomes for the quantitative review:<br>• Death within a few days.<br>Qualitative review:<br>• Thematic analysis regarding symptoms and dealing with uncertainties.<br>Framework:<br>• Theoretic map integrating quantitative and qualitative findings. |

| Chapter | Type of review | Review questions | Outcomes |
|---|---|---|---|
| | overarching framework | | |
| Chapter 6, Section 6.2 | Qualitative | 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? | Themes will be identified from the literature found. |
| Chapter 7, Section 7.1 | Qualitative | What are the facilitators and barriers to the multiprofessional 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? | Themes will be identified from the literature found. |
| Chapter 8 | Intervention | For people in the last days of life is clinically assisted hydration effective compared to oral hydration or placebo? | Critical:<br>• Quality of Life (comfort), pre and post intervention, using validated scales.<br>• Symptom improvement on rating scales pre and post intervention.<br>Important:<br>• Symptoms related to dehydration including fatigue, delirium, sedation, myoclonus.<br>• Hydration status using both objective and subjective measures ( for example hydration of oral mucosa, measuring vital signs and skin turgor)<br>• Adverse events both procedural (phlebitis, or line infections for example) and from positive fluid balance (for example, pleural effusions)<br>• Subjective ratings from informal carers on quality of care received. |
| Chapter 9, Section 9.1 | Intervention | For people in the last days of life, which pharmacological agents are most effective in relieving troublesome respiratory secretions and what degree of sedation do they cause? | Critical:<br>• Subjective or objective improvement in respiratory secretions (patient-rated, clinician-rated, carer-rated).<br>• Sedation (either patient-rated, clinician-rated, carer-rated).<br>• Quality of life (comfort, either patient-rated, clinician-rated, carer-rated).<br>Important:<br>• Frequency of adverse events - |

| Chapter | Type of review | Review questions | Outcomes |
|---|---|---|---|
| | | | paradoxical agitation, failure to expectorate, dry mouth.<br>• Subjective ratings from a person in distress related to noisy breathing /respiratory secretions.<br>• Subjective ratings from informal carers' on distress relating to noisy breathing/respiratory secretions. |
| Chapter 9, Section 9.3 | Intervention | 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? | Critical:<br>• Subjective or objective improvement in specific symptoms (patient-rated, clinician-rated, carer-rated).<br>• Sedation (either patient-rated, clinician-rated, carer-rated)<br>• Quality of life (comfort, either patient-rated, clinician-rated, carer-rated)<br>Important:<br>• Adverse effects of treatment:<br>○ For antipsychotics, benzodiazepines, antihistamines and opioids; this may include sedation.<br>○ For benzodiazepines, this may include hypotension respiratory depression or increased restlessness, confusion, ataxia and falls.<br>○ For antipsychotics, this may include extrapyramidal side effects, akathisia (restlessness) neuroleptic malignant syndrome, urinary retention and constipation.<br>○ For opioids, this may include respiratory depression, nausea and vomiting, drowsiness, itching dry mouth and constipation.<br>○ For steroids, this may include a change in mental state or gastritis.<br>○ For antihistamines this may include urinary retention or dizziness.<br>• Length of survival. |
| Chapter 9, Section 9.2 | Intervention | For people in the last days of life, which pharmacological agents are most effective in relieving nausea and vomiting and what degree of | Critical:<br>• Subjective or objective improvement in nausea and |

| Chapter | Type of review | Review questions | Outcomes |
|---|---|---|---|
| | | sedation do they cause? | vomiting control<br>• Sedation (either patient-rated, clinician-rated, carer-rated)<br>• Quality of life (comfort, either patient-rated, clinician-rated, carer-rated)<br>Important:<br>• Frequency of adverse events<br>• Subjective ratings from informal carers' on distress. |
| Chapter 10 | Qualitative and intervention | • What are the experiences, opinions and attitudes of healthcare professionals, the dying person and those important to them regarding access to anticipatory prescribing?<br>• How effective is anticipatory prescribing at improving comfort in adults in the last days of life compared with prescribing at the bed side? | Themes will be identified from the literature found.<br>Intervention outcomes:<br>Critical<br>• Quality of life (comfort as rated by the dying person or those important to them or health care professional)<br>• Control of specific symptoms (agitation, terminal restlessness, breathlessness, pain, nausea and vomiting, respiratory secretions and anxiety).<br>Important:<br>• Subjective ratings from informal carers on quality of care received.<br>• The amount of medication prescribed that is administered.<br>• Incidence of prescribed medication misused<br>Admissions to hospitals for symptom management. |

## 4.2 Searching for evidence

### 4.2.1 Clinical literature search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE guidelines manual.[78,79] Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English. All searches were conducted in MEDLINE, Embase, and The Cochrane Library. Additional subject specific databases were used for some questions: such as PsychINFO and CINAHL. Searches were not re-run prior to final submission because this guideline is classified as a short guideline.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking Committee members to highlight

any additional studies. The questions, the study types applied, the databases searched and the dates or years covered can be found in Appendix G.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below from organisations relevant to the topic. Searching for unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov)
- National Institute for Health and Care Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov)
- NHS Evidence Search (www.evidence.nhs.uk).

### 4.2.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to the dying adult in the NHS Economic Evaluation Database (NHS EED), the Health Technology Assessment database (HTA) and the Health Economic Evaluations Database (HEED) with no date restrictions. Additionally, the search was run on MEDLINE and Embase from 2013, using a specific economic filter, to ensure recent publications that had not yet been indexed by the economic databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English.

The health economic search strategies are included in Appendix G. Searches were not re-run prior to final submission because this guideline is classified as a short guideline.

### 4.2.3 Evidence of effectiveness

The evidence was reviewed following the steps shown schematically in Figure 1

Potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.

- Full papers were reviewed against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population (review protocols are included in Appendix C).
- Relevant studies were critically appraised using the appropriate checklist as specified in the NICE guidelines manual.[79]
- Key information was extracted on the study's methods, according to the factors specified in the protocols and results. These were presented in summary tables (in each review chapter) and evidence tables (in Appendix H).
- Summaries of evidence were generated by outcome (included in the relevant review chapters) and were presented in Committee meetings:
    - Randomised studies: data were meta-analysed where appropriate and reported in GRADE profiles (for intervention reviews).
    - Observational studies: data were presented as a range of values in GRADE profiles.

- Prognostic studies: data were presented as reported by the authors, as adjusted odds ratios, risk ratios or hazard ratios along with the 95% confidence intervals. A range of values, usually in terms of the relative effect.
- Diagnostic studies were presented as measures of diagnostic test accuracy (sensitivity, specificity and area under the curve).
- Qualitative studies: each study was summarised by theme and meta-synthesis was carried out where appropriate to identify an overarching framework of themes and subthemes.

A 20% sample of each of the above stages of the reviewing process was quality assured by a second reviewer to eliminate any potential of reviewer bias or error.

**Figure 1: Step-by-step process of review of evidence in the guideline**


### 4.2.4 Inclusion and exclusion criteria

The inclusion and exclusion of studies was based on the review protocols, which can be found in Appendix C. Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix L. The Committee was consulted about any uncertainty regarding inclusion or exclusion.

There are particular inclusion and exclusion criteria to be highlighted here for the following areas of the scope:

#### 4.2.4.1 Guideline population

The guideline population was defined to be adults (over 18) in the last days of life, defined as the last 2 to 3 days of life. There was complete agreement in the Committee that in relation to any review of evidence, this should correspond to a population of adults likely to die within 14 days (which has been classified by the Department of Health's review[30] of the Liverpool Care Pathway as 'last days'). This meant that any study with groups of people who have a prognosis of less than 14 days or where qualitative research was aimed at covering this time period were classed as a direct study population. It was recognised that there would be some uncertainty around prognosis for this timeframe and with evidence anticipated to be sparse, it was decided that groups of people with a prognosis of up to 30 days could be considered as an indirect population. Studies that included groups of people described as dying within a timeframe longer than 1 month were excluded from the outset.

#### 4.2.4.2 Recognising dying

Delphi consensus studies were included for the topic of 'recognising dying' (chapter 6) The Committee considered Delphi consensus studies applicable for this topic as they provide useful consensus information to support the extracted themes. Furthermore, the quantitative section of this review aimed to identify pre-specified signs and symptoms that were independently related to recognising that a person is in the last days of life, that is, independent of other characteristics. Therefore the focus of the evidence was on studies using multivariable analysis.

In accordance with the scope of the guideline, the role of laboratory and biological evidence was not directly included in this review. This meant that direct search terms for all possible biological tests or markers added were not added to the database search. However, when tests were considered in combination with signs or symptoms to identify a possible combination of clinical presentations that improves the recognition of the last days of life or signs of recovery, then this was included as a surrogate sign or symptom (such as kidney function test results).

#### 4.2.4.3 Communication, shared decision making and anticipatory prescribing

Delphi and other descriptive surveys (such as frequency of people who responding to closed-ended questions) were not included in the other qualitative reviews (communication, shared decision making and anticipatory prescribing). The Committee considered qualitative data such as studies using interviews, focus groups, or surveys with rich qualitative open-ended options the most appropriate study design. The shared decision making review focussed on evidence from different perspectives (that is, healthcare professionals, the person who is dying, or those important to them) on the barriers and facilitators to shared decision making. There was a large evidence base on this topic but mainly from a healthcare professional perspective; as such the evidence base was restricted to UK studies only. However, there was only 1 UK study on the family's perspective on shared decision making, hence studies from other countries were also included (this issue is re-visited in the section 4.2.5.5 on combining evidence from qualitative studies).

#### 4.2.4.4 Intervention reviews (clinically assisted hydration and pharmacological symptom management)

Randomised controlled trials (RCTs), non-randomised trials, and observational studies (including diagnostic or prognostic studies) were included in the evidence reviews, according to the review protocols. For the intervention reviews, both randomised and non-randomised comparative studies were included to provide the most informative evidence base possible for the Committee decision making.

#### 4.2.4.5 Other general study type inclusions or exclusions

Conference abstracts were not automatically excluded from the review but were initially assessed against the inclusion criteria and then further processed only if no other full publication was available for that review question, in which case the authors of the selected abstracts were contacted for further information. None of the reviews included evidence from conference abstracts.

Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

The review protocols are presented in Appendix C.

### 4.2.5 Methods of combining clinical studies

#### 4.2.5.1 Data synthesis for intervention reviews (maintaining hydration and pharmacological symptom management – see chapters 8 and 9.)

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes, such as rate of adverse events or rate of people with symptom improvements.

For continuous outcomes, measures of central tendency (mean) and variation (standard deviation) were required for meta-analysis. Data for continuous outcomes (such as number of episodes of vomiting) were analysed using an inverse variance method for pooling weighted mean differences and, where the studies had different scales, standardised mean differences were used. A generic inverse variance option in RevMan5 was used if any studies reported solely the summary statistics and 95% confidence interval (95% CI) or standard error; this included any hazard ratios reported. However, in cases where standard deviations were not reported per intervention group, the standard error (SE) for the mean difference was calculated from other reported statistics (p values or 95% CIs); meta-analysis was then undertaken for the mean difference and SE using the generic inverse variance method in RevMan5. When the only evidence was based on studies that summarised results by presenting medians (and interquartile ranges), or only p values were given, this information was assessed in terms of the study's sample size and was included in the GRADE tables without calculating the relative or absolute effects. Consequently, aspects of quality assessment such as imprecision of effect could not be assessed for evidence of this type.

Where reported, time-to-event data were presented as a hazard ratio.

Stratified analyses were predefined for some review questions at the protocol stage when the Committee identified that these strata are different in terms of biological and clinical characteristics and the interventions were expected to have a different effect. For example, in the combined review on pharmacological symptom management for pain, anxiety, breathlessness, and agitation and delirium, people with reported individual symptoms were classified as strata because the Committee wanted to ideally make recommendations about the effectiveness of pharmacological treatments for specific symptoms.

Statistical heterogeneity was assessed by visually examining the forest plots, and by considering the chi-squared test for significance at p less than0.1 or an I-squared inconsistency statistic (with an I-squared value of more than 50% indicating considerable heterogeneity). Where considerable heterogeneity was present, we carried out predefined subgroup analyses. For instance, in the pharmacological management of nausea and vomiting, causes leading to the symptom would be a subgroup. The guideline group also considered route of administration, delivery system, and drug

class were also possible reasons for heterogeneity in results. Sensitivity analysis based on the quality of studies was also carried out, eliminating studies at overall high risk of bias (randomisation, allocation concealment and blinding, missing outcome data).

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity then a random-effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

The means and standard deviations of continuous outcomes were required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p values or 95% CIs were reported and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in RevMan5.

For interpretation of the binary outcome results, differences in the absolute event rate were calculated using the GRADEpro software, for the median event rate across the control arms of the individual studies in the meta-analysis. Absolute risk differences were presented in the GRADE profiles and in clinical summary of findings tables, for discussion with the Committee.

For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

#### 4.2.5.2 Data synthesis for prognostic factor reviews (recognising dying quantitative section – see chapter 5)

Signs and symptoms that indicate someone is in the last days of life could be construed as a characteristic that predicts death occurring in the last days of life. This would be classified as a prognostic factor. In this respect odds ratios (ORs), risk ratios (RRs) or hazard ratios (HRs), with their 95% confidence intervals (95% CIs) for the effect of the pre-specified prognostic factors were extracted from the papers when reported. Evidence would come from observational studies because signs and symptoms that may indicate that someone is in the last days of life are not factors that could ever be randomised. For this topic we looked for studies that took into account possible key confounders as reported in multivariable analyses. The reported measures would therefore be adjusted to take into account other characteristics less likely to be actual signs and symptoms of being in the last days of life. The studies did not adjust for this in a pre-specified manner, but used statistical methods that included variables that were likely signs and symptoms related to dying and modelled them using statistical methods (such as multivariable logistic regressions) which would then indicate which characteristics were the most likely independent prognostic factors rather than a factor only spuriously related. Data were not combined in meta-analyses for prognostic studies.

#### 4.2.5.3 Data synthesis for diagnostic test accuracy reviews (recognising dying quantitative section – see chapter 5)

**Data and outcomes**

Recognising dying could also be viewed akin to a diagnostic process in which you either display a sign or not and later identify people with or without the sign who have died in the next days. For this part it was anticipated that studies would report results indicating that the person had a particular sign as assessed by a value above a threshold value or could have a test along a continuously measured characteristic (such as kidney function tests for renal signs or symptoms). There are a number of diagnostic test accuracy measures. Area under the Receiver Operating Characteristics (AUC of a ROC) curve shows true positive rate (sensitivity) as a function of false positive rate (1 minus specificity). Sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood

ratio would be reported. The threshold of a diagnostic test is defined as the value at which the test can best differentiate between those with and without the target condition (for instance a particular serum creatinine value) and, in practice, it varies amongst studies. For this particular question specificity was regarded as particularly important. When specificity is high, a positive test rules in the diagnosis and when sensitivity is high, a negative test rules out the diagnosis – researchers have created the mnemonic SoPin and SnNout for this[86] In other words in the case of high specificity with low sensitivity someone who has this sign or symptom (that is, akin to testing positive) would be likely to die within the next few days whereas for those who do not have the sign or symptom (akin to having a negative test) we are uncertain about when they may die. Sensitivity (ruling out), was also recognised as being important in order not to miss people who may be dying in the next few days.

#### 4.2.5.4 Data synthesis

Diagnostic paired sensitivity-specificity forest plots would usually be produced for each sign or symptom, using RevMan5. In order to do this, 2×2 tables (the number of true positives, false positives, true negatives and false negatives) would be extracted.

However, the data that was identified in the 'recognising dying' chapter did not allow for direct extraction of 2x2 tables, because only summary data were presented (sensitivity and specificity with 95% confidence intervals).

Area under the ROC curve (AUC) data for continuous test results were given as AUC values with 95% confidence intervals. The accuracy of the test depends on how well the test separates the group being tested into those with and without the condition in question. The Committee agreed on the following criteria for AUC:

- ≤0.50: no better than chance
- 0.50–0.60: very poor
- 0.61–0.70: poor
- 0.71–0.80: moderate
- 0.81–0.92: good
- 0.91–1.00: excellent or perfect test.

Diagnostic meta-analysis could not be carried out because 2x2 data could not be extracted.

#### 4.2.5.5 Data synthesis for qualitative reviews

Where possible a meta-synthesis was conducted to combine qualitative study results. The main aim of the synthesis of qualitative data was a description of the topics that may influence the experience of the person who is dying, those people important to them and healthcare professionals involved in their care, rather than build new theories or reconceptualise the topic under review. Whenever studies identified a qualitative theme, this was extracted and the main characteristics were summarised. When all themes were extracted from studies, common concepts were categorised and tabulated. This included information on how many studies had contributed to an identified overarching theme. In qualitative synthesis the frequency of themes across studies is not necessarily an indicator of the importance of a theme. The aim of qualitative research is to identify new perspectives on a particular topic. Hence study type and population in qualitative research can differ widely meaning that themes that may only be identified by 1 or a few studies can provide important new information. Therefore, for the purpose of the qualitative reviews in this guideline, the addition of studies was not exhaustive because the emphasis was on conceptual robustness rather than the quantitative completeness of evidence. This has implications for the types and numbers of studies

that are included in qualitative reviews. Sampling continued until no new relevant data seemed to emerge regarding a topic either to extend or contradict it, a concept referred to as 'theoretical saturation' in the literature.[31] The most relevant evidence in this respect would originate from studies set in a target context, that is, carried out in the UK NHS setting. Therefore, when the evidence base was particularly large, we were able to focus on UK studies only, but widened study inclusion when important perspectives were not or insufficiently covered. For instance, this was the case for barriers and facilitators in shared decision making where we identified sufficient UK evidence on healthcare professionals' views, but only 1 UK study on family experiences of perspectives on shared decision making. We therefore widened the inclusion to evidence from other countries to achieve theoretical saturation. The final selection of included or excluded studies from those that were identified in the literature search was carried out by at least 2 researchers. Themes from individual studies were then integrated into a wider context and when possible overarching categories of themes with sub-themes were identified. This was then placed into a thematic map that would present the relationship between themes and subthemes. The mapping part of the review was drafted by 1 researcher but the final framework of themes was further shaped and when necessary re-classified through discussions with at least 1 other researcher.

The Committee could then draw conclusions on the relative merits of each of the themes in each of the settings or countries and how they may help in forming recommendations.

#### 4.2.5.6 Integrative (mixed methods) synthesis of findings (recognising dying and dealing with uncertainty – see chapter 5)

An integrative type of review allows for the inclusion of different study designs (both quantitative as well as qualitative) in order to fully understand an area of concern, that is, the signs and symptoms that may indicate that someone is in the last days of life.[86] The quantitative section of the review included both prognostic and diagnostic components (described in the relevant sections above). The incorporation of qualitative elements (perspective on recognising dying from healthcare professionals and information from published Delphi consensus surveys) would provide additional information to purely quantitative data which may be limited in quantity in this area (see data synthesis for qualitative reviews above). An 'integrative review' has all of the components of other systematic reviews that are regularly used in NICE guideline development, but further to the synthesis of the relevant studies it includes a thematic analysis to provide a conceptual map of the topic (that is, a theoretical framework). The results are presented as a summary and narrative synthesis and would therefore capture results that may not be directly apparent from a quantitative or narrative synthesis alone (such as the uncertainties of recognising the signs in the final days of life which will have implications for all other topics in this guideline).

### 4.2.6 Type of studies

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects. The Committee believed that there would be limited evidence of this type (due to the study population being in the last days of life); therefore non-randomised studies were also considered.

For diagnostic reviews, cross-sectional and retrospective studies were included. For prognostic reviews, prospective and retrospective cohort studies were included. Case–control studies were not included.

Where data from observational studies were included, the Committee decided that the results for each outcome should be presented separately for each study and meta-analysis was not conducted.

### 4.2.7 Appraising the quality of evidence using 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE)

For intervention reviews, the evidence for outcomes from the included RCTs and observational studies were evaluated and presented using GRADE developed by the international GRADE working group (http://www.gradeworkinggroup.org/). Modified GRADE assessments were also carried out for outcomes per risk factor in prognostic reviews, for accuracy measures in diagnostic reviews and themes in qualitative reviews.

The software developed by the GRADE working group (GRADEpro) was used to assess the quality of each outcome, taking into account individual study quality factors and the meta-analysis results. This software is used mainly for intervention reviews, but can also be used for prognostic reviews. It is not presently designed to assess evidence from diagnostic and qualitative reviews. Therefore the modified GRADE approach for diagnostic and qualitative evidence was carried out without the software but using similar tables and concepts which are described below. Results were presented in GRADE profiles ('GRADE tables'), which consist of 2 sections: the 'Clinical evidence profile' table includes details of the quality assessment while the 'Clinical evidence summary of findings' table includes pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures and measures of dispersion (such as mean and standard deviation or median and range) for continuous outcomes and frequency of events (n/N: the sum across studies of the number of people with events divided by sum of the number of completers as well as 95% confidence intervals) for binary outcomes. Reporting or publication bias was only taken into consideration in the quality assessment and included in the 'Clinical evidence profile' table if it was apparent.

The evidence for each outcome was examined separately for the quality elements listed and defined in Table 2 for intervention,

**Table 3** for prognostic, Table 4 for diagnostic, and for qualitative reviews. Each element was graded using the quality levels listed in **ere specified in the footnotes.**

**Table 6**. The main criteria considered in the rating of these elements are discussed below (see Section 0 Grading of evidence). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome (Table 7)

The GRADE toolbox is currently designed only for randomised trials and observational studies but we adapted the quality assessment elements and outcome presentation for all other review types, that is; diagnostic, prognostic and qualitative studies.

**Table 2: Description of the elements in GRADE used to assess the quality of intervention studies**

| Quality element | Description |
|---|---|
| Risk of bias ('Study limitations') | Limitations in the study design and implementation may bias the estimates of the treatment effect. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect. |
| Inconsistency | Inconsistency refers to an unexplained heterogeneity of results. |
| Indirectness | Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made, such that the effect estimate is changed. |
| Imprecision | Results are imprecise when studies include relatively few patients and few events and |

| Quality element | Description |
|---|---|
| | thus have wide confidence intervals around the estimate of the effect. Imprecision results if the confidence interval includes the clinically important threshold. |
| Publication bias | Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies. |

For evidence from diagnostic studies, with regards to recognising signs and symptoms of dying, an adapted GRADE approach was used. This looked at whether the identification of a particular sign or symptom could accurately indicate ('diagnose') that someone is in the last days of life.

Table 3: Description of the elements in GRADE and how they are used to assess the quality for diagnostic accuracy reviews

| Quality element | Description |
|---|---|
| Risk of bias ('Study limitations') | Limitations in the study design and implementation may bias the estimates of the diagnostic accuracy. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect. Diagnostic accuracy studies are not usually randomised and therefore would not be downgraded for study design from the outset and start as High level evidence. |
| Inconsistency | Inconsistency refers to an unexplained heterogeneity of test accuracy measures such as sensitivity and specificity between studies. |
| Indirectness | Indirectness refers to differences in study population, differences in index tests across studies, reference standard and outcomes between the available evidence and the review question. |
| Imprecision | Results are imprecise when studies include relatively few patients and the probability to be diagnosed correctly in this group is low. Accuracy measures would therefore have wide confidence intervals around the estimate of the effect. |

For prognostic factors (that is, signs and symptoms as risk factors for entering the last days of life), an adapted GRADE approach was used. This looked at the body of the evidence for each risk factor across studies for 1 outcome (in the case of this guideline the outcome would be death occurring within 14 days).

**Table 4: Description of the elements in GRADE and how they are used to assess the quality for prognostic reviews**

| Quality element | Description |
|---|---|
| Risk of bias ('Study limitations') | Limitations in the study design and implementation may bias the estimates of the diagnostic accuracy. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect. Prognostic studies are not usually randomised and therefore would not be downgraded for study design from the outset and start as High level evidence. |
| Inconsistency | Inconsistency refers to an unexplained heterogeneity between studies looking at the same sign or symptom resulting in wide variability between ORs, RRs, or HRs with little or no overlap in confidence intervals. |
| Indirectness | Indirectness refers to any departure from the review protocol, for instance differences in study population or risk factor that may affect how results can be generalised from the reviewed evidence. |
| Imprecision | Results are imprecise when studies include relatively few people and also when the number of people is too low for a multivariable analysis (as a rule of thumb a number of 10 participants per variable). This would be assessed by looking at the confidence interval and where it lies in relation to the point estimate of the study. |

### 4.2.8 Appraising the quality of qualitative evidence

For qualitative studies (that is, qualitative review on recognising dying, communication, shared decision making and anticipatory prescribing) themes were assessed using elements described in

Table 5. These themes may have originated from an individual study or may have been identified through a number of individual themes or components of themes across a number of included studies.

**Table 5: Description of the elements used to assess qualitative studies by theme**

| Quality element | Description |
|---|---|
| Risk of bias ('Study limitations') | Limitations in the study design and implementation may bias the estimates of the diagnostic accuracy. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect. Qualitative studies are not usually randomised and therefore would not be downgraded for study design from the outset and start as High level evidence. |
| Coherence of findings | The extent to different individual themes or components of themes from studies fit into a wider network of overarching themes, for instance many components (relationship and rapport, clinical experience, information provision) can contribute to an overarching theme of healthcare professional factors in shared decision making. Even though each individual study may not mention each factor the overall theme is coherent. |
| Applicability (or relevance) of evidence | The extent to which the evidence supporting the review finding is applicable to the context specified in the review question. In the case of this guideline qualitative evidence from the UK was prioritised over and above data from other contexts. |
| Theme saturation / sufficiency | Individual studies that may have contributed to a theme or subtheme may have been conducted in a manner that, by design, would have not reached theoretical saturation on an individual study level. We can therefore not be sure that the theme was sufficiently covered by the evidence and are less confident in the findings. |

The main criteria considered in the rating of these elements are discussed below (see Section 4.2.9 Grading of evidence). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome (Table 7).

### 4.2.9 Grading the quality of clinical evidence

After data were synthesised, the overall quality of evidence was assessed for each outcome (in intervention or prognostic reviews), by diagnostic sign and symptom, or qualitative theme. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start as High in intervention review, observational studies as Low, and uncontrolled case series as Low or Very low. In diagnostic, prognostic and qualitative reviews, evidence from non-randomised studies start as High.
2. The rating was then downgraded for the specified criteria: risk of bias (study limitations), inconsistency, indirectness, imprecision and publication bias. These criteria are detailed below. In intervention reviews, evidence from observational studies (which had not previously been downgraded) was upgraded if there was: a large magnitude of effect, a dose–response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have 'serious' or 'very serious' risk of bias was rated down by 1 or 2 points respectively.

3. The downgraded or upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as High and the overall quality became Moderate, Low or Very low if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

**Table 6: Levels of quality elements in GRADE**

| Level | Description |
|---|---|
| None | There are no serious issues with the evidence. |
| Serious | The issues are serious enough to downgrade the outcome evidence by 1 level. |
| Very serious | The issues are serious enough to downgrade the outcome evidence by 2 levels. |

**Table 7: Overall quality of outcome evidence in GRADE**

| Level | Description |
|---|---|
| High | Further research is very unlikely to change our confidence in the estimate of effect. |
| Moderate | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. |
| Low | Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. |
| Very low | Any estimate of effect is very uncertain. |

The details of the criteria used for each of the main quality element are discussed further in the following Sections 4.2.10 to 4.2.13.

### 4.2.10 Risk of bias

#### 4.2.10.1 Intervention studies

Bias can be defined as anything that causes a consistent deviation from the truth. Bias can be perceived as a systematic error, for example, if a study was to be carried out several times and there was a consistently wrong answer, the results would be inaccurate.

The risk of bias for a given study and outcome is associated with the risk of over or underestimation of the true effect.

The risks of bias are listed in Table 8.

A study with a poor methodological design does not automatically imply high risk of bias; the bias is considered individually for each outcome and it is assessed whether this poor design will impact on the estimation of the intervention effect.

**Table 8: Risk of bias in randomised controlled trials**

| Risk of bias | Explanation |
|---|---|
| Allocation concealment | Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (this is a major problem in 'pseudo' or 'quasi' randomised trials with, for example, allocation by day of week, birth date, chart number). |
| Lack of blinding | Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated. |
| Incomplete | Missing data not accounted for and failure of the trialists to adhere to the intention- |

| Risk of bias | Explanation |
|---|---|
| accounting of patients and outcome events | to-treat principle when indicated. |
| Selective outcome reporting | Reporting of some outcomes and not others on the basis of the results. |
| Other risks of bias | For example:<br>• Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules<br>• Use of unvalidated patient-reported outcomes (for example, rating scales for noise intensity of respiratory secretions).<br>• Recruitment bias in cluster-randomised trials. |

#### 4.2.10.2 Diagnostic studies

For diagnostic accuracy studies, the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) checklist was used (see Appendix H in the NICE guidelines manual 2014[79]). Risk of bias and applicability in primary diagnostic accuracy studies in QUADAS-2 consists of 4 domains:

**Table 9: Risk of bias for typical diagnostic accuracy studies (according to QUADAS-2)**

| Risk of bias | Explanation |
|---|---|
| Patient selection | It is assessed whether all patients undergo all index tests or were the index tests appropriately randomised amongst the patients? Did all patients undergo all index tests or were the index tests appropriately randomised amongst the patients? |
| Index test (or sign/symptom) | For instance when thresholds are not pre-specified this could introduce bias because this directly affects the sensitivity or specificity estimate for the study. |
| Reference standard | Usually this would be assessed by how well the reference standard is conducted. However, in the context of recognising dying this was not considered to be an appropriate factor. |
| Flow and timing | This is with regards to the timing of when the sign and symptom occurred in relation to when the person died. |

#### 4.2.10.3 Prognostic studies

For prognostic studies, quality was assessed using the checklist for prognostic studies (Appendix H in the NICE guidelines manual 2014[79]).

This risk of bias for each risk factor across studies was derived by assessing the risk of bias across 6 domains for each study: selection bias, attrition bias, prognostic factor bias, outcome measurement bias, control for confounders and appropriate statistical analysis, with the last 4 domains being assessed for each outcome. A summary table on the quality of prognostic studies is presented at the beginning of each review to summarise the risk of bias across the 5 domains. More details about the quality assessment for prognostic studies are shown below:

**Table 10: Risk of bias for prognostic factor studies**

| Risk of bias | Explanation |
|---|---|
| Patient selection | If there is only 1 risk factor considered, there may be risk of bias when there was no attempt to achieve roughly comparable groups, and/or there is evidence of biased selection. If there are 2 or more risk factors considered the same may not apply for patient selection issues and then have to assess control for confounders. |

| Risk of bias | Explanation |
|---|---|
| Prognostic factor bias (or sign/symptom) | This refers to any biases that could directly be linked to the validity of the prognostic factor under investigation, such as how the signs or symptoms are assessed or measured. |
| Attrition bias | Usually this would be assessed by whether there are similar numbers of people who were followed up in groups who have or have not got this sign or symptom. |
| Outcome measurement bias | This usually refers to whether or not the outcome has been measured on a validated scale or was otherwise reliably assessed. However, for the purpose of the 'recognising dying' review this was not considered to be an appropriate factor to assess. |
| Control for confounders / statistical analysis | Confounders would be signs and symptoms that may be related to dying but that are not under direct investigation. For instance age is related to dying, but we would not assess age in general as a sign or symptom of dying. We therefore would want to assess whether signs and symptoms are independent predictors regardless of other non-related factors. |

#### 4.2.10.4 Qualitative studies

For qualitative studies, quality was assessed using a checklist for qualitative studies (as suggested in Appendix H in the NICE guidelines manual 2014[79]). This was based on the Critical Appraisal Skills Programme (CASP) checklist for qualitative studies (http://www.casp-uk.net/#!casp-tools-checklists/c18f8). The quality rating (Low, High, Unclear) was derived by assessing the risk of bias across 6 domains:

**Table 11: Risk of bias for qualitative studies**

| Risk of bias | Explanation |
|---|---|
| Aim and appropriateness of qualitative evidence. | This refers to an assessment of whether the aims and relevance of the study is clearly described and whether qualitative research methods are appropriate for investigating the research question. |
| Rigour in study design or validity of theoretical approach | It is assessed whether the study approach has been clearly described, for example, is based on a theoretical framework (for example, ethnography or grounded theory). This does not necessarily mean that the framework has to be explicitly stated, but that at least a detailed description is provided which makes it transparent and reproducible. |
| Sample selection | The background, the procedure, and reasons for the chosen method of selecting participants should be stated. It should also be assessed whether the relationship between the researcher and the informant and how this may have influenced findings is described. |
| Data collection | Consideration was given to who well the method of data collection (that is, in-depth interviews, semi-structured interviews, focus groups, or observations) was described. Whether details were provided and how the data were collected, that is, who conducted the interviews, how long did they last and where did they take place). |
| Data analysis | For this criterion it is assessed whether sufficient detail is provided about the analytical process and whether it is in accordance to the theoretical approach. For instance if a thematic analysis was used, it is assessed whether there was a clear description of how the theme was arrived at. Data saturation is also part of this section. This could be explicitly stated or it may be clear from the citations presented that it may have been possible to find more themes. |
| Results | In relation to this section the reasoning about the results are important, for instance whether a theoretical proposal or framework is provided rather than being restricted to citations or presentation of data. |

### 4.2.11 Inconsistency and coherence of findings

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect, prognostic risk factor or diagnostic accuracy measures varies widely across studies (that is, there is heterogeneity or variability in results), this suggests true differences in underlying effects.

Heterogeneity in meta-analyses was examined and sensitivity and subgroup analyses performed as pre-specified in the protocols (Appendix C).

When heterogeneity exists (chi-squared p less than 0.1, I-squared inconsistency statistic of more than 50%, or evidence from examining forest plots), but no plausible explanation can be found (for example, duration of intervention or different follow-up periods), the quality of evidence was downgraded by 1 or 2 levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. For diagnostic evidence this was assessed visually according to the differences in point estimates and overlap in confidence intervals on the sensitivity or specificity forest plots. In addition to the I-squared and chi-squared values and examination of forest plots, the decision for downgrading was also dependent on factors such as whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

For qualitative research a similar concept, coherence, is used in the quality assessment across themes. This does not mean that contradictory data are downgraded automatically, but that it is highlighted and presented and that reasoning is provided. As long as the themes, or components of themes, from individual studies fit into a theoretical framework they do not necessarily have to have the same perspectives but it should be possible to explain these by differences in context (that is, views of healthcare professionals might not be the same as those of family members but could contribute to the same overarching theme).

### 4.2.12 Indirectness and applicability or relevance of findings

Directness refers to the extent to which the populations, intervention, risk factor, index test, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

Relevance of findings in qualitative research is the equivalence of indirectness for quantitative outcomes and refers to how closely the aims and context of the studies contributing to a theme reflect the objectives outlined in the review protocol of the guideline question.

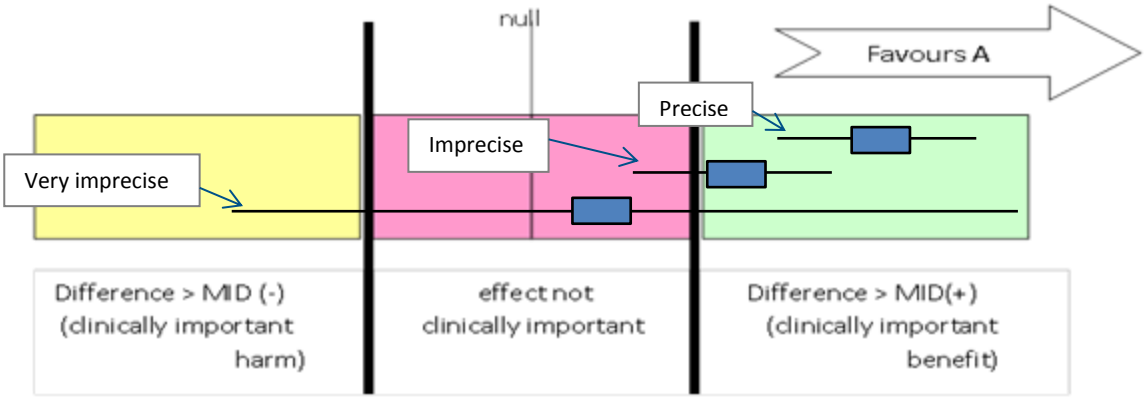
### 4.2.13 Imprecision and theme saturation or sufficiency

Imprecision in guidelines concerns whether the uncertainty (confidence interval) around the effect estimate means that it is not clear whether there is a clinically important difference between interventions or not, that is, whether the evidence would clearly support 1 recommendation or may lead us to believe that it could be consistent with several different types of recommendations. Therefore, imprecision differs from the other aspects of evidence quality; in that it is not really concerned with whether the point estimate is accurate or correct (has internal or external validity) instead it is concerned with the uncertainty about what the point estimate is. This uncertainty is reflected in the width of the confidence interval.

The 95% confidence interval (95% CI) is defined as the range of values that contain the population value with 95% probability. The larger the trial, the smaller the 95% CI and the more certain the effect estimate.

Imprecision in the evidence reviews was assessed by considering whether the width of the 95% CI of the effect estimate is relevant to decision-making, considering each outcome in isolation. Figure 2 considers a positive outcome for the comparison of treatment A versus B. Three decision-making zones can be identified, bounded by the thresholds for clinical importance (minimal important difference – MID) for benefit and for harm. The MID for harm for a positive outcome means the threshold at which drug A is less effective than drug B by an amount that is clinically important to people (favours B).

**Figure 2: Illustration of precise and imprecise outcomes based on the confidence interval of outcomes in a forest plot**




When the confidence interval of the effect estimate is wholly contained in 1 of the 3 zones (for example, clinically important benefit), we are not uncertain about the size and direction of effect (whether there is a clinically important benefit, or the effect is not clinically important, or there is a clinically important harm), so there is no imprecision.

When a wide confidence interval lies partly in each of 2 zones, it is uncertain in which zone the true value of effect estimate lies, and therefore there is uncertainty over which decision to make (based on this outcome alone). The confidence interval is consistent with 2 decisions and so this is considered to be imprecise in the GRADE analysis and the evidence is downgraded by 1 level ('serious imprecision').

If the confidence interval of the effect estimate crosses into 3 zones, this is considered to be very imprecise evidence because the confidence interval is consistent with 3 clinical decisions and there is a considerable lack of confidence in the results. The evidence is therefore downgraded by 2 levels in the GRADE analysis ('very serious imprecision').

Implicitly, assessing whether the confidence interval is in, or partially in, a clinically important zone, requires the Committee to estimate an MID or to say whether they would make different decisions for the 2 confidence limits.

The literature we searched for established MIDs for the selected outcomes in the evidence reviews, such as symptom measurement tools. No relevant published MIDs were identified. In addition, the Committee was asked whether they were aware of any acceptable MIDs in the clinical community but they were not aware of any. Finally, the Committee considered whether it was clinically acceptable to use the GRADE default MID to assess imprecision: a 25% relative risk reduction or relative risk increase was used, which corresponds to clinically important thresholds for a risk ratio of 0.75 and 1.25 respectively. This default MID was used for all the outcomes in the interventions evidence reviews as a starting point and decisions on clinical importance were then considered based on the absolute risk difference.

The same principle was used for prognostic factors; for example, using the default MID as a starting point for the Committee discussion, to assess whether the size of the outcome effect would be large enough to be meaningful in clinical practice.

In diagnostic accuracy measures, it was first of all considered whether sensitivity or specificity (or AUC for continuous variables) was going to be given more weight in the decision making process. If 1 was given more importance than the other, imprecision was rated on this statistical measure. It was not possible to pool the diagnostic data in this guideline. Therefore, imprecision was assessed on individual study results. For the purpose of the 'recognising dying' review the focus was on specificity. A specificity value of above 90% was considered by the Committee a good indicator of a sign or symptom that, if found positive, would be associated with death in the next days (that is, 90% or above of people who were classified positive as having this sign or symptom). This was then used in the same manner as an MID described above. A specificity value would be described as imprecise if it crosses this 90% and very imprecise if it also crossed the chance value of 50%.

Theme saturation or sufficiency refers to a similar concept in qualitative research. This refers to whether a theoretical point of theme saturation was achieved at which point no further citations or observations would provide more insight or suggest a different interpretation of this theme. As already highlighted in a previous section on qualitative reviewing methods it is not equivalent to the number of studies contributing to a theme, but rather to the depth of data and whether sufficient quotes or observations were provided that could underpin these findings.

### 4.2.14 Assessing clinical importance (of intervention effects)

The Committee assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.

The assessment of benefit, harm, or no benefit or harm was not based on the default MID of the relative risk which was only used as a starting point, but on the point estimate of the absolute effect for intervention studies taking into consideration the precision around this estimate. The same point estimate but in the opposite direction would apply if the outcome was negative.

This assessment was carried out by the Committee for each critical outcome, and an evidence summary table was produced to compile the Committee's assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision).

### 4.2.15 Assessing clinical importance (of prognostic, diagnostic or thematic findings)

Absolute risk differences were not calculated for prognostic findings in this guideline. The Committee considered the size of the relative effects and whether this was large enough to constitute a sign or symptom predicting that someone would die within the next few days.

In a similar manner this was carried out for diagnostic accuracy statistics to interpret how likely this size of the effect reflects a clinically meaning association between people having this sign and symptom and whether or not they die in the next few days.

For themes stemming from qualitative findings, clinical importance is decided upon by the Committee taking into account the generalizability of the context from which the theme was derived and whether it was convincing enough to support or warrant a change in current practice.

### 4.2.16 Evidence statements

Evidence statements are summary statements that are presented after the GRADE profiles, summarising the key features of the clinical effectiveness evidence presented.

The narrative evidence statements focus on the critical outcomes and encompass key features of the evidence, such as:

- the number of studies and the number of participants for a particular outcome
- a brief description of the participants
- an indication of the direction of effect a description of the overall quality of evidence (GRADE overall quality).

Qualitative evidence statements provide a summary of the themes identified along with characteristics listed above. A statement is also given where no evidence is identified.

## 4.3 Evidence of cost effectiveness

The Committee is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost effectiveness') rather than the total implementation cost.[79] Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per person treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist undertook a systematic review of the published economic literature.

### 4.3.1 Literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in the NICE guidelines manual.[78,79]
- Studies initially considered eligible but which were then excluded can be found in Appendix M with reasons for exclusion explained.

#### 4.3.1.1 Inclusion and exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action (cost–utility, cost-effectiveness, cost–benefit and cost–consequences analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported cost per hospital (not per person), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. Studies published before 1999 and studies from non-OECD countries or the USA were also

excluded, on the basis that the applicability of such studies to the present UK NHS context is likely to be too low for them to be helpful for decision-making.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (Appendix G of the NICE guidelines manual 2012[78]) and the health economics review protocol in Appendix D.

When no relevant economic studies were found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the Committee to inform the possible economic implications of the recommendations.

### 4.3.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, the feasibility of developing a new economic analysis was discussed with the Committee. A new economic analysis was not undertaken for this guideline given the lack of good quality clinical data and the issues related to settings and uncertainties around the quantification of health benefit in the last few days of life.

### 4.3.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that the Committee s should consider when judging whether an intervention offers good value for money.[77] In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention provided clinically significant benefits at an acceptable additional cost when compared with the next best strategy.

### 4.3.4 In the absence of economic evidence

When no relevant published studies were found, the Committee made a qualitative judgement about cost effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the clinical review of effectiveness evidence.

The UK NHS costs reported in the guideline are those that were presented to the Committee and were correct at the time recommendations were drafted. They may have changed subsequently before the time of publication but, we have no reason to believe they have changed substantially.

## 4.4 Developing recommendations

Over the course of the guideline development process, the Committee was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in the Appendices (H and I).

- Summaries of clinical and economic evidence and quality (as presented in Chapters [5 - 10]).
- Forest plots and summary ROC curves (Appendix K).
- A description of the methods and results of the cost-effectiveness analyses undertaken for the guideline (Appendix N).

Recommendations were drafted on the basis of the Committee's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally in an economic model, or informally. Firstly, the net benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the Committee took into account the clinical benefits and harms when 1 intervention was compared with another. The assessment of net benefit was moderated by the importance placed on the outcomes (the Committee's values and preferences), and the confidence the Committee had in the evidence (evidence quality). Secondly, whether the net benefit justified any differences in costs was assessed.

When clinical and economic evidence was of poor quality, conflicting or absent, the Committee drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared with the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the Committee. The Committee also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation.

The Committee considered the 'strength' of recommendations. This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the Committee believes that the vast majority of healthcare and other professionals and patients would choose a particular intervention if they considered the evidence in the same way that the Committee has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost effective. However, there is often a closer balance between benefits and harms, and some people would not choose an intervention whereas others would. This may happen, for example, if some people are particularly averse to some side effect and others are not. In these circumstances the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of people.

The Committee focused on the following factors in agreeing the wording of the recommendations:

- The actions health professionals need to take.
- The information readers need to know.
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations).
- The involvement of patients (and their carers if needed) in decisions on treatment and care.
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions (see Section 9.3 in the NICE guidelines manual[78]).

For recommendations where there was equivocal, limited or no evidence, for example for signs or symptoms or drugs, alphabetical ordering of lists were used to rather than prioritize based solely on the Committee consensus.

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter.

### 4.4.1 Research recommendations

When areas were identified for which good evidence was lacking, the Committee considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

### 4.4.2 Validation process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website.

### 4.4.3 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual[79], NICE will undertake a review of whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

### 4.4.4 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of this guideline and the literature used in support of this guideline.

### 4.4.5 Funding

The National Clinical Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

# 5 Recognising when a person may be in the last days of life

## 5.1 Introduction

The recognition and weighing up of factors that may indicate that someone is in the last days or hours of life are complex and subtle. This can be a difficult task, even for an experienced palliative care clinician. Prognostic tools have been developed to assist clinicians in making a more accurate prognosis, but they are not used in routine clinical practice so clinicians are not familiar with them.

The current approach to recognising imminent dying utilises a range of signs and symptoms that are best observed over days to weeks, if the dying person's clinical course allows such observations. Over a period of days these include multiple organ failure, progressive weakness, reduced mobility and ability to carry out normal activities of daily living, increased periods of sleep, reduced oral intake and a general reduction in cognitive function, awareness and communication (with family or other important people as well as professionals). Changes that may indicate impending death within hours, that have been prioritised for inclusion in this review, include variations in respiratory cycle, weakening of pulse, and shutting down of skin circulation, and noisy respiratory secretions.

A further challenge arises when a person who was thought to be imminently dying, starts to show signs of recovery such as increased alertness and communication, desire for oral intake and improved mobility. Such reversals may be temporary, or may signify a true recovery from the dying process. Therefore it is important to determine the evidence base in this area to implement any necessary changes in clinical management to assist the person with living for a longer period of time, for example, reinstatement of medications, hydration and nutrition that may have been withdrawn.

The 'More Care Less Pathway' review[30] recommended that clear guidance be issued on the clinical decision-making process at the end of life and, in particular, managing the uncertainties around diagnosing the dying or recovery phases. The Committee chose to ask the following question.

## 5.2 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?

For full details see review protocol in Appendix C.

This is an integrative review[86] which allows for the inclusion of different study designs (experimental, observational as well as qualitative) in order to fully understand an area of concern. The incorporation of qualitative elements (and information from published Delphi consensus surveys) enabled further exploration of these areas. Mixed methodology is often used to capture a wide range of evidence in systematic review, but further to the synthesis of the relevant studies it includes a thematic analysis to provide a conceptual map of the topic (that is, a theoretical framework). The results are presented as a summary, and narrative synthesis captures results that may not be directly apparent from a quantitative or narrative synthesis alone (such as the uncertainties of recognising the signs in the final stages which will be useful for the other topics in this guideline).

**Table 12: PICO characteristics of review question**

| | |
|---|---|
| **Population** | Adults (aged 18 years and over) |
| **Study design** | Quantitative/prognostic review component: Prospective or retrospective cohorts.<br><br>Qualitative review component: Qualitative review such as large scale or Delphi consensus surveys, interviews.<br><br>Exclusions: Editorials/commentaries/opinion pieces (other than large consensus surveys). |
| **Prognostic or diagnostic factors** | Signs and symptoms including at least 1 of the following categories:<br>• Acute – bleeding, renal failure<br>• Breathing (including rattle and irregular breathing)<br>• Consciousness/cognition (including reduced cognition)<br>• Emotional state (including anxiety)<br>• General deterioration (including extreme weakness)<br>• Intake of fluid, food<br>• Related to condition of skin (including discolouration)<br>• Social withdrawal<br>• Urine output |
| **Confounders** | Treatments that may suppress conscious level<br>Artificial organ support, such as ventilation |
| **Outcomes/themes** | Death (within a few days/hours) including time to event data, if available. |
| **Qualitative review strategy** | A thematic analysis of the data will be conducted and findings presented as a theoretical framework/conceptual map. |

## 5.3 Quantitative review: clinical evidence

Seven studies were included in the review;[21,33,47,52,61,62,65] these are summarised in Table 13 below. Evidence from these studies is summarised in the GRADE clinical evidence profile below (

Table 14: Clinical evidence profile: Diagnostic performance of predictors of mortality

| Index Test (Threshold) | No. of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | Sensitivity % (median/ 95% CI) | Specificity % (median/ 95% CI) | Area Under Curve (range) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|
| Mortality at 3 days[46,48] | | | | | | | | | | |
| PPS≤20% | 1 | 357 | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | 64 (63.4 - 64.7) | 81.3 (80.9 - 81.7) | NR | MODERATE |
| RASS - 2 or lower | 1 | 357 | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | 50.5 (49.9 - 51.1) | 89.3 (88.9 - 89.7) | NR | MODERATE |
| Dysphagia of liquids | 1 | 357 | Serious risk of biasa | No serious inconsistency | No serious indirectness | No serious imprecision | 40.9 (40.1 - 41.7) | 78.8 (78.3 - 79.2) | NR | LOW |
| Urine output over last 12 hours <100 ml | 1 | 357 | Serious risk of biasa | No serious inconsistency | No serious indirectness | No serious imprecision | 24.2 (23.2 - 25.1) | 98.2 (98 - 98.5) | NR | LOW |
| Death rattle | 1 | 357 | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | 22.4 (21.8 - 22.9) | 97.1 (96.9 - 97.3) | NR | MODERATE |
| Apnea periods | 1 | 357 | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | 17.6 (17.1 - 18) | 95.3 (95.1 - 95.6) | NR | MODERATE |
| Respiration with mandibular movement | 1 | 357 | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | 22 (21.5 - 22.4) | 97.5 (97.3 - 97.6) | NR | MODERATE |
| Peripheral cyanosis | 1 | 357 | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | 26.7 (26.1 - 27.3) | 94.9 (94.7 - 95.2) | NR | MODERATE |
| Cheyne-Stokes breathing | 1 | 357 | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | 14.1 (13.6 - 14.5) | 98.5 (98.4 - 98.7) | NR | MODERATE |
| Pulselessness of radial artery | 1 | 357 | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | 11.3 (10.9 - 11.8) | 99.3 (99.2 - 99.5) | NR | MODERATE |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Mortality at 2 days (emergency department)[62] | | | | | | | | | | |
| Urea ≥8.75 | 1 | 71453 | Serious risk of biasb | No serious inconsistency | No serious indirectness | No serious imprecision | 70.3 (67.3 - 73.2) | 76.0 (75.8 - 76.3) | 0.790 (0.776 - 0.805) | LOW |
| Creatinine ≥0.1145 | 1 | 71453 | Serious risk of biasb | No serious inconsistency | No serious indirectness | No serious imprecision | 63.6 (60.4 - 66.6) | 79.6 (79.4 - 79.8) | 0.764 (0.749 - 0.780) | LOW |
| White cell count ≥11.75 | 1 | 71453 | Serious risk of biasb | No serious inconsistency | No serious indirectness | No serious imprecision | 55.2 (51.9 - 58.4) | 78.8 (78.6 - 79.0) | 0.691 (0.671 - 0.709) | LOW |
| Bilirubin ≥17.5 | 1 | 71453 | Serious risk of biasb | No serious inconsistency | No serious indirectness | No serious imprecision | 36.2 (32.5 - 40.0) | 77.3 (77.0 - 77.6) | 0.579 (0.557 - 0.602) | LOW |
| Haemoglobin ≤128.5 | 1 | 71453 | Serious risk of biasb | No serious inconsistency | No serious indirectness | No serious imprecision | 58.8 (55.5 - 62.0) | 64.0 (63.7 - 64.2) | 0.633 (0.613 - 0.653) | LOW |
| Haematocrit ≤0.375 | 1 | 71453 | Serious risk of biasb | No serious inconsistency | No serious indirectness | No serious imprecision | 47.5 (44.2 - 50.8) | 69.7 (69.5 - 70.0) | 0.578 (0.556 - 0.600) | LOW |
| Total bicarbonate ≤21.5 | 1 | 71453 | Serious risk of biasb | No serious inconsistency | No serious indirectness | No serious imprecision | 56.9 (53.7 - 60.0) | 84.7 (84.5 - 84.9) | 0.731 (0.712 - 0.751) | LOW |
| pH≤7.325 | 1 | 71453 | Serious risk of biasb | No serious inconsistency | No serious indirectness | No serious imprecision | 70.4 (67.5 - 73.2) | 79.4 (79.0 - 80.0) | 0.806 (0.791 - 0.821) | LOW |
| Albumin ≤34.5 | 1 | 71453 | Serious risk of biasb | No serious inconsistency | No serious indirectness | No serious imprecision | 71.8 (68.4 - 75.0) | 72.4 (72.1 - 72.7) | 0.779 (0.761 - 0.796) | LOW |
| Mortality at 2 days (admitted to hospital more than 24 hours)[61] | | | | | | | | | | |
| Urea | 1 | 42701 | Serious risk of biasb | No serious inconsistency | No serious indirectness | No serious imprecision | NR | NR | 0.772 (0.762 - 0.781) | LOW |
| Creatinine | 1 | 42701 | Serious risk of biasb | No serious inconsistency | No serious indirectness | No serious imprecision | NR | NR | 0.687 (0.67 6- 0.697) | LOW |
| White cell count | 1 | 42701 | Serious risk of biasb | No serious inconsistency | No serious indirectness | No serious imprecision | NR | NR | 0.706 (0.693 - 0.718) | LOW |
| Bilirubin | 1 | 42701 | Serious risk of biasb | No serious inconsistency | No serious indirectness | No serious imprecision | NR | NR | 0.613 (0.594 - 0.631) | LOW |
| Haemoglobin | 1 | 42701 | Serious risk of bias[(b)] | No serious inconsistency | No serious indirectness | No serious imprecision | NR | NR | 0.558 (0.545 - 0.570) | LOW |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Haematocrit | 1 | 42701 | Serious risk of biasb | No serious inconsistency | No serious indirectness | No serious imprecision | NR | NR | 0.530 (0.518 - 0.542) | LOW |
| Total bicarbonate | 1 | 42701 | Serious risk of biasb | No serious inconsistency | No serious indirectness | No serious imprecision | NR | NR | 0.650 (0.635 - 0.663) | LOW |
| pH | 1 | 42701 | Serious risk of biasb | No serious inconsistency | No serious indirectness | No serious imprecision | NR | NR | 0.725 (0.703 - 0.749) | LOW |
| Albumin | 1 | 42701 | Serious risk of biasb | No serious inconsistency | No serious indirectness | No serious imprecision | NR | NR | 0.662 (0.647 - 0.680) | LOW |

*Abbreviations: PPS, palliative performance scale; RASS, Richmond agitation sedation scale; NR, not reported.*

*(a) 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.*

*(b) 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.*

**Table 15: Clinical evidence profile: Prognostic indicators of mortality**

| Predictor | No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | n | Adjusted OR/RR/HR (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|
| Mortality at 1 week [21] | | | | | | | | | |
| Cognitive (1 to 3 vs. 0) | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | Serious imprecisionb | 374 | OR 2.29 (1.18, 4.43) | LOW |
| Edema (1 to 3 vs. 0) | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | Serious imprecisionb | 374 | OR 1.94 (1.04, 3.62) | LOW |
| Jaundice (1 to 3 vs. 0) | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | Very serious imprecisionb | 374 | OR 1.00 (0.47, 2.15) | VERY LOW |
| ECOG score (3, 4 vs., 1, 2) | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | No imprecision | 374 | OR 3.45 (1.65, 7.19) | MODERATE |
| Ascites (1 to 3 vs. 0) | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | Very serious imprecisionb | 374 | OR 1.01 (0.49, 2.11 | VERY LOW |
| BUN (mg/dl) | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | No imprecision | 374 | OR 1.02 (1.00, 1.03) | MODERATE |
| Respiratory rate | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | Serious imprecisionb | 374 | OR 1.12 (1.04, 1.20) | VERY LOW |
| Mortality at 1 week, 65 and over [52] | | | | | | | | | |
| Systolic blood pressure (per mm Hg) | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | No imprecision | 459 | OR 0.985 (0.974 - 0.997) | MODERATE |
| Heart rate (per 1 beat/min) | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | No imprecision | 459 | OR 1.017 (1.003 - 1.032) | MODERATE |
| Haemoglobin (per 1 mg/dl) | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | Serious imprecisionb | 459 | OR 1.216 (1.067 - 1.385) | VERY LOW |

| Predictor | No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | n | Adjusted OR/RR/HR (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|
| ECOG (per 1 score) | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | No imprecision | 459 | OR 2.018 (1.397 - 2.915) | MODERATE |
| Muscle power (per 1 score) | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | Serious imprecisionb | 459 | OR 0.722 (0.542 - 0.961) | VERY LOW |
| Mortality at 2 weeks33- | | | | | | | | | |
| Triage pulse | 1 | Retrospective cohort | Serious risk of biasa | No serious inconsistency | Serious Indirectness | No imprecision | 122 | RR 4.92 (1.4 - 16.9) | LOW |
| Triage respiration | 1 | Retrospective cohort | Serious risk of biasa | No serious inconsistency | Serious Indirectness | No imprecision | 122 | RR 12.72 (3.1 - 52.8) | LOW |
| Mortality at 2 weeks65 | | | | | | | | | |
| Anorexia | 1 | Retrospective cohort | Serious risk of biasa | No serious inconsistency | Serious Indirectness | Serious imprecisionb | 93 | HR 2.57 (1.14 - 5.88) | LOW |
| Fatigue | 1 | Retrospective cohort | Serious risk of biasa | No serious inconsistency | Serious Indirectness | No imprecision | 93 | HR 5.9 (2.04 - 17.0) | LOW |
| Desaturation | 1 | Retrospective cohort | Serious risk of biasa | No serious inconsistency | Serious Indirectness | No imprecision | 93 | HR 3.3 (1.42 - 7.65) | LOW |
| Hyponatremia | 1 | Retrospective cohort | Serious risk of biasa | No serious inconsistency | Serious Indirectness | Serious imprecisionb | 93 | HR 2.17 (1.01 - 4.68) | LOW |
| Hypoalbuminemia | 1 | Retrospective cohort | Serious risk of biasa | No serious inconsistency | Serious Indirectness | Serious imprecisionb | 93 | HR 2.37 (1.05 - 5.36) | LOW |

*Abbreviations: ECOG, Eastern Cooperative Oncology Group performance scale*

*(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.*

). See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, forest plots in Appendix K, GRADE tables in Appendix J and excluded studies list in Appendix L.

The Eastern Cooperative Oncology (ECOG) performance status was included in the review, which is a scale ranging from 0 (fully active, able to carry on all pre-disease performance without restriction) to 5 (dead).

**Table 13: Summary of studies included in the review**

| Study | Population | Analysis | Prognostic/diagnostic variable(s) | Outcomes |
|---|---|---|---|---|
| Chiang 2009 (and Kao 2009 - age ≥65 subgroup)[21,52] | Prospective cohort<br>n=729<br><br>People with terminal cancer admitted to a palliative care unit.<br><br>Taiwan, China | Multivariate analysis (logistic regression) | Cognitive status, edema, jaundice, ECOG score, ascites | Mortality at 7 days (adjusted OR) |
| Escalante 2000[33] | Retrospective cohort<br>n=122<br><br>People with cancer presenting to an emergency department with acute dyspnoea as a primary or secondary complaint.<br><br>USA | Multivariate analysis (logistic regression) | Triage blood pressure, respiration, pulse, response to treatment, history if metastasis, cancer diagnosis | Mortality at 14 days (adjusted OR) |
| Hui 2014B[47] | Prospective cohort<br>n=357<br>People with terminal cancer admitted to a palliative care unit<br><br>USA and Brazil | Diagnostic performance of signs and symptoms | Apnea periods, Cheyne-Stokes breathing, death rattle, dysphagia of liquids, decreased level of consciousness, sedation, Palliative Performance Scale, peripheral cyanosis, pulselessness of radial artery, respiration with mandibular movement and urine output. | Mortality at 3 days |
| Loekito 2013A[61] | Retrospective cohort<br>n=42701<br><br>People admitted to hospital for more than 24 hours.<br><br>Australia | Diagnostic performance of signs and symptoms | Haemoglobin, haematocrit, total bicarbonate, white cell count, albumin, pH, bilirubin, creatinine, urea. | Mortality at 2 days |

| Study | Population | Analysis | Prognostic/diagnostic variable(s) | Outcomes |
|---|---|---|---|---|
| Loekito 2013[62] | Retrospective cohort<br>n=71453<br><br>People in the emergency department<br><br>Australia | Diagnostic performance of signs and symptoms | Haemoglobin, haematocrit, total bicarbonate, white cell count, albumin, pH, bilirubin, creatinine, urea. | Mortality at 2 days |
| Matsunuma 2014[65] | Retrospective cohort<br>n=93<br><br>People with terminal lung cancer admitted to a palliative care unit<br><br>Japan | Multivariate analysis (Cox proportional hazards regression) | Anorexia, fatigue, hyponatremia, hypoalbuminemia | Mortality at 14 days (adjusted HR) |

**Table 14: Clinical evidence profile: Diagnostic performance of predictors of mortality**

| Index Test (Threshold) | No. of studies | n | Risk of bias | Inconsistency | Indirectness | Imprecision | Sensitivity % (median/ 95% CI) | Specificity % (median/ 95% CI) | Area Under Curve (range) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|
| Mortality at 3 days[46,48] | | | | | | | | | | |
| PPS≤20% | 1 | 357 | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | 64 (63.4 - 64.7) | 81.3 (80.9 - 81.7) | NR | MODERATE |
| RASS - 2 or lower | 1 | 357 | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | 50.5 (49.9 - 51.1) | 89.3 (88.9 - 89.7) | NR | MODERATE |
| Dysphagia of liquids | 1 | 357 | Serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 40.9 (40.1 - 41.7) | 78.8 (78.3 - 79.2) | NR | LOW |
| Urine output over last 12 hours <100 ml | 1 | 357 | Serious risk of bias[a] | No serious inconsistency | No serious indirectness | No serious imprecision | 24.2 (23.2 - 25.1) | 98.2 (98 - 98.5) | NR | LOW |
| Death rattle | 1 | 357 | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | 22.4 (21.8 - 22.9) | 97.1 (96.9 - 97.3) | NR | MODERATE |
| Apnea periods | 1 | 357 | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | 17.6 (17.1 - 18) | 95.3 (95.1 - 95.6) | NR | MODERATE |
| Respiration with mandibular movement | 1 | 357 | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | 22 (21.5 - 22.4) | 97.5 (97.3 - 97.6) | NR | MODERATE |
| Peripheral cyanosis | 1 | 357 | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | 26.7 (26.1 - 27.3) | 94.9 (94.7 - 95.2) | NR | MODERATE |
| Cheyne-Stokes breathing | 1 | 357 | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | 14.1 (13.6 - 14.5) | 98.5 (98.4 - 98.7) | NR | MODERATE |
| Pulselessness of radial artery | 1 | 357 | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | 11.3 (10.9 - 11.8) | 99.3 (99.2 - 99.5) | NR | MODERATE |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Mortality at 2 days (emergency department)[62] | | | | | | | | | | |
| Urea ≥8.75 | 1 | 71453 | Serious risk of bias[b] | No serious inconsistency | No serious indirectness | No serious imprecision | 70.3 (67.3 - 73.2) | 76.0 (75.8 - 76.3) | 0.790 (0.776 - 0.805) | LOW |
| Creatinine ≥0.1145 | 1 | 71453 | Serious risk of bias[b] | No serious inconsistency | No serious indirectness | No serious imprecision | 63.6 (60.4 - 66.6) | 79.6 (79.4 - 79.8) | 0.764 (0.749 - 0.780) | LOW |
| White cell count ≥11.75 | 1 | 71453 | Serious risk of bias[b] | No serious inconsistency | No serious indirectness | No serious imprecision | 55.2 (51.9 - 58.4) | 78.8 (78.6 - 79.0) | 0.691 (0.671 - 0.709) | LOW |
| Bilirubin ≥17.5 | 1 | 71453 | Serious risk of bias[b] | No serious inconsistency | No serious indirectness | No serious imprecision | 36.2 (32.5 - 40.0) | 77.3 (77.0 - 77.6) | 0.579 (0.557 - 0.602) | LOW |
| Haemoglobin ≤128.5 | 1 | 71453 | Serious risk of bias[b] | No serious inconsistency | No serious indirectness | No serious imprecision | 58.8 (55.5 - 62.0) | 64.0 (63.7 - 64.2) | 0.633 (0.613 - 0.653) | LOW |
| Haematocrit ≤0.375 | 1 | 71453 | Serious risk of bias[b] | No serious inconsistency | No serious indirectness | No serious imprecision | 47.5 (44.2 - 50.8) | 69.7 (69.5 - 70.0) | 0.578 (0.556 - 0.600) | LOW |
| Total bicarbonate ≤21.5 | 1 | 71453 | Serious risk of bias[b] | No serious inconsistency | No serious indirectness | No serious imprecision | 56.9 (53.7 - 60.0) | 84.7 (84.5 - 84.9) | 0.731 (0.712 - 0.751) | LOW |
| pH≤7.325 | 1 | 71453 | Serious risk of bias[b] | No serious inconsistency | No serious indirectness | No serious imprecision | 70.4 (67.5 - 73.2) | 79.4 (79.0 - 80.0) | 0.806 (0.791 - 0.821) | LOW |
| Albumin ≤34.5 | 1 | 71453 | Serious risk of bias[b] | No serious inconsistency | No serious indirectness | No serious imprecision | 71.8 (68.4 - 75.0) | 72.4 (72.1 - 72.7) | 0.779 (0.761 - 0.796) | LOW |
| Mortality at 2 days (admitted to hospital more than 24 hours)[61] | | | | | | | | | | |
| Urea | 1 | 42701 | Serious risk of bias[b] | No serious inconsistency | No serious indirectness | No serious imprecision | NR | NR | 0.772 (0.762 - 0.781) | LOW |
| Creatinine | 1 | 42701 | Serious risk of bias[b] | No serious inconsistency | No serious indirectness | No serious imprecision | NR | NR | 0.687 (0.67 6- 0.697) | LOW |
| White cell count | 1 | 42701 | Serious risk of bias[b] | No serious inconsistency | No serious indirectness | No serious imprecision | NR | NR | 0.706 (0.693 - 0.718) | LOW |
| Bilirubin | 1 | 42701 | Serious risk of bias[b] | No serious inconsistency | No serious indirectness | No serious imprecision | NR | NR | 0.613 (0.594 - 0.631) | LOW |
| Haemoglobin | 1 | 42701 | Serious risk of bias[(b)] | No serious inconsistency | No serious indirectness | No serious imprecision | NR | NR | 0.558 (0.545 - 0.570) | LOW |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Haematocrit | 1 | 42701 | Serious risk of bias[b] | No serious inconsistency | No serious indirectness | No serious imprecision | NR | NR | 0.530 (0.518 - 0.542) | LOW |
| Total bicarbonate | 1 | 42701 | Serious risk of bias[b] | No serious inconsistency | No serious indirectness | No serious imprecision | NR | NR | 0.650 (0.635 - 0.663) | LOW |
| pH | 1 | 42701 | Serious risk of bias[b] | No serious inconsistency | No serious indirectness | No serious imprecision | NR | NR | 0.725 (0.703 - 0.749) | LOW |
| Albumin | 1 | 42701 | Serious risk of bias[b] | No serious inconsistency | No serious indirectness | No serious imprecision | NR | NR | 0.662 (0.647 - 0.680) | LOW |

*Abbreviations: PPS, palliative performance scale; RASS, Richmond agitation sedation scale; NR, not reported.*

*(c) 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.*

*(d) 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.*

**Table 15: Clinical evidence profile: Prognostic indicators of mortality**

| Predictor | No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | n | Adjusted OR/RR/HR (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|
| Mortality at 1 week [21] | | | | | | | | | |
| Cognitive (1 to 3 vs. 0) | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | Serious imprecision[b] | 374 | OR 2.29 (1.18, 4.43) | LOW |
| Edema (1 to 3 vs. 0) | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | Serious imprecision[b] | 374 | OR 1.94 (1.04, 3.62) | LOW |
| Jaundice (1 to 3 vs. 0) | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | Very serious imprecision[b] | 374 | OR 1.00 (0.47, 2.15) | VERY LOW |
| ECOG score (3, 4 vs., 1, 2) | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | No imprecision | 374 | OR 3.45 (1.65, 7.19) | MODERATE |
| Ascites (1 to 3 vs. 0) | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | Very serious imprecision[b] | 374 | OR 1.01 (0.49, 2.11 | VERY LOW |
| BUN (mg/dl) | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | No imprecision | 374 | OR 1.02 (1.00, 1.03) | MODERATE |
| Respiratory rate | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | Serious imprecision[b] | 374 | OR 1.12 (1.04, 1.20) | VERY LOW |
| Mortality at 1 week, 65 and over [52] | | | | | | | | | |
| Systolic blood pressure (per mm Hg) | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | No imprecision | 459 | OR 0.985 (0.974 - 0.997) | MODERATE |
| Heart rate (per 1 beat/min) | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | No imprecision | 459 | OR 1.017 (1.003 - 1.032) | MODERATE |
| Haemoglobin (per 1 mg/dl) | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | Serious imprecision[b] | 459 | OR 1.216 (1.067 - 1.385) | VERY LOW |

| Predictor | No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | n | Adjusted OR/RR/HR (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|
| ECOG (per 1 score) | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | No imprecision | 459 | OR 2.018 (1.397 - 2.915) | MODERATE |
| Muscle power (per 1 score) | 1 | Prospective cohort | No serious risk of bias | No serious inconsistency | No serious indirectness | Serious imprecision[b] | 459 | OR 0.722 (0.542 - 0.961) | VERY LOW |
| Mortality at 2 weeks[33]- | | | | | | | | | |
| Triage pulse | 1 | Retrospective cohort | Serious risk of bias[a] | No serious inconsistency | Serious Indirectness | No imprecision | 122 | RR 4.92 (1.4 - 16.9) | LOW |
| Triage respiration | 1 | Retrospective cohort | Serious risk of bias[a] | No serious inconsistency | Serious Indirectness | No imprecision | 122 | RR 12.72 (3.1 - 52.8) | LOW |
| Mortality at 2 weeks[65] | | | | | | | | | |
| Anorexia | 1 | Retrospective cohort | Serious risk of bias[a] | No serious inconsistency | Serious Indirectness | Serious imprecision[b] | 93 | HR 2.57 (1.14 - 5.88) | LOW |
| Fatigue | 1 | Retrospective cohort | Serious risk of bias[a] | No serious inconsistency | Serious Indirectness | No imprecision | 93 | HR 5.9 (2.04 - 17.0) | LOW |
| Desaturation | 1 | Retrospective cohort | Serious risk of bias[a] | No serious inconsistency | Serious Indirectness | No imprecision | 93 | HR 3.3 (1.42 - 7.65) | LOW |
| Hyponatremia | 1 | Retrospective cohort | Serious risk of bias[a] | No serious inconsistency | Serious Indirectness | Serious imprecision[b] | 93 | HR 2.17 (1.01 - 4.68) | LOW |
| Hypoalbuminemia | 1 | Retrospective cohort | Serious risk of bias[a] | No serious inconsistency | Serious Indirectness | Serious imprecision[b] | 93 | HR 2.37 (1.05 - 5.36) | LOW |

*Abbreviations: ECOG, Eastern Cooperative Oncology Group performance scale*

*(c) 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.*

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

## 5.4 Qualitative review: clinical evidence

Three qualitative studies[29,51,99] and 5 surveys[2,13,22,32,54] were identified. These papers are summarised in Table 16 below. Key findings from these studies are summarised in the clinical evidence summary Table 17. See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, and excluded studies list in Appendix M.

Two of the qualitative studies interviewed nursing staff with experience in nursing oncological patients on the signs and symptoms that they believe indicate someone with cancer is in the last days of life.[29,99] A further qualitative study interviewed junior doctors about prognosis and approach to care decisions when caring for seriously ill hospitalised people with conditions other than cancer.

Five surveys reporting descriptive data around recognising dying were found which both supported the themes found in the qualitative reviews and provided further information. Two of these were Delphi studies, 1 of which focused on nurses' opinions of gastrointestinal cancer patients[54] whilst the other Delphi included both the multiprofessional team and a lay person's opinions on people dying from any cause.[32]

There were 2 prospective observational studies[13,22] and 1 retrospective study[2] which investigated the factors that affect prognostic accuracy of doctor's assessments of dying people. These included all causes of deaths.

### 5.4.1 Summary of included studies

**Table 16: Summary of studies included in the review**

| Study | Design | Population (n) | Research aim | Comments |
|---|---|---|---|---|
| Qualitative studies | | | | |
| Dendaas 2002[29] | Individual interviews | n=15, nursing staff from hospices and inpatient oncology units who had recent experiencing of caring for multiple oncological patients in the last days of life.<br><br>USA | 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. | A standard interview with open questions was developed but not all questions asked to all applicants. Reliable methods of analysis including external groups to transcribe the interviews and another group of experts to code the interviews were used. |
| Johnson 2003[51] | Individual interviews with set open questions | n=8 junior doctors with limited experience of intensive care medicine discussed their care of a person (the person had to be a current inpatient. If the person had either died or been discharged the discussions were excluded from | To discuss with junior doctors their recent experiences on prognosis and how they approach care decisions when caring for seriously ill hospitalised people. | The people discussed by the junior doctors were not necessarily recognised in the last days of life by the junior doctor, although they were prompted to consider whether they might die. There was no information provided on the time of death of the people discussed. |

| Study | Design | Population (n) | Research aim | Comments |
|---|---|---|---|---|
| | | analysis).<br>USA | | |
| Van Der Werff 2012[99] | Focus group design | n=18 nursing staff that had recent experiencing of caring for an oncological patient in the last days of life.<br><br>Netherlands | To assess nurse perspectives on the signs and symptoms that suggest oncological patients are entering the last days of life. | A small study but good methodology on analysis. Study aimed to focus on oncological patients but this was not reflected in the example stem questions the facilitator of the focus group used. |
| Surveys | | | | |
| Abarshi 2011[1] | Retrospective survey design with closed and open questions. Self-reported. | n=251. General practitioners who had looked after people in the last 3 months of their life (includes details of last 1 week of life).<br><br>Netherlands | 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. | Multivariate analysis undertaken, taking into account the person demographics. 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. |
| Domeisen 2013[32] | Delphi survey | n=252 Nurses, physicians, psycho-social-spiritual professionals, volunteers and carers from 9 participating countries:<br>Switzerland, Italy, Netherlands, Sweden, Germany, UK, Argentina, New Zealand, and Slovenia. | To describe the most pertinent phenomena in identifying whether a person is in the last hours or days of life from any condition. | The population of experts for the Delphi included both the multiprofessional team and lay members but not for all rounds of the Delphi. The different rounds had different populations and it wasn't clear how these were formed. |
| Brandt 2005[13] | Prospective observational study | n=474 All long term nursing home care people 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 | 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 with categories of cardiovascular disease, mental/behavioural disorders, and malignant | The doctors were asked to enter people into the study when they believed they were in the last 6 weeks of life. Even though this is indirect from the protocol looking at the last days of life, the majority of the people who were included had died by day 9 of the study. |

| Study | Design | Population (n) | Research aim | Comments |
|---|---|---|---|---|
| | | home.<br><br>Netherlands | neoplasms. | |
| Christakis 2000[22] | Prospective survey design | n=468 people were discussed with 343 doctors who estimated their likely time of death. The actual date of death was then later collated from national records.<br><br>USA | To investigate factors (such as optimism, and pessimistic and medical experience) that affect doctors' prognostication of people in outpatient hospice settings. | Included an indirect population- the median survival was 24 days of the people included. |
| Kumagai 2012[54] | Delphi survey | n=72 community palliative nurses who had experience in looking after people who had died from either lung or gastrointestinal cancer.<br><br>Japan | To identify predictors of the last 10 and 3 days of life in people with lung, gastric, or colorectal cancer at home. | The methods were well described with a good use of existing literature to formulate the initial Delphi. There was poor response rate in the study. The study only focuses on symptoms from 2 particular conditions. |

### 5.4.2 Summary of themes

**Table 17: Themes and sub-themes derived from the evidence**

| Main theme | Sub-themes |
|---|---|
| Physical changes | • Cardiovascular and respiratory changes<br>• Deterioration of physical condition<br>• Reduced oral intake<br>• Worsening Pain |
| Spiritual and psychosocial changes | • Social withdrawal<br>• Changes in mood<br>• Changes in spiritual experience |
| Difficulty in recognising dying | • Complexity of recognising dying<br>• Factors affecting prognostic accuracy |
| The trajectory of dying | • Symptom changes in the last days of life<br>• Variable in length |
| Managing uncertainty | • Changes in patient management |

**Table 18: Summary of evidence: Theme 1 - physical changes – *health care professionals experiences in recognising adults that are likely to be entering their final days of life or who may be recovering, and how the uncertainties about either situation can be dealt with.***

| Study design and sample | | | Quality assessment | | |
|---|---|---|---|---|---|
| **n** | **Design** | **Descriptors of themes** | **Criteria** | **Rating** | **Overall** |
| Sub-theme 1: Cardiovascular changes | | | | | |
| 5 | 2 interviews<br>2 Delphi studies<br>1 prospective cohort study | Two qualitative studies[29,99] interviewed nursing staff with experience of caring for oncology patients in the last days of life. They described cardiovascular changes as important in recognising that people were entering this phase of their illness. Observations they identified included:<br>• tachycardia<br>• hypotension<br>• pyrexia<br>• increased respiratory rate<br>• desaturation on pulse oximetry.<br>• "*you often see them (patients) being restless at night: they can hardly sleep due to this feeling of dyspnoea and their anxiety*"<br>• terminal secretions<br>• periods of Cheyne stokes respiration.<br><br>These findings were reflected in 2 Delphi studies. One Delphi study[54] asked a population of community hospice nursing staff (n=72) to identify relevant symptoms that enabled them to recognise when people with lung or gastrointestinal cancer were entering the last days of life. They reported the following as useful in recognising the last 3 days of life in these people which overlap with the qualitative findings:<br>• Breathlessness at rest<br>• mandibular breathing | Limitations of evidence | Minor limitations | MODERATE |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Saturated | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| n | Design | | Criteria | Rating | Overall |
| | | • terminal secretions<br>• changes in respiratory rhythm<br>• apnoea<br>• increases of sputum<br>• difficulty coughing up sputum<br>• low oxygen saturations<br>• forced breathing<br><br>A further Delphi study[32] asked all healthcare professionals and lay members (n=252) to identify the symptoms they found relevant in recognising people in the last hours and days of life dying from all conditions. A number of the symptoms identified overlapped with those mentioned in the qualitative studies including:<br>• death rattle<br>• changed breathing rhythm<br>• changes in breathing<br>• changes in breathing pattern<br>• cold extremities<br><br>A further prospective observational study[13] asked doctors who had recognised people were entering the last 6 weeks of life which symptoms were most important in making this diagnosis (n=474). Increasing breathlessness was 1 of the top 4 reported symptoms rated in 21.3% of the cases included. This was then later analysed with data on the disease that the person died from. The study reported that increasing breathlessness was most useful in recognising people dying from diseases of the circulatory system. | | | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **n** | **Design** | | **Criteria** | **Rating** | **Overall** |
| Sub-theme 2: Deterioration of physical condition | | | | | |
| 5 | 2 interviews<br>2 Delphi studies<br>1 prospective cohort study | Two qualitative studies[29,99] interviewed nursing staff with experience of caring for oncology patients in the last days of life. They described deterioration of physical condition as important in recognising that people were entering this phase of their illness. Signs and symptoms they identified as important included:<br>• fatigue<br>• lack of energy<br>• extreme weakness<br>• somnolence or difficulty sleeping<br>• decreased level of consciousness<br>• bed bound and loss of mobility<br>• a glazed look in the eye<br>• delirium<br><br>These findings were reflected in 2 Delphi studies. One Delphi study[54] asked a population of community hospice nursing staff (n=72) to identify relevant symptoms that enabled them to recognise when people with lung or gastrointestinal cancer were entering the last days of life. They reported the following as useful in recognising the last 3 days of life in these people which overlap with the qualitative findings:<br>• cannot move limbs independently<br>• cannot open eyes to call<br>• drowsy<br>• confusion/delirium<br>• coma | Limitations of evidence | Minor limitations | MODERATE |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Saturated | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **n** | **Design** | | **Criteria** | **Rating** | **Overall** |
| | | A further Delphi study[32] asked all healthcare professionals and lay members (n=252) to identify the symptoms they found relevant in recognising people in the last hours and days of life dying from all conditions. A number of the symptoms identified overlapped with those mentioned in the qualitative studies including:<br>• irreversible deterioration of consciousness<br>• physical deterioration<br>• restlessness<br>• semi-comatose<br>• organ failure<br><br>A further prospective observational study[13] asked doctors who had recognised people were entering the last 6 weeks of life which symptoms were most important in making this diagnosis (n=474). Generalised weakness was 1 of the top 4 reported symptoms rated in 31.8% of the cases included. This was then later analysed with data on the disease that the person died from. The study reported that generalised weakness and tiredness were most useful in recognising people dying from malignant neoplasms. | | | |
| Sub-theme 3: Reduced oral intake | | | | | |
| 5 | 2 interviews<br>2 Delphi studies<br>1 prospective cohort study | Two qualitative studies[29,99] interviewed nursing staff with experience of caring for oncology patients in the last days of life. They described reduced oral intake as important in recognising that people were entering this phase of their illness. Signs and symptoms they identified as important included:<br>• anorexia and weight loss<br>• cachexia and diminished mimetic muscles<br>• reduced oral intake<br>• reduced sense of taste | Limitations of evidence | Minor limitations | MODERATE |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Saturated | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| n | Design | | Criteria | Rating | Overall |
| | | • reduced urine output or anuria<br>• constipation/diarrhoea<br>• problems with swallowing medication<br><br>These findings were reflected in 2 Delphi studies. One Delphi study[54] asked a population of community hospice nursing staff (n=72) to identify relevant symptoms that enabled them to recognise when people with lung or gastrointestinal cancer were entering the last days of life. They reported the following as useful in recognising the last 3 days of life in these people which overlap with the qualitative findings:<br>• anorexia<br>• constipation/diarrhoea<br>• dry mouth<br><br>A further Delphi study[32] asked all healthcare professionals and lay members (n=252) to identify the symptoms they found relevant in recognising people in the last hours and days of life dying from all conditions. A number of the symptoms identified overlapped with those mentioned in the qualitative studies including:<br>• no fluid or food intake<br>• cannot drink<br>• cheeks hollow and sunken<br>• swallowing impossible<br><br>A further prospective observational study[12] asked doctors who had recognised people were entering the last 6 weeks of life which symptoms were most important in making this diagnosis (n=474). Reduced oral and nutritional intake were 2 of the top 4 | | | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **n** | **Design** | | **Criteria** | **Rating** | **Overall** |
| | | reported symptoms rated in the cases included, identified in 42.6% and 24.8% cases respectively. This finding was then later analysed with data on the disease that the person died from. The study reported that reduced oral and nutritional intake were most useful in recognising people dying from mental or behavioural disorders (predominantly dementia). It was also useful in recognising people with diseases of the circulatory system were in the last 6 weeks of life. | | | |
| Sub theme 4: Worsening pain | | | | | |
| 2 | 2 interviews | Two qualitative studies[29,99] interviewed nursing staff with experience of caring for oncology patients in the last days of life. They described worsening pain as important in recognising that people were entering this phase of their illness. Observations they identified included:<br>• *'"sometimes the pain is increased and sometimes the pain is just gone"'*<br>• less respondent to analgesia. | Limitations of evidence | Minor limitations | MODERATE |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Saturated | |
| Sub theme 5: Skin changes | | | | | |
| 3 | 2 interview studies<br>1 Delphi study | Two qualitative studies[29,99] interviewed nursing staff with experience of caring for oncology patients in the last days of life. They described skin changes as important in recognising that people were entering this phase of their illness. Observations they identified included:<br>• skin mottling<br>• *'"it is so clear for us [nurses and colleagues] when we see a pointed nose"'*<br>These findings were reflected in a Delphi[12] study that asked all healthcare professionals and lay members (n=252) to identify the symptoms they found relevant in recognising people in the last hours and days of life dying from all conditions. A number of the | Limitations of evidence | Minor limitations | MODERATE |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Saturated | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| n | Design | | Criteria | Rating | Overall |
| | | symptoms identified overlapped with those mentioned in the qualitative studies including:<br>• marble like skin<br>• pale around the nose and mouth | | | |

**Table 19: Summary of evidence: Theme 2 - spiritual and psychosocial changes - *health care professionals experiences in recognising adults that are likely to be entering their final days of life or who may be recovering, and how the uncertainties about either situation can dealt with.***

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| No. of studies | Design | | Criteria | Rating | Overall |
| Sub-theme 1:Social withdrawal | | | | | |
| 2 | 2 interview studies | Two qualitative studies[29,99] interviewed nursing staff with experience of caring for oncology patients in the last days of life. They described social isolation and declining interest in daily life as important in recognising that people were entering this phase of their illness.<br>*'"you see a…change in behaviour, a kind of separation from the world I guess"'*<br>*'"…[when you know what] their usual pattern of things are, and when that pattern changes, that's the biggest indicator for me"'* | Limitations of evidence | Minor limitations | MODERATE |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Saturated | |
| Sub-theme 2: Changes in mood | | | | | |
| 2 | 1 interview study | One qualitative study[99] interviewed nursing staff with experience of caring for oncology patients in the last days of life. They described people becoming agitated and anxious as important in recognising that people were entering this phase of their illness. One nurse reported '"*Yes, a couple of days before, they [patients] get anxious, especially in the evening and night and they want to* | Limitations of evidence | No limitations | HIGH |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme | Saturated | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | | **Criteria** | **Rating** | **Overall** |
| | | *have family around then. They also become socially withdrawn, and can make despondent comment things such as '"It is finished for me now"".* | saturation/sufficiency | | |
| Sub-theme 3: Changes in spiritual experience | | | | | |
| 2 | 2 interview studies | Two qualitative studies[29,99] interviewed nursing staff with experience of caring for oncology patients in the last days of life. They described a change in a person's spiritual experience as important in recognising that people were entering this phase of their illness. This could be reflected in:<br>• existential changes (for example lack of hope, 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]*"'<br>• the use of symbolic language. '"*Symbolic language is pretty common…. They talk about going on a trip*"' | Limitations of evidence | Minor limitations | MODERATE |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Saturated | |

**Table 20: Summary of evidence: Theme 3 - difficulty in recognising dying- *health care professionals experiences in recognising adults that are likely to be entering their final days of life or who may be recovering, and how the uncertainties about either situation can dealt with.***

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | | **Criteria** | **Rating** | **Overall** |
| Sub-theme 1: Complexity of recognising dying | | | | | |
| 3 | 2 interviews<br>1 Delphi study | Two qualitative studies[29,99] interviewed nursing staff with experience of caring for oncology patients in the | Limitations of evidence | Minor limitations | MODERATE |
| | | | Coherence of findings | Coherent | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | | **Criteria** | **Rating** | **Overall** |
| | | last days of life. They described the complexity of recognising dying and acknowledged the importance of their intuition rather than people's presentations.<br>• *'"I hardly ever see a transition or something like that, that makes me think: these are the final days [for that patient]"'*<br>• 84% of nurses in 1 study acknowledged that death had occasionally '"*caught them by surprise*"'<br>• The importance of intuition in recognising people entering the last days of life.<br><br>This was further reflected in 1 Delphi study[12] that asked all healthcare professionals and lay members (n=252) to identify the symptoms they found relevant in recognising people in the last hours and days of life dying from all conditions. They identified '*the intuition of professional, gut feeling*' as relevant in recognising people entering the end of life. | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Saturated | |
| Sub-theme 2: Factors that affect prognostic accuracy | | | | | |
| 2 | 2 surveys | Two surveys[2,22] explored the factors that improved doctors' ability to recognise dying people, through questions relating to the person, and their relationship with the doctor. One study found that only 20% of the diagnoses were accurate, 63% underestimated the survival time of the person and 17% over estimated. The study showed statistically significant relationships after multivariate analysis between:<br>• doctors in non-oncological medical subspecialties were the least likely to give correct estimates | Limitations of evidence | Minor limitations | MODERATE |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Saturated | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| No. of studies | Design | | Criteria | Rating | Overall |
| | | • predications that overestimated the survival time were associated with the most recent examinations and longer patient doctor relationships<br>• no relationship found between accuracy and number of years of practice of the doctor and the number of hospice referrals that doctor had made in the past year.<br>A further survey found an association between patient factors and accuracy in recognising dying in the near future. On multivariate analysis a diagnosis of cancer and low functional states both increased the chance of recognising death in the near future. Death in the near future was not recognised 3 times as often among people with cardiorespiratory (26%) and other (43%) illnesses compared to cancer (12%). | | | |

**Table 21: Summary of evidence: Theme 4 - the trajectory of dying- *health care professionals experiences in recognising adults that are likely to be entering their final days of life or who may be recovering, and how the uncertainties about either situation can dealt with.***

| Study design and sample | | | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | **Descriptors of themes** | **Criteria** | **Rating** | **Overall** |
| Sub-theme 1: Symptom Changes in the last days of life | | | | | |
| 1 | 1 survey | One Delphi study[54] reflected on the trajectory of disease. The survey asked a population of community hospice nursing staff (n=72) to identify relevant symptoms that enabled them to recognise when people with lung or gastrointestinal cancer were entering the last days of life. They asked nursing staff to choose symptoms for the last 10 days and the last 3 days. They symptoms differed quite significantly, with the following only being significant in the last 3 days:<br>• Cardiovascular symptoms<br>• Level of consciousness<br>• Respiratory muscles.<br><br>This was further reflected in another Delphi study[32] that asked all healthcare professionals and lay members (n=252) to identify the symptoms they found relevant in recognising people in the last hours and days of life dying from all conditions. They identified *'irreversible status'* as relevant in recognising people entering the end of life. | Limitations of evidence | Minor limitations | MODERATE |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Saturated | |
| Sub-theme 2: Variability in length of time. | | | | | |
| 1 | 1 Interview | One qualitative study[29] interviewed nursing staff with experience of caring for oncology patients in the last days of life. 93% of the nurses interviewed described the process of dying as variable in length. | Limitations of evidence | Minor limitations | MODERATE |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| No. of studies | Design | | Criteria | Rating | Overall |
| | | | Theme saturation/sufficiency | Saturated | |

**Table 22: Summary of evidence: Theme 5 - managing uncertainty-** ***health care professionals' experiences in recognising adults that are likely to be entering their final days of life or who may be recovering, and how the uncertainties about either situation can dealt with.***

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| No. of studies | Design | | Criteria | Rating | Overall |
| Theme 5: Managing uncertainty | | | | | |
| 1 | 1 interview | One qualitative study[51] explored junior doctors' perceptions on how they would manage people differently if they thought they were going to die.<br>• They would clarify the person's goals- '"*When you're talking about working up-micromanaging- every little thing, you should probably figure out [what] the patient and family would really want… I think [that] talks with the family would clarify these things*"'<br>• They reported they would improve communication with people and their families. *'"Yeah I would probably spend more time with the patient and the family- I would listen to their story"'*<br>• They also commented they would spend more time with people and order less investigations – *'"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 of evidence | Minor limitations | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Not applicable | |
| | | | Theme saturation/sufficiency | Saturated | |

## 5.5 Economic evidence

**Published literature**

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

## 5.6 Evidence statements

**Clinical - quantitative**

The quantitative evidence review found that there is moderate quality evidence from observational studies using multivariate analysis of people with terminal cancer admitted to a palliative care unit, reporting Eastern Cooperative Oncology Group (ECOG) score, fatigue and desaturation. One study of 374 people showed a reduced ECOG score as a predictor of mortality within 7 days, OR 3.45 (1.65, 7.20). An associated study of people aged 65 years and over (n=459) supported this finding, OR 2.02 (1.40, 2.92). A low quality study of 93 people in the same setting determined fatigue and desaturation as predictors of mortality within 2 weeks, HR 5.90 (2.04, 17.03) and HR 3.30 (1.42, 7.66), respectively.

An increased triage pulse (greater than or equal to 110 bpm) and increased triage respiration (greater than 28/min) was identified as a predictor of mortality within 2 weeks, RR 4.92 (1.42, 17.09) and RR 12.72 (3.08, 52.49), respectively (low quality evidence). This was from 1 observational study (n=122) using multivariate analysis of people with cancer presenting to an emergency department with acute dyspnoea as a primary or secondary complaint.

Moderate quality evidence from a diagnostic observational study of 357 people with terminal cancer admitted to a palliative care unit, indicated that clinical signs and symptoms (palliative prognostic score, Richmond agitation scale, death rattle, apnoea periods, respiration with mandibular movement, peripheral cyanosis, Cheyne-Stoke breathing and pulselessness of radial artery) have a high specificity (81.3% - 99.2%) and varying sensitivities (11.3% - 64.0%) for diagnosing mortality within 3 days. Two large, but low quality, diagnostic retrospective observational studies of people admitted to hospital for more than 24 hours (n=42701) and presenting at the emergency department (n=71453), showed that laboratory tests can diagnose mortality within 2 days (sensitivity 36.2 - 71.8%, specificity 64 - 84.7%). Area under the curve for these tests ranged from 0.53 - 0.80, indicating very poor to moderate test accuracy.

**Clinical - qualitative**

Qualitative evidence indicated several themes around healthcare professionals' experiences in recognising adults that are entering their final days of life or who may be recovering. Moderate quality evidence from 5 studies (2 qualitative studies, n=33; 2 Delphi studies, n=324; and 1 observational study, n=474) indicated that physical changes, including cardiovascular changes, deterioration of physical condition, reduced oral intake, worsening pain and skin changes, were observed. Two moderate quality qualitative studies of 33 healthcare professionals identified presentation of spiritual and psychosocial changes, such as social withdrawal, changes in mood and changes in spiritual experience.

The theme of difficulty in recognising dying was found to include the following subthemes; complexity of recognising dying (2 interviews and 1 survey of moderate quality, n=285) and factors that affect prognostic accuracy (2 surveys of moderate quality, n=719). The dying trajectory was recognised as variable in length of time (1 study of moderate quality, n=15).

Little evidence was identified for managing uncertainty for those entering the last days of life or who may be recovering. One low quality qualitative study (n=8) was identified that explored junior doctors' perceptions on how they would manage people differently if they thought they were going to die.

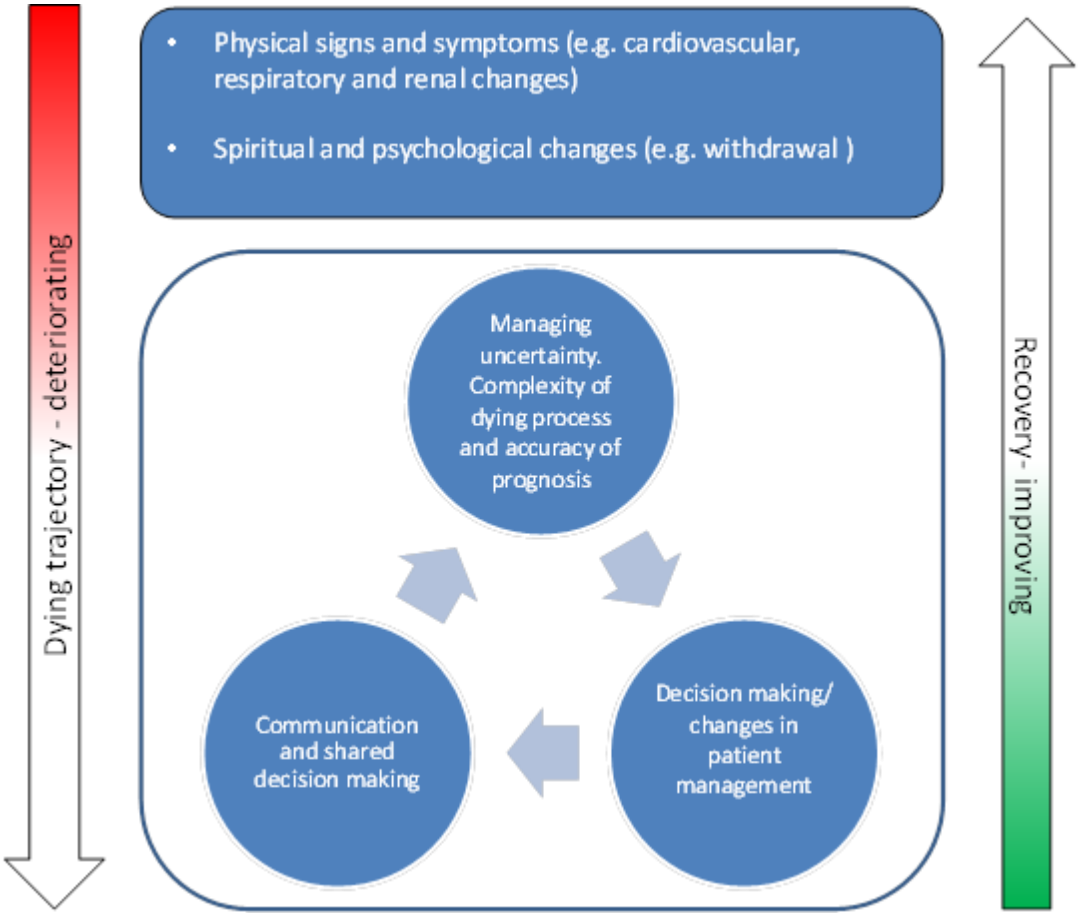
**Economic**

No relevant economic evaluations were identified.

## 5.7 Conceptual framework

The evidence identified from the quantitative and qualitative reviews has been summarised graphically in a conceptual framework shown in **Figure 3**. This reflects the themes identified from the qualitative review along with the evidence from the quantitative review. The Committee were keen to represent the dying trajectory and the potential for improving within this framework. The Committee considered it an important tool for bringing together the mixed methods review and aided formulation of recommendations.

**Figure 3: Conceptual framework for recognising dying**



## 5.8 Recommendations and link to evidence

| | |
|---|---|
| **Recommendations** | **1. If it is thought that a person may be entering the last days of life, gather and document information on:**<br>**• the person's physiological, psychological, social and spiritual needs**<br>**• current clinical signs and symptoms**<br>**• medical history and the clinical context, including underlying diagnoses**<br>**• the person's goals and wishes**<br>**• the views of those important to the person about future care.**<br><br>**2. Assess for changes in signs and symptoms in the person and review any investigation results that have already been reported that may suggest a person is entering the last days of life. These changes include the following:**<br>**• signs such as agitation, Cheyne–Stokes breathing, deterioration in level of consciousness, mottled skin, noisy respiratory secretions and progressive weight loss**<br>**• symptoms such as increasing fatigue and loss of appetite**<br>**• functional observations such as changes in communication, deteriorating mobility or performance status, or social withdrawal.**<br><br>**3. Be aware that improvement in signs and symptoms or functional observations could indicate that the person may be stabilising or recovering.**<br><br>**4. Avoid undertaking investigations that are unlikely to affect care in the last few days of life unless there is a clinical need to do so, for example, when a blood count could guide the use of platelet transfusion to avoid catastrophic bleeding.**<br><br>**5. Use the knowledge gained from the assessments and other information gathered from the multiprofessional team, the person and those important to them, to help determine whether the person is nearing death, deteriorating, stable or improving.**<br><br>**6. Monitor for further changes in the person at least every 24 hours and update the person's care plan.**<br><br>**7. Seek advice from colleagues with more experience of providing end of life care when there is a high level of uncertainty (for example, ambiguous or conflicting clinical signs or symptoms)about whether a person is entering the last days of life, may be stabilising or if there is potential for even temporary recovery.** |
| Relative values of different outcomes | The Committee designed the protocol for this review on the symptom categories as described in Domeisen et al., 2013,[32] and felt critical outcomes included:<br>- Breathing (including rattle and irregular breathing)<br>- General deterioration (including extreme weakness)<br>- Consciousness or cognition (including reduced cognition) |

| | |
|---|---|
| | - Related to condition of skin (including discolouration).<br>The Committee considered the issues around uncertainty in recognising death and what signs and symptoms are present in deteriorating or recovering people. The review included quantitative and qualitative questions constructed to capture a wider pool of evidence, including the perspectives of the dying person and those important to them.<br>Prognostic and diagnostic outcomes were prioritised for inclusion in the review with confounding factors such as treatments that may supress levels of consciousness or artificial organ support, such as ventilation.<br>Although biochemical markers were not specifically included in the scope in relation to their role in recognising dying, the Committee recognised that many people, particularly those being cared for in hospital, will be having laboratory tests. They requested that, where available in the evidence reviewed, this information should be captured and presented. The literature search was performed around recognising dying and signs and symptoms, and any laboratory test data were presented to the Committee.<br>The Committee noted that there are tools which can help clinicians to prognosticate if a person has years or months (and possibly just weeks) to live – these tools exist for cancer and Chronic Obstructive Pulmonary Disease (COPD). These tools are not sensitive enough for use in our remit, that is, to recognise when a person is shifting into the last days or hours and therefore prognostic tools were excluded from the evidence review. |
| Trade-off between clinical benefits and harms | The quantitative review identified evidence of a range of clinical signs and symptoms that may indicate imminent mortality, such as the Eastern Cooperative Oncology Group (ECOG) scale, death rattle, apnoea periods, respiration with mandibular movement and peripheral cyanosis, although sensitivity was low. Weak evidence was identified for laboratory tests for diagnosing imminent death. It is noted that the majority of the studies were conducted in specific populations (for example, people with terminal cancer). The Committee discussed the trade-off of having a high sensitivity versus a high specificity of identifying imminent death and considered that both were very important, but that a high specificity is key, so that nearing death is not mistakenly diagnosed.<br>The clinical signs and symptoms identified in the review are non-invasive tests or measures and therefore should not cause any harm to the dying person. Benefits of correctly recognising imminent death may allow opportunity for shared decision making and allow valuable time between the dying person and those important to them. No harms were identified for using signs or symptoms for recognising when a person is entering the last days of life. |
| Trade off between net health benefits and resource use | No economic evaluations were identified for strategies that recognised when the individual was entering the dying phase.<br>Such strategies will have economic consequences as once it is recognised that an individual is entering the dying phase, they will receive different treatment that will impact resource use. Correctly predicting when an individual is in the dying phase is integral to patient outcomes to ensure protocols are in place and unnecessary interventions are not initiated.<br>Most of the symptoms used to predict when an individual is entering the dying phase do not require any equipment or tests for detection and can be gathered from examining the person. These signs and symptoms will likely have been gathered through regular monitoring anyway. The Committee stressed the need for improved communication between healthcare professionals and that a specialist should be consulted when there is great uncertainty. However, in most cases, this assessment should be completed by clinicians, therefore it is unlikely there are increased upfront costs incurred for recognising dying, apart from within community settings where there could be some additional costs if the clinician has to be called to do the |

| | |
|---|---|
| | assessment.<br>An increase in the number of correctly predicted cases could reduce downstream costs as they prevent unnecessary interventions being initiated. |
| Quality of evidence | Low to moderate quality prognostic and diagnostic outcomes were identified for the quantitative review. The Committee was not surprised that several signs and symptoms were highlighted as predictors of mortality, such as ECOG status, triage pulse and triage respiration, especially given the specific populations of the studies (people with terminal cancer and people with terminal lung cancer with acute dyspnoea, respectively). Other signs and symptoms were of interest to the Committee and gave high specificities, but low sensitivities for diagnosis of mortality within 3 days,[47,48] such as noisy respiratory secretions, apnoea periods, and respiration with mandibular movement, peripheral cyanosis, Cheyne-Stoke breathing and pulselessness of radial artery. No evidence could be pooled given the variation in outcomes.<br>Moderate to high quality evidence across themes were identified in the qualitative review. These included the following main themes:<br>• physical changes<br>• spiritual and psychological changes<br>• difficulty in recognising dying<br>• the trajectory of dying<br>• managing uncertainty.<br>The themes identified in the qualitative study supported those identified in the quantitative review. These have been used to construct the conceptual framework used to highlight both the deteriorating and recovering aspects of the person's trajectory and links between uncertainty, managing accuracy of prognosis, communication and shared decision making. |
| Other considerations | From the evidence review, the Committee recognised similar factors that they use in their clinical practice to recognise entering the dying phase. They drew on the importance of gathering information from multiple sources in order to do this, including different members of the multiprofessional team. These included a review of the person's medical history and trajectory of symptom deterioration. The Committee recognised that in some people this can be a reflection of a growing need for physiological support, particularly in the intensive care setting. The Committee also discussed the importance of clarifying any change in the dying person's social, spiritual and psychological needs, and also eliciting any goals and wishes they may have, which may be listed in the dying person's advance care plan. The Committee wanted to highlight the importance of basic principles of care when interacting with the dying person in the last days of life, considering the views of the person and those important to them.<br>The Committee wanted to emphasise to those recognising dying that the trajectory also includes potential recovery and improvement and that uncertainty in diagnosing the individual should be taken into account when assessing for potential recovery. The Committee also discussed the reversibility of each individual symptom, for example for a person presenting with progressive weight loss there may be treatable causes that are inhibiting someone from eating.[37] The Committee therefore made a consensus recommendation that noted that changes in signs and symptoms could also represent stabilizing of the person's condition , even if temporarily, or that recovery was possible.<br>The evidence review highlighted numerous signs and symptoms that could be used in recognising dying, including fatigue or progressive weight loss. The Committee highlighted that some signs and symptoms may be specific to the last days of life including Cheyne Stokes breathing and noisy respiratory secretions but, whilst specific, they are not universal symptoms. |

The evidence review suggested functional observations were predictors of mortality; in particular the Eastern Cooperative Oncology Group (ECOG) score. The Committee noted that this was not widely used in the UK, but is similar to the WHO performance scale (also called the Zubrod score). The Committee noted that it is specifically deterioration in the ECOG score that would indicate a likelihood of entering the last days of life, recognising that some disabled people may be at a score of 4 outside of illness. Although not identified in the evidence review, the Committee discussed other scores that may be useful, such as the Barthel Activities of Daily Living Index, Karnofsky Performance Status Scale and the Australia-modified Karnofsky Performance Scale. The value of laboratory tests, such as renal function tests or radiological imaging, in recognising dying was discussed. The Committee noted that, whilst these can be useful tests in practice in an acute setting, these tests may not be appropriate to support recognising dying when people are dying in community settings, as they are invasive and may be considered inappropriate to measure. They chose therefore only to include them in their recommendation if they were available and noted that any data should be used in conjunction with other information of signs and symptoms as discussed above. The Committee made a further consensus recommendation that acknowledged that there may be some circumstances where undertaking clinical tests, even in the last 2-3 days of life, should be undertaken if there was a clinical imperative to do so. That is, the results would directly impact on the care of that person. The Committee felt that such examples would include situations where a full blood count could guide the use of platelet transfusion to avoid catastrophic bleeding. Additionally, measurement of serum electrolytes may helpfully indicate a cause for persistent agitation and seizures.

The Committee discussed the evidence base and noted that it was in small and specific populations, such as people with lung cancer, whereas this guidance is looking at a broader population. The Committee recognised that the likely time of death is particularly difficult to anticipate in some chronic conditions, for example dementia, when the disease trajectory is typically variable and there may be a long-standing reduced level of functioning. The Committee also discussed that specialist advice should be sought when there is continued uncertainty or for specialist conditions, for example, in circumstances when an individualised assessment is required for multimorbidity. Colleagues with more experience may include specialist palliative care teams, but these may also include other specialties such as geriatrics, cardiologists or renal physicians. The Committee also felt strongly that reversible conditions should be assessed and noted that some signs and symptoms of improvement may be temporary. This links in to considering the whole disease trajectory and ensuring that there is recognition of recovery as well as when the person may die.

From the qualitative review the Committee noted the theme of overestimation of a prognosis by consultants with long-term relationships with people. This is due to consultants not wanting to disrupt their relationship with the person, which may happen as a result of the bad news. They also noted the other extreme, where doctors who have never seen the person before are less concerned about informing the person of a poor prognosis or diagnosis.

The Committee discussed the importance of monitoring for further changes in the person at least every 24 hours, but that more frequent monitoring may be required as symptoms can change quickly.

The attitude of the person was recognised as a very important determinant; especially if they have decided themselves that the time is right for them to die. For example, reversible factors may have been identified, but the person may not want interventions to treat them. An important part of decision making was identified to ensure that the person is asked what they wish and how long they may wish to continue treatment for. The Committee discussed the importance of good communication and shared decision making as being critical components of care (see

| | |
|---|---|
| | Chapters 1 and 7).<br><br>The Committee agreed that it is important that the likelihood that a person is entering the last few days of life is clearly communicated to all concerned including the person (if appropriate), the family and others important to them, as well as to other professionals involved in delivering care. They noted that not all people in the dying phase wished to be informed of their prognosis and, as such, chose to make this point specifically in their recommendations. The uncertainty around recognising the dying phase often lies uncomfortably with many healthcare professionals and the Committee noted that this may lead to poor communication and avoidance of frank discussions with the dying person and others. This approach in turn may give rise to delayed or inappropriate clinical decision-making and cause unnecessary distress.<br><br>The Committee noted the importance of updating the care plan with any decisions regarding recognising dying. This is of paramount importance to alerting colleagues to the person's deteriorating condition, or possible recovery, so consistent care is given from all involved, preventing unnecessary distress to the dying person in their last days of life.<br><br>The Committee agreed that managing uncertainty around recognising dying remained a challenge in practice beyond the use of any clinical judgement. The review of the evidence identified potential predictive signs and symptoms for recognising death, but uncertainty still remains. The Committee were interested in the role of the multiprofessional team and how they may be able to manage this uncertainty to reduce its impact on clinical care, shared decision making and communication, and therefore chose to make a research recommendation.<br><br>The Committee made a separate recommendation around seeking advice from colleagues with more experience of providing end of life care and agreed this may include specialist palliative care teams or other relevant specialties whose input would reduce the uncertainty in recognising dying. |

## 5.9 Research recommendation

1. **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?**
   - **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.**

# 6 Communication

## 6.1 Introduction

Communication is crucial when a person is entering the last days of life. As well as a biological process involving physical changes, dying is also an important social and spiritual time when the person may experience psychological changes. It is important that the dying person and those important to them are able to prepare for death and make any necessary arrangements.

The need for good communication at the end of life is an issue that arose in the More Care Less Pathway review of the Liverpool Care Pathway.[30] The report highlighted many examples of substandard patient care, including inadequate documentation of care plans, use of euphemisms such as 'making them comfortable' and inexperienced junior doctors having discussions about dying without consulting senior colleagues.

Poor communication at this stage of life can lead to possible misunderstandings and unnecessary distress in dying people and those important to them and lose people precious time that they could be using to put their affairs in order or saying goodbye. It can also create a loss of confidence and trust in healthcare professionals. For example, relatives may misconstrue cessation of routine observations as a lack of care. It has been perceived that much of the distress and controversy surrounding the Liverpool Care Pathway could have been prevented by sensitive and timely communication between clinicians, relatives and other carers. The More Care Less Pathway report highlighted this as a "non-negotiable aspect of best practice in end of life care".

The Committee noted that NICE had already published related guidance on patient experience in adult NHS services[74] that contained relevant recommendations for effective communication that would be applicable to this population. However, given their observation in the previous chapter that some clinicians are uncomfortable with discussing this sensitive topic, the Committee felt that, in order to provide useful guidance for effective communication at the end of life and to identify areas for potential training in communication skills, they would ask the following question that specifically aimed to identify the barriers and facilitators to effective communication.

## 6.2 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?

For full details see review protocol in Appendix C.

**Table 23: Characteristics of review question**

| | |
|---|---|
| **Population and setting** | Adult people 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. |
| **Topic of interest** | • 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<br>• 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. |

| | |
|---|---|
| **Context** | **Context**:<br>Communication about the likelihood of entering the last days of life or recovering.<br><br>**Outcomes**:<br>Themes will be identified from the literature found. |
| **Review strategy** | Study designs to be considered: qualitative studies (for example, interviews, focus groups, observations). A thematic analysis of the data will be conducted and findings presented.<br><br>If any studies include informationon advance directives we will extract this information for discussion with the **Committee**. |

## 6.3 Clinical evidence

Four qualitative studies and 2 retrospective surveys were included in the review,[7,8,40,42,49,90] these are summarised in Table 13 below. Key findings from these studies are summarised in the clinical evidence summary below (Table 24 to Table 29). See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, and excluded studies list in Appendix L.

We searched for qualitative studies to explore the experiences, opinions and attitudes of the dying person, family members and healthcare providers 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.

No studies were identified that elicited experiences or perceptions of the dying person. One American study[40]described the experiences and opinions of relatives of critically ill people on an intensive care unit, while 2 other studies (from Canada[7], and America[8]) focused on experiences of healthcare providers as part of a general medical ward team and intensive care unit nurses respectively. A further UK[49] study was identified which interviewed both bereaved carers and healthcare professionals about people that had died in acute hospital settings, about the general care they received including communication of prognosis.

Two additional surveys from Norway and the USA were identified that investigated associations with communication of likelihood of entering last days of life, again, focusing on the experiences of healthcare providers.

While none of the studies focused their analysis specifically on the communication of likelihood of entering the last days of life, communication of prognosis (including likelihood of death in hospital) was a facet of the discussions analysed in each of the papers.

### 6.3.1 Summary of included studies

**Table 24: Summary of studies included in the review**

| Study | Design | Population | Research aim | Comments |
|---|---|---|---|---|
| Qualitative studies (including 1:1 interviews, focus groups, partner interviews, semi-structured interviews focus groups) | | | | |
| Anselm 2005[7] | Focus groups | n=10 attending physicians<br>n=24 residents<br>n=33 nurses<br><br>Canada | To elicit perspectives of healthcare professionals on barriers to communication regarding end-of- | Unclear what "end-of-life discussions" that were explored entailed specifically. |

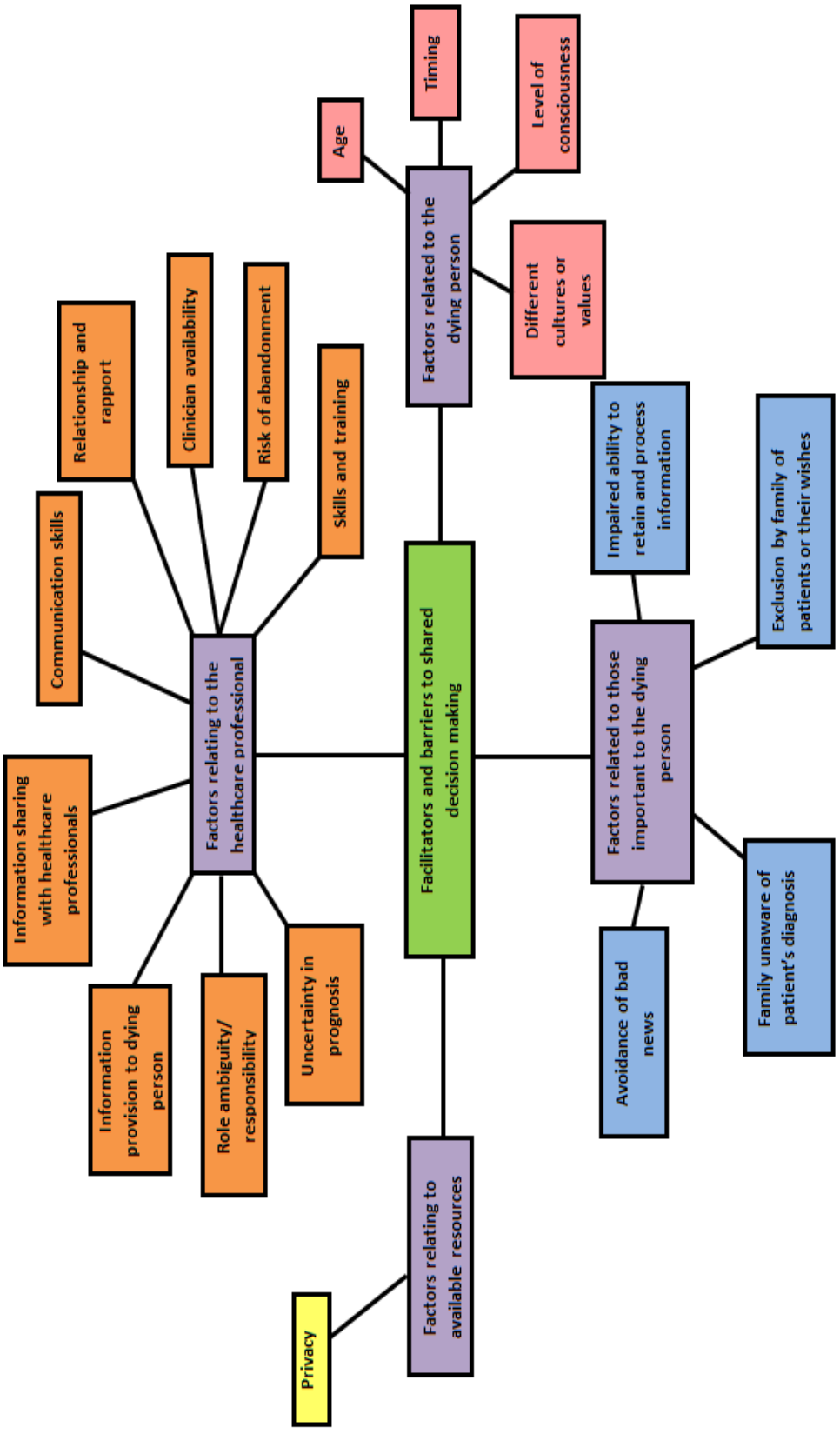
| | | | | |
|---|---|---|---|---|
| | | | life. | |
| Aslakson 2012[8] | Focus groups | n=32 surgical intensive care unit nurses<br><br>USA | To identify barriers to 2 key components of palliative care; optimal communication regarding prognosis and, optimal end of life care. | Prognosis defined specifically as "likelihood of in hospital death" in conversations with participants. |
| Gutierrez 2012[40] | In-depth interviews | n=20 family members of ICU patients with >50% risk of in-hospital mortality<br><br>USA | To describe the experiences of needs of family members surrounding prognostic communication for people at high risk of death in an ICU. | Data collection and analysis thorough. |
| Jackson 2010[49] | Semi structured interviews | n=38 bereaved carers and healthcare professionals involved in the care of people who had passed away in a hospital setting.<br><br>UK | To explore the perceptions of relatives and health care professionals of care received in the last 48 hours of life of people in hospital settings. | Very poorly reported methodology. Although a direct setting, the nature of the semi structured interview was not given, resulting in the context of the quotes and themes hard to ascertain. |
| Surveys | | | | |
| Houttekier[42] | Retrospective survey | Physicians surveyed after patient death in hospital.<br><br>n=228 people<br><br>Netherlands | To examine whether physician awareness of impending death is related to communication and quality of care and of dying in last 3 days of life. | Closed questions only, analysed quantitatively. |
| Sullivan[90] | Retrospective survey | Physicians surveyed after patient death in hospital.<br><br>n=196 people<br><br>USA | To describe whether and when physicians recognise and communicate the imminence of death and to identify potential barriers and facilitators. | Secondary analysis of cross-sectional survey. No qualitative analysis. |

### 6.3.2 Themes and sub-themes derived from the evidence

**Table 25: Themes and sub-themes**

| Main theme | Sub-themes |
|---|---|
| Factors related to those important to them | Impaired ability to retain and process information<br>Family unaware of patient diagnosis<br>Avoidance<br>Exclusion by family of patients or their wishes |
| Factors relating to the dying person | Timing<br>Different cultures or values<br>Level of consciousness<br>Age |
| Healthcare provider factors | Uncertainty in prognosis<br>Information provision to patient<br>Information sharing between healthcare professionals<br>Communication skills<br>Discomfort with discussion<br>Relationship to patient<br>Role ambiguity<br>Training and experience<br>Scheduling difficulties |
| Resource factors | Privacy |

**Figure 4: Theme map**



### 6.3.2.1 Evidence summary

**Table 26: Summary of evidence: Theme 1 – factors relating to those important to the dying person that can act as a facilitator or barriers in the communication of the likelihood of entering the last days of life.**

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | | **Criteria** | **Rating** | **Overall** |
| Sub-theme 1: Impaired ability to retain and process information | | | | | |
| 3 | 1 interview<br><br>2 focus groups | Three studies[7,8,40] reported on the dying person and those important to them as having impaired abilities to retain and process information surrounding the end of life. This acts as a barrier to communication surrounding end of life care. These studies incorporated the opinions of nursing staff, doctors and family members in the USA and Canada. Particularly they highlighted:<br><br>Difficulty hearing and retaining information<br><br>*"… you're so overwhelmed that you forget everything that has been in place (discussion of the patient's wishes) before this crisis happened"*<br><br>Not remembering to ask all questions<br><br>*"Patients and patient families have difficulty forming their questions and asking about their concerns."*<br><br>Confusion<br><br>"*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* | Limitations of evidence | Minor limitations | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Unclear | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | | **Criteria** | **Rating** | **Overall** |
| | | *family doesn't necessarily understand you."* | | | |
| Sub-theme 2: Family unaware of patient diagnosis | | | | | |
| 1 | 1 focus group | One study[8] that interviewed nursing staff on surgical intensive care units in America reported that family members being unaware of a dying person's diagnosis acted as a barrier to communication regarding prognosis. | Limitations of evidence | No limitations | MODERATE |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Saturated | |
| Sub-theme 3- Avoidance | | | | | |
| 2 | 1 focus group<br>1 interview | Two American studies[8,40] with populations of family members and healthcare professionals commented on family avoidance of bad news as a potential barrier to communication regarding prognosis. One study[40] commented that the majority of family members did not comment on this, but for 1 family member her method of coping "*…with this devastating news was to deny that it was happening... and refused to listen to any bad news."* | Limitations of evidence | Minor limitations | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Unclear | |
| Sub- theme 4: Exclusion by family of patients or their wishes | | | | | |
| 1 | 1 focus group | One study interviewing Canadian doctors and nursing staff[7] described the family shielding the patient's from end of life discussions as a barrier to communication of | Applicability of evidence | Minor limitations | LOW |
| | | | Theme | Coherent | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | **Descriptors of themes** | **Criteria** | **Rating** | **Overall** |
| | | prognosis.<br><br>*"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."* | saturation/sufficiency | | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Unclear | |

**Table 27: Summary of evidence: Theme 2 – factors relating to the dying person that can act as facilitators or barriers in the communication of the likelihood of entering the last days of life.**

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| No. of studies | Design | | Criteria | Rating | Overall |
| Sub-theme 1: Timing | | | | | |
| 1 | 1 focus group | One Canadian study[7] of doctors and nursing staff reported on the theme of timed discussion in relation to patient factors. They reported that "*poorly timed discussion may raise anxiety in or alienate patients 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.*" | Limitations of evidence | Minor limitations | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Unclear | |
| Sub-theme 2: Different cultures or values | | | | | |
| 2 | 1 interview<br>1 focus group | Two studies [7,8] with populations of doctors and nursing staff from America and Canada reported differences in cultures or values between the healthcare professional and the dying person or those important to them as a barrier to communication.<br>*'"Unfortunately, our concepts of patient autonomy and about decisions about treatment are very Anglo-Saxon based ideologies where it is a little more open in terms of dialogue among family members. In other cultures it just doesn't work that way…"'*<br>Societal values in general around death such as not | Limitations of evidence | Minor limitations | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Unclear | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| No. of studies | Design | | Criteria | Rating | Overall |
| | | recognising or appreciating death as a natural and acceptable part of life were also reported.<br><br>*"Another barrier is the perception of the general public and the perception of the families in terms of the success of a resuscitation effort…and how it's altered by the media and television shows…"* | | | |
| Sub-theme 3: Level of consciousness | | | | | |
| 1 | 1 survey | One survey[90,91] investigated the association between patient factors and the occurrence of communicating about death in America. They report that on multivariate analysis, decreased consciousness of the patient was an independent factor that increased the probability that someone had not discussed the possibility of dying with the patient. | Limitations of evidence | Major limitations | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | N/A | |
| Sub-theme 4: Age | | | | | |
| 1 | 1 survey | One survey[90,91] investigated the association between patient factors and the occurrence of communicating about death in America. They report that on multivariate analysis, the age of the patient was an independent factor that predicted whether or not someone had discussed the possibility of dying with the person. Older people were less likely to be told about the possibility of death compared with younger people, with the average age of people who were told being 60 years, compared with 72 years for those who | Limitations of evidence | Major limitations | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | N/A | |

| Study design and sample | | | Quality assessment | | |
|---|---|---|---|---|---|
| No. of studies | Design | Descriptors of themes | Criteria | Rating | Overall |
| | | were not told. | | | |

**Table 28: Summary of evidence: Theme 2 – factors relating to the dying person that can act as facilitators or barriers in the communication of the likelihood of entering the last days of life.**

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| No. of studies | Design | | Criteria | Rating | Overall |
| Sub-theme 1: Uncertainty in prognosis | | | | | |
| 4 | 2 focus groups<br>2 survey | Two studies[7,8] reported doctors and nursing staff in America and Canada who believe that uncertainty in diagnosis can act as a barrier to discussing prognosis in the end of life with people. One healthcare provider reported:<br>*"Often you 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."*<br>This theme was supported in the descriptive data collected in 2 surveys.[42,90] Both of these surveys collected data from doctors on people who had recently died in hospital in the Netherlands and the USA. They enquired at what point the physicians were confident that the patient was in the last days of life, and when the prognosis was discussed with the patient. Both studies reported that the more confident the physicians were in the diagnosis the more likely they were to discuss prognosis with the patient and family members. | Limitations of evidence | Major limitations | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Unclear | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | | **Criteria** | **Rating** | **Overall** |
| Sub-theme 2: Information provision to patient | | | | | |
| 3 | 1 interview<br><br>1 focus groups | Information provision was reported in 2 American studies[8,40] with populations including family members and nursing staff in ICUs as an important factor in communicating prognosis effectively. The following aspects of information provision to people were highlighted as potential barriers:<br><br>Use of terminology<br><br>*"Physicians both use language that the families do not understand and do not recognise it."*<br><br>Not ensuring understanding<br><br>*"People 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."*<br><br>Accuracy in information rather than optimism<br><br>*"We need hope, but we also need accurate information. We would rather have accurate information, rather than hope."*<br><br>*"…the most difficult part of communication, from our (families) point of view is getting perspective."*<br><br>*"Prognosis are unrealistic and often portray 'small victories' instead of overall prognosis."* | Limitations of evidence | Minor limitations | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Unclear | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | | **Criteria** | **Rating** | **Overall** |
| Sub-theme 3: Information sharing between healthcare professionals | | | | | |
| 2 | 2 interview<br><br>2 focus groups | Two studies[7,8] interviewed doctors and nursing staff in Canada and the USA. They reported that impaired information transfer between healthcare professionals could act as a barrier for effective communication of prognosis. Other professionals were felt to *"(not) communicate optimally with each other or with other institutions regarding end of life discussion"*. This lack of information transfer between the professions acts as a barrier to communication of prognosis, as they are unsure what other involved "*specialists and consultants have said regarding prognosis"*. This leads to *"inconsistencies between team members in communicating prognosis to families".*<br><br>This theme was linked with the difficulty in having multiple doctors involved in individual patient care. This was reported to act as a barrier to the communication of prognosis in 1 study[40] interviewing family members of ICU patients. One family member reported:<br><br>"*Ideally I would have loved to have 1 primary. One that does all the, you know…communicates."*<br><br>In another American study interviewing nursing staff in ITU,[8] the *"different opinions about prognosis between care provider"* was also reported to act as potential barrier to communication of prognosis. This was | Limitations of evidence | Minor limitations | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Unclear | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | | **Criteria** | **Rating** | **Overall** |
| | | further reported by a relative in a UK study that interviewed bereaved carers and healthcare professionals[49,50]: *'"You know, I had asked how long [until death] and [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."'* | | | |
| Sub-theme 4: Communication skills | | | | | |
| 2 | 1 interview<br><br>1 focus group | Two American studies interviewing nursing staff and family members of people on ITU both commented on communication skills as important in facilitating effective communication of prognosis.[8,40] Family members reported that it was far easier to hear bad news when it was delivered in "*a sensitive, caring, compassionate manner*", often drawing on the issue of rapport to convey this. One patient reports:<br><br>*"I…I think the medical is only 1 part of the equation. The quality of life, the human spirit… and being treated humanely, is so critically important and I think its lacking in the, in the education".*<br><br>Nursing staff on ITU reported that *"poor bedside manner by surgeons"* acted as a barrier in communicating prognosis. | Limitations of evidence | Minor limitations | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Unclear | |
| Sub theme 5: Discomfort with discussion | | | | | |
| 2 | 2 focus groups | Two studies[7,40] interviewing doctors and nursing staff in Canada and America reported that discomfort with | Limitations of evidence | Minor limitations | LOW |
| | | | Coherence of findings | Coherent | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | | **Criteria** | **Rating** | **Overall** |
| | | emotion involved acted as a barrier to end of life communication.<br><br>*"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".* | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Unclear | |

| | | | | | |
|---|---|---|---|---|---|
| Sub-theme 6: Relationship to patient | | | | | |
| 2 | 1 interview<br>1 focus group | Two studies[7,40] interviewed family members, doctors and nursing staff in America and Canada. They reported that the short term relationships they often have with people can act as a barrier in hospital settings to communicating prognosis.<br>*"It's not easy. Decisions for us are different than 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."* | Limitations of evidence | Minor limitations | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Unclear | |
| Sub-theme 7: Role ambiguity | | | | | |
| 2 | 1 interview<br>2 focus group | Three studies[7,8,40] with populations of family members, doctors and nurses in America and Canada reported role ambiguity as a barrier to the communication of prognosis. They report that when it is unclear whose role it is to discuss prognosis it can sometimes result in no one communicating it. One healthcare provider commented:<br>*"I think overall we need the development of clear definitions of roles… What the role of the physician, the role of the nurse?"*<br>Family members of people in ITU also commented on role ambiguity as a barrier to communication as there are often multiple teams involved and it is difficult to know who is responsible for the patient and who to ask questions to. | Limitations of evidence | Minor limitations | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Unclear | |
| Sub-theme 8: Training and experience | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 3 | 1 interview<br><br>2 focus groups | Three studies[7,8,40] with populations of family members, doctors and nurses reported healthcare professionals' lack of training and experience in communicating prognosis acted as a barrier to this happening. Some have commented that this is due to a lack of exposure in some specialities of communicating prognosis. One healthcare provided commented that:<br><br>*"No one teaches us how to do these things. There no course on this and quite frankly our role models for this are few…a lot of this is learned at the bedside. I think there is a role to be had for educating physicians in an approach."*<br><br>One family member interviewed commented:<br><br>*"I would like to see all staff have to go through more bedside manners"* | Limitations of evidence | Minor limitations | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Unclear | |
| Sub-theme 9: Scheduling difficulties | | | | | |
| 3 | 1 interview<br><br>2 focus groups | Three studies[7,8,40] with populations of family members, doctors and nurses in America and Canada reported scheduling difficulties as a barrier in end of life communication.<br><br>• Busy work schedules:<br><br>*"We are very busy and by definition if you are going to discuss this you have to be prepared to do it very slowly and patiently and wait for questions, answer questions. That's the biggest barrier for me. The absence of time that this sort of thing merits."*<br><br>• Frustration with the amount of time waiting to talk to a physician | Limitations of evidence | Minor limitations | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Unclear | |

| | | | | | |
|---|---|---|---|---|---|
| | | *"there is a lot of wait time since we've been here… waiting in the ICU family room for someone to come and talk to us after she was admitted"*<br>• Surgical team rounds before family is present<br>• other support resources not always available (social work, pastoral care, palliative). | | | |

**Table 29: Summary of evidence: Theme 4 – factors relating to resources that can act as facilitators or barriers in the communication of the likelihood of entering the last days of life.**

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | | **Criteria** | **Rating** | **Overall** |
| Sub-theme 1: Privacy | | | | | |
| 1 | 1 interview | One UK study[49,50] interviewed bereaved carers and healthcare professionals about the care of dying persons in hospital. Privacy, or lack of it, was raised as an important barrier or facilitator to good care. One bereaved carer reported this in terms of the communication of prognosis:<br><br>*"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 of evidence | Major limitations | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Unclear | |

## 6.4 Economic evidence

### Published literature

No relevant economic studies were identified. See also the economic article selection flow chart in Appendix F.

## 6.5 Evidence statements

### Clinical

Qualitative evidence indicated several themes around healthcare professionals' and family members' experiences, opinions and attitudes on the factors that encourage and prevent good communication between the dying person and those important to them and the healthcare professional when conveying the likelihood they are entering the last days of life. Low to moderate quality evidence was reported from 3 studies (3 qualitative studies, n=62) from the opinions of nursing staff, doctors and family members on factors relating to those important to the dying person that affect communication. These included an impaired ability to retain and process information, avoidance of discussing prognosis, family being unaware of the patient's diagnosis and exclusion by the family of the patient during the communication.

Low quality evidence on the factors relating to the dying person that facilitate or inhibit communication of prognosis were obtained from 2 studies (n=99) including people having a wide range of cultural and societal beliefs, or current circumstances meaning that communication is likely to raise anxiety. 1 observational study (n=196) also provided low quality evidence that people who had a higher level of consciousness and were younger were more likely to be informed of prognosis. 5 studies (3 qualitative studies n=119, and 2 observational surveys n=424) reported on factors related to the healthcare professional that can facilitate or hinder communication of prognosis. The low quality themes identified included uncertainty in prognosis, poor communication skills, lack of information provision to the patient, lack of training and expertise, and discomfort with discussion as acting as a barrier to communication.

1 qualitative study (n=38) reported low quality evidence on privacy acting as a barrier to communication of prognosis.

### Economic

- No relevant economic evaluations were identified.

## 6.6 Recommendations and link to evidence

| | |
|---|---|
| **Recommendations** | **8. Establish the communication needs and expectations of people who may be entering their last days of life, taking into account:**<br>• **if they would like a person important to them to be present when making decisions about their care**<br>• **their current level of understanding that they may be nearing death**<br>• **their cognitive status and if they have any specific speech, language or other communication needs**<br>• **how much information they would like to have about their prognosis**<br>• **any cultural, religious, social or spiritual needs or preferences.** |

| | |
|---|---|
| | **9. Identify the most appropriate available multiprofessional team member to explain the dying person's prognosis. Base this decision on the professional's:**<br>• **competence and confidence**<br>• **rapport with the person.**<br><br>**10. Discuss the dying person's prognosis with them (unless they do not wish to be informed) as soon as it is recognised that they may be entering the last days of life and include those important to them in the discussion if the dying person wishes.**<br><br>**11. Provide the dying person, and those important to them, with:**<br>• **accurate information about their prognosis (unless they do not wish to be informed), explaining any uncertainty and how this will be managed, but avoiding false optimism**<br>• **an opportunity to talk about any fears and anxieties, and to ask questions about their care in the last days of life**<br>• **information about how to contact members of their care team**<br>• **opportunities for further discussion with a member of their care team.**<br><br>**12. Explore with the dying person and those important to them:**<br>• **whether the dying person has an advance statement or has stated preferences about their care in the last days of life (including any anticipatory prescribing decisions or an advance decision to refuse treatment or details of any legal lasting power of attorney for health and welfare)**<br>• **whether the dying person has understood and can retain the information given about their prognosis.**<br><br>**13. Discuss the dying person's prognosis with other members of the multiprofessional care team, and ensure that this is documented in the dying person's record of care.** |
| Relative values of different outcomes | The Committee agreed that outcomes which highlighted the barriers and facilitators to communication of prognosis in the last days of life were vital to this review. These outcomes included the experiences, opinions and attitudes of the dying person, those important to them, and the healthcare professionals involved in their care, as it was felt each population would offer a unique and informative perspective on this topic. |
| Trade-off between clinical benefits and harms | The evidence identified a number of barriers and facilitators to effective communication of prognosis. These were divided into factors relating to the dying person, those important to them, and healthcare professionals. The Committee agreed with the findings presented, as they reflected observations from their practice. They agreed that adequate communication of prognosis improves the end of life care of dying people. It also improves the post death bereavement experiences of people important to the dying person, although this was not evidenced in the literature reviewed. Harms identified include the impact of poor communication of prognosis, causing unnecessary anger and confusion in the last days of life and beyond. The Committee felt that the benefit of good communication |

| | |
|---|---|
| | would always outweigh any potential distress caused. |
| Trade off between net health benefits and resource use | This review question focuses mainly on the content and methods of how communication should be delivered. The recommendations made are unlikely to have any economic consequences. |
| Quality of evidence | A qualitative review was conducted. Qualitative studies were identified from the perspective of those important to the family member and healthcare professionals. There were no identified studies from the perspective of the dying person. The quality of evidence ranged from low to moderate; this was due to limitations in studies, risk of bias and the applicability of the findings given that the studies were conducted in other healthcare settings to the UK, and were examining wider topics than the communication of prognosis. The recommendations were based on the evidence and the consensus opinion of the Committee members. There were no themes the Committee could identify from their experience that were not picked up in the evidence review, and similarly none of the included themes were felt to be out of place. |
| Other considerations | The Committee was aware of the guidance on effective communication contained within the NICE guideline on Patient experience in adult NHS services[74] and wished to draw attention to these as part of their overall recommendations in this section.<br><br>The Committee commented on the importance of tailoring communication for people with different needs, for instance cultural preferences, those for whom English is not their first language, people who have dementia or other cognitive impairments, and people with speech and language impairments. These and other factors, including their current understanding of their condition, should be assessed before communication takes place. The Committee felt that simple assessments of cognitive status, such as orientation to time or place, could be conducted by any healthcare professional delivering care, without the need for specialist help. The Committee noted the importance of reviewing and documenting communication needs, as these may change over the last days of life. The Committee recognised that some people prefer not to be informed of their prognosis fully and felt that the dying person's information requirements and wishes needed to be explored before communicating prognosis. The Committee also noted the importance of competent decision making using the dying person's advance care plan or any other stated preferences around care in the last days of life, including anticipatory prescribing decisions or refusals to specific treatments and made a recommendation in this regard.<br><br>Timing of communication of prognosis was recognised as important to good end of life care. The Committee recognised that it is difficult to judge when to initiate these discussions and there is no fixed appropriate time, as it will vary among dying people. They also agreed with the uncertainty in prognosis, identified as part of the evidence review, as a common barrier in practice to communicating prognosis early. They felt, however, that health and care professionals need to manage uncertainty effectively and that it should not be allowed to act as a barrier to communicating prognosis in a timely fashion. Instead discussions should take place as early as possible and include discussions with the dying person and those important to them.<br><br>The Committee was aware of anecdotal evidence of bereaved family members left angry and bereft at having no time to say goodbye or to reconcile with their relative when communication about the person dying was left too late. It was noted that, whilst some dying people and the people important to them may appear to want to avoid bad news, as reflected in the evidence review, most would rather have prognosis communicated with them as soon as it is recognised.<br><br>The Committee noted that a close relationship and good rapport between health and care professionals and the dying person helps with the sharing of information. It was noted that this contradicts the discussion in a previous evidence review on |

recognising dying, where a close relationship can lead to doctors overestimating a prognosis. However, the Committee felt that a good relationship facilitates communication of the sensitive subject of prognosis. However, if a health professional with prior knowledge or rapport was not available this could not be used as a reason not to communicate the information.

The Committee felt that health and care professionals sometimes do not have, or may lose, their skills and confidence in delivering difficult news, which can be experienced in a period of time where death is imminent and otherwise unexpected. Training programmes are available and health and care professionals should be encouraged to keep their skills updated. The General Medical Council has outlined specific general duties on doctors to keep their knowledge and skills up to date (see paragraph 8 of the core guidance Good medical practice).[37] However, while training is important it was recognised that it can be hard to sustain what has been learnt if the professional does not regularly use these skills. The Committee was not aware of any research found which identifies whether training in difficult conversations has been successful, or whether the communication skills of staff have improved after training. Because of these reasons, and the fact that training was outside the scope of this guideline, a recommendation was not made.

The Committee discussed the content of discussion of prognosis with the dying person or those important to them. They felt that this should be individualised to the dying person based on initial assessment. However, there were some areas of good practice the Committee highlighted as important, including providing accurate information, avoiding false optimism, and appropriately ascertaining and addressing any fears or concerns of the dying person. The Committee discussed that it may be relevant to sensitively talk about the dying person's mode of death with the person and those important to them, such as the likeliness of catastrophic haemorrhage or severe vomiting, or the management of implantable cardioverter defibrillators at the end of life to minimise distress. The Committee felt it was important to provide a contact detail for the named lead clinician or other members of the multiprofessional team such as social workers or faith advisors for further discussion about any questions the dying person may have.

The Committee noted in the evidence review that those important to the dying person may wish to try and withhold information regarding prognosis from the dying person. The Committee recognised this was a problem in their clinical experience. They noted that any requests of this nature should be dealt with sensitively and respectfully. but that clinicians should always act in the dying person's best interest. The Committee felt that this could be achieved by exploring the reasons why the family (or others) may wish to withhold information from the dying person, explaining why the dying person might find it difficult to have information withheld and explaining that the clinicians have the responsibility to act in the dying person's best interest whilst trying to find a mutually agreeable way forward. The General Medical Council has also provided guidance for doctors in this area in its document: Treatment and care towards the end of life: good practice in decision making. [37] The committee did not intend their recommendations to address, in any detail, any legal requirements related to notification or consent further to the Tracey case[27] or the obligation to provide information on material risk of any treatment based on the Montgomery judgment[95] but felt that clinicians should be aware of the impact of these legal issues as part of their practice.

# 7 Shared decision making

## 7.1 Introduction

Recognising and communicating that a person is in the last few days of life is essential for good end of life care. Ensuring good communication about this with the person and those important to them is a crucial part of shared decision making.

Shared decision making is considered by the Committee to be an important factor to enable appropriate changes in clinical management. This ensures that the dying person's expressed wishes are considered and met. The Committee noted that NICE had already published related guidance on patient experience in adult NHS services[74] that contained relevant recommendations linked to shared decision making which would be applicable to this population.

Caring for people who are probably going to die within hours or days carries special responsibilities for the clinicians, which may not apply in other medical scenarios. One particular issue that the Committee recognised is when a dying person had expressed specific preferences or wishes regarding their care, but circumstances in their final illness indicate that their interests might be better served if these were not observed. For example, a person may have indicated a preference not to have a syringe pump for medication as they were dying, but then the person develops status epilepticus as a result of cerebral disease associated with their condition. It would place the clinician in a very difficult situation professionally if they followed the patient's preference and treated the fitting over several hours or days with short-acting injections of anti-epileptic drugs. This course of action would also have a significant impact on the experience of those important to the patient who had to observe the fitting. In this case, it could be argued that it would be better to start a syringe pump with a continuous infusion of anti-epileptic drug to control the fitting. If the patient recovers and regains consciousness, the decision could be explained and a new course of action could be agreed between the dying person, those important to them and the multiprofessional team.

Shared decision making in the last few days of life should ensure that the dying person, wherever possible, those important to them and all relevant health and social care professionals are involved in the development and delivery of an individualised care plan. Those important to the dying person will often have been involved in their care during any preceding illness and may be able to provide information about their needs and wishes to health care professionals; this could include social, spiritual and cultural needs as well as clinical aspects of care. There should also be a multiprofessional approach to ensure that all aspects of the dying person's care are considered in all care settings.

As death approaches, a person may lack capacity to make a decision about their care either because they are unconscious or too drowsy or because they have another condition that affects the functioning of the mind or brain, such as delirium or intracerebral haemorrhage.

Increasingly, people may have expressed and recorded their preferences for end of life care in advance care plans. They may have appointed someone to have an Enduring Power of Attorney (which would only be valid if made before 1st October 2007), or a Lasting Power of Attorney for health and welfare decisions which came into effect after the introduction of the Mental Capacity Act[4] in 2005. In some instances, people with reduced mental capacity may also have an Independent Mental Capacity Advocate (IMCA). It is crucial that appointed individuals continue to participate in the care of the dying adult and are included in the shared decision-making process.

There are a number of factors that influence shared decision making at the end of life. In practice, the personalised care plan is the vehicle by which these decisions and their impact on care is put into place. In order to develop useful guidance about care of the dying adult, this review seeks to explore

the facilitators and barriers around shared decision making and personalised care plans in the last few days of life.

## 7.2 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 few days of life?

For full details see review protocol in Appendix C.

**Table 30: Characteristics of review question**

| | |
|---|---|
| **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. |
| **Topic of interest** | • To consider which positive or 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.<br>• To consider which positive or 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. |
| **Context** | **Context**: Care planning in the last days of life.<br>**Outcomes**: Themes will be identified from the literature. |
| **Review strategy** | Study designs to be considered: qualitative studies (for example, interviews, focus groups, observations). A thematic analysis of the data will be conducted and findings presented. |

## 7.3 Clinical evidence

Qualitative studies were searched for on the perspectives of healthcare professionals, and the dying person and those important to them about shared decision making in the last days of life. Twenty one papers reporting 19 qualitative studies were included in the review, these are summarised in Table 31 below.[3,5,6,10,18,19,35,43,59,60,68,81,82,84,87,89,93,96,97,100,108]

Directly applicable evidence was found with 9 studies identified from UK healthcare professionals (HCP) perspectives. These used a mix of interviews and focus groups to gather information and featured opinions from nursing staff to physicians, in a wide variety of settings from hospital and hospice to community services. One study from Canadian HCP's was also included as this focused specifically on the experiences of surrogate decision makers, which did not feature in the UK studies.

Only 1 study[6] was identified from UK family members' perspectives. Twelve studies were identified from the USA, Canada, and Norway which gave family members opinions.

On meta-synthesis of these papers, 4 key common themes were identified. These are listed in Table 32, and Figure 5. Key findings from these studies are summarised in the clinical evidence summary below (Table 32, Table 33, Table 34, and Table 36). See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, and excluded studies list in Appendix L.

### 7.3.1 Summary of included studies

**Table 31: Summary of studies included in the review**

| Study | Design | Population | Research aim | Comments |
|---|---|---|---|---|
| From family and patient perspectives | | | | |
| Abbott 2001[3] | Semi-structured interviews | n=48 family members of critically ill people for whom the issue of withdrawing or withholding life-sustaining treatment was discussed in 1 of 6 intensive care units (ICU)<br>USA. | To identify critical psychosocial support and areas of conflict for families of people in an intensive care unit during decisions to withdraw or withhold life sustaining treatment. | The participants were interviewed between 18-22 months after the experience, potentially affecting the validly of the experiences and opinions reported. |
| Almack 2012[6] | Semi-structured interviews | n=18 people They each nominated a family carer/relative (11) and a healthcare professional (15) that were involved with their care at home to also be interviewed.<br>UK | 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 people involved and how such preferences are discussed and are recorded. | People included had diagnoses ranging from cancer to cardiovascular diseases. |
| Caron 2005[19] | Interviews | n=24 care givers<br>Canada | To examine the experiences and preoccupations of family caregivers about end-of-life issues, and more specifically, about treatment decision-making processes in the context of advanced dementia. | Not all included participants had experience in decision-making in last days of life. |
| Hsieh 2006[43] | Clinician-family conferences | n=51<br>Intensive care units<br><br>Seattle. | To identify inherent tensions that arose during family conferences in the intensive care unit and the communication strategies clinicians used in response. | The interviews were undertaken by clinicians known to the family. |
| Lind 2011[59] | Interviews | n=27 bereaved family members of 21 former ICU patients 3-12 months after the | To examine family members' experiences of end-of-life decision-making processes in Norwegian intensive | The interviews were held on average 9 months post death of the relative introducing recall bias. |

| | | | | |
|---|---|---|---|---|
| | | patient's death.<br>ICU setting.<br><br>Norway | care units to ascertain the degree to which they felt included in the decision-making process and whether they received necessary information. | |
| Lind 2013 [60] | Interviews | n=11 family members of 6 former ITU patients, that were awake and had assumed competence to make decisions.<br><br>Norway | 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. | This was a subset of the population of the Lind 2011[59] |
| Nolan 2008[81] | Semi-structured interviews and survey/descriptive data. | n=16 people recently (within 8 weeks) diagnosed with ALS and 16 matched family members they felt might participate in healthcare decisions with them.<br><br>USA | To compare 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. | The people were followed every 3 months up to death, and the family members post death. |
| Royak-Schaler 2006[84] | Focus group discussions. | n=24 spouses and first degree relatives of deceased people with cancer.<br><br>USA | To assess healthcare provider communication about end-of-life and hospice care with people with terminal cancer and their families, from the perspective of family members. | The educational back ground of the participants was higher than that of the general population which may limit generalizability. |
| Tilden 1995[97] | Semi-structured interview. | n=44 Tertiary hospital in a major university medical centre and level I trauma centre.<br><br>USA | To describe how families reason about a decision to withdraw life support.<br>To describe the positive and negative effects of physicians' and nurses' behaviours on families during the process. | Participants were selected from intensive care settings. |
| Vig 2007 [100] | Semi structured telephone interviews. | n=50 surrogate decision makers of older, chronically ill, veteran people | To gain an understanding of the experience and challenges of surrogate decision making. | Only 76% of the included population had made end of life decisions. |

| | | | | |
|---|---|---|---|---|
| | | USA | | |
| From healthcare professionals prospective | | | | |
| Addicott 2012[5] | Interviews | n=141 NHS and other service providers<br><br>UK | To identify what particular barriers exist for people with non-cancer conditions in accessing end of life care support. | Poor description of methodology, and difficult to establish whether direct to end of life decisions in the last days of life, or in a wider time frame. |
| Boot 2014[10] | Semi-structured interviews | n=12 community-based clinical nurse specialists from 2 teams, 1 based in a more rural and 1 based in an urban area.<br><br>UK | To identify the challenges experienced by clinical nurse specialists when facilitating advance care planning conversations. | Methods are described in insufficient detail (for example, interview questions/prompts not provided) and only 1 researcher seems to have coded the transcripts. |
| Fields 2013[35] | Semi-structured interviews | n=6 hospice clinicians from a Marie Curie Hospice which provides specialist palliative care services.<br><br>UK | To explore clinicians' experiences of discussing preferred place of death with people receiving palliative care. | This study is restricted to decisions about preferred place of death. But, the extracted themes are generalisable to the overall topic of shared decision making. |
| Minto 2011[68] | Semi-structured interviews. | n=6 One GP and 1 district nurse from each of 3 GP practices.<br><br>UK | To determine the factors that assist or hinder the primary care health professionals having discussions about the end of life. | The interviews were undertaken by clinicians known to the family. |
| Seymour 2010[87] | Focus group discussions. | n=23 community nurses from 2 Cancer Networks<br><br>UK | To examine how community palliative care nurses in England understand ACP and their roles within ACP<br>To identify factors that may facilitate or constrain community nurses' implementation of ACP and nurses' educational needs. | Nurses who participated were self-selecting and therefore likely had a particular interest in the topic. |
| Stevens 2011[89] | Focus group discussions. | n=34 healthcare professionals.<br><br>UK | To investigate the views of healthcare professionals regarding ACP. | Included non-cancer conditions such as COPD. |
| Tan 2013 [94] | Semi-structured interviews. | n=11 family physicians with experience of dealing with | To describe the conflict experience that family physicians have with substitute decision | The study only explores physicians who had experience of dealing with conflict, |

| | | | | |
|---|---|---|---|---|
| | | conflict with surrogate decision makers of dying people.<br><br>Canada | makers of dying people and to identify the factors that may facilitate or hinder the end of life decision making process. | and did not speak to those who reported no conflict, this group may have had refined skills in preventing or handling conflict. |
| Thompson 2003 [96] | Semi-structured interviews and focus groups. | n=12 interviews (4 hospital doctors, 4 GPs and 4 nurses); 6 focus groups (hospital nurses, hospice staff, GPs, consultant geriatricians, geriatricians in training and an interdisciplinary group, n=34)<br><br>UK | To discover the views of health professionals on advance directives. | This study is indirect evidence since advance directives are not the focus of the review question. However, 1 theme relates directly to the directive having a facilitating effect for discussions of other areas of end-of-life decision making. It is therefore included. |
| Willard 2006[108] | Observation and semi-structured interviews. | n=29 cancer nurse specialists from 5 hospital trusts.<br><br>UK | To 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. | |

### 7.3.2 Themes and sub-themes derived from the evidence

**Table 32: Themes and sub-themes**

| Main theme | Sub-themes |
|---|---|
| Factors relating to healthcare professionals (HCP) | • Communication skills<br>• Relationship and rapport<br>• Information provision<br>• Uncertainty in prognosis<br>• Role of nursing staff<br>• Clinical experience<br>• Clinician availability<br>• Timing of decision-making<br>• Role responsibility |
| Factors relating to family members and surrogate decision makers. | • Family support and conflict<br>• Lack of medical knowledge<br>• Denial about prognosis<br>• Competing responsibilities<br>• Previous decision making experience<br>• Knowledge of the dying persons opinion<br>• Emotional burden |
| Factors relating to patients | • Denial about prognosis<br>• Willingness to discuss |
| Factors relating to available resources | • Private room availability<br>• Available equipment and staff<br>• Documentation tools |

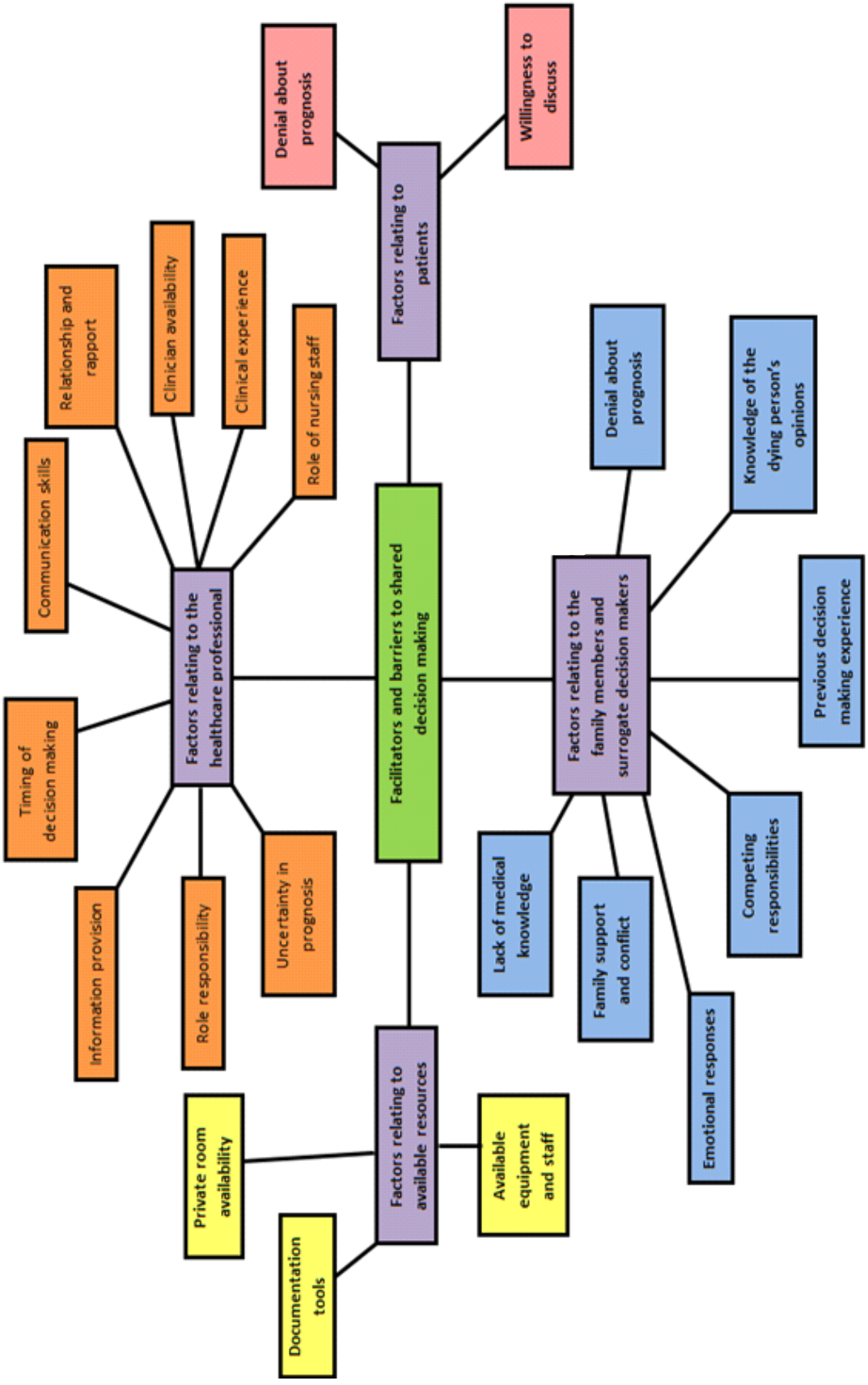



**Figure 5: Themes**

### 7.3.3 Evidence summary

**Table 33: Summary of evidence: Theme 1 – factors relating to healthcare professionals**

| Study design and sample | | | Quality assessment | | |
|---|---|---|---|---|---|
| No. of studies | Design | Descriptors of themes | Criteria | Rating | Overall |
| Sub-theme 1: Communication skills | | | | | |
| 5 | 2 interview<br>3 focus group | Five studies with populations of family members and health care professionals in the UK, Norway and the USA reported poor communication skills acted as a barrier to shared decision making[59,84,87-89,108]. The following points were identified:<br>• use of medical terminology led to family members reduced involvement in shared decision making[84]<br>• Rushed consultations prevented them from having involvement in decision making[59]. A further study interviewed health care professionals who reported that practitioners often prioritise treatment and routine care which prevented discussion of patient's views and preferences [89]<br>• The benefit of communication skills training through mentoring was reported by UK district nursing staff.[87,88] | Limitations of evidence | Serious | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Unclear | |
| Sub-theme 2: Relationship and rapport | | | | | |
| 7 | 6 interview<br>1 focus group | Seven studies from populations of family members, surrogate decision makers and health care professionals in the UK, USA and Canada commented on the importance of a trusting relationship between | Limitations of evidence | Serious | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| No. of studies | Design | | Criteria | Rating | Overall |
| | | healthcare professionals and dying people and their loved ones in facilitating shared decision making[3,6,10,18,19,89,93,100]. Respect and rapport as well as the length of time known to each other were reported as central to building a trusting relationship. When respect was perceived to be given it facilitated shared decision making, but when there was a perceived lack of respect it acted as a barrier:<br>• *"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".*<br>• "*there was 1 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 1 that should have been; he should have been talking directly to".* | Theme saturation/sufficiency | Unclear | |
| Sub-theme 3: Information provision | | | | | |
| 6 | 4 interviews<br>2 focus groups | Six included studies with populations of family members surrogate decision makers and healthcare professionals in the USA and UK commented on the importance of information provision in facilitating or preventing shared decision making.[3,84,87,89,97,100] Family members desired frank information about their relatives in order to help them facilitate shared decision making with 1 member in a USA study describing this as "*starving for* | Limitations of evidence | Serious | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Unclear | |

| Study design and sample | | | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | **Descriptors of themes** | **Criteria** | **Rating** | **Overall** |
| | | *information*".[97] Family members want this information in lay terms. One family member in an American study reported:<br>• *'"I think the medical people assume that we know a lot about these diseases and things, 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… why do they assume I know that stage IV cancer is?"'*<br><br>Poor information transfer of clinical information between health care professionals was also reported as a barrier to shared decision making. One UK study [108] interviewing health care professionals highlighted that this was both between teams and across care settings. The same study also reported that there was real concern from community staff regarding the time hospital discharge letters could take to arrive, meaning people could be readmitted before they had received corresponding to the first admission. | | | |
| Sub-theme 4: Uncertainty in prognosis | | | | | |
| 3 | 1 interview<br>2 focus groups | Three reported studies of UK health care professionals identified uncertainty of prognosis as a barrier to shared decision making.[6,87,89] One study[87,88] of district nurses reported concerns about particular difficulties in prognostication of people with non-cancer long term conditions and the risk of raising issues about end of life care at an inappropriate time. | Limitations of evidence | Serious | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Unclear | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| No. of studies | Design | | Criteria | Rating | Overall |
| | | • *"...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."* | | | |
| Sub-theme 5: Role of nursing staff | | | | | |
| 2 | 1 interview<br>1 focus group | Two studies from the UK and Canada interviewed surrogate decision makers and nurses who reported on the role of nursing staff in facilitating shared decision making.[19,87] Often the nursing staff have more time to interact with the family and dying person better allowing them to elicit care preferences, facilitate family communication and enable a shift of care focus towards palliative care.[87,88] | Limitations of evidence | Serious | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | No theme saturation | |
| Sub-theme 6: Clinical experience | | | | | |
| 4 | 4 interviews | Four studies with UK and Canadian health care professionals identified experience in communicating and formulating advance care plans as a facilitator for shared decision making.[6,35,68,93]<br>• *"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 of evidence | Serious | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Unclear | |
| Sub-theme 7: Clinician availability | | | | | |
| 5 | 5 interviews | One American study with a population of surrogate decision makers reported clinician availability as a | Limitations of evidence | Serious | LOW |
| | | | Coherence of findings | Coherent | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| No. of studies | Design | | Criteria | Rating | Overall |
| | | facilitator for shared decision making, but too many clinicians acted as a barrier due to undefined role responsibility.[100]<br><br>Conversely 4 studies with population of UK, Norwegian, and American family members and health care professionals list clinical unavailability as a barrier to shared decision making.[18,19,59,84,100]<br>• *"…Perhaps if we met regularly, we'd have a little more say in the decisions being made."*<br>• *"It seems a bit of an uphill path to get information and arrange a meeting with a doctor"* | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Unclear | |
| Sub-theme 8: Timing of decision-making | | | | | |
| 4 | 2 interviews<br>2 focus groups | Four included studies from UK health care professionals commented on the difficulty in timing as a barrier to initiating shared decision making. Concern that initiating the discussions too early could be perceived as uncaring was reported in 3 studies.[35,87,89] Conversely a further study reported critical junctures in the course of a serious illness as an opportunity where current treatment plan could be re-evaluated and patient and family preferences could be explored.[108] | Limitations of evidence | Serious | LOW |
| | | | Coherence of findings | Unclear | |
| | | | Applicability of evidence | Very applicable | |
| | | | Theme saturation/sufficiency | Unclear | |
| Sub-theme 9: Role responsibility | | | | | |
| 1 | 1 interview | One study of UK health care professionals reported that it was the responsibility of the consulting doctor and specialists, and not nursing staff, who can be involved but only after initial communication and shared decision | Limitations of evidence | Very Serious | LOW |
| | | | Coherence of findings | Unclear | |
| | | | Applicability of evidence | Very applicable | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| No. of studies | Design | | Criteria | Rating | Overall |
| | | making have occurred.[5] 1 nurse reported:<br>• *"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".* | Theme saturation/sufficiency | Unclear | |

**Table 34: Summary of evidence: Theme 2 – factors relating to family members and surrogate decision makers.**

| Study design and sample | | Themes and findings | Quality assessment | | |
|---|---|---|---|---|---|
| No. of studies | Design | | Criteria | Rating | Overall |
| Sub-Theme 1:Family support and conflict | | | | | |
| 4 | Five interviews | Three studies conducted in the USA interviewed family members who had acted as surrogate decision makers.[3,100] They commented on the importance of family support as a facilitator in being involved in shared decision making on issues relating to the last days of life.<br>Four studies commented on family conflict (or lack of support) as a barrier to surrogates being involved in shared decision making. Two of these interviewed surrogate decision makers[100 81], 1 family member, discussing withdrawal of life support [97], and 1 healthcare professional[93,94]. One study that interviewed family members acting as surrogate | Limitations of evidence | Serious | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Unclear | |

| Study design and sample | | Themes and findings | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | | **Criteria** | **Rating** | **Overall** |
| | | decision makers in the USA reported:<br>• *"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"* | | | |
| Sub-Theme 2: Lack of medical knowledge | | | | | |
| 1 | One interview | One Canadian study[18] interviewed surrogate decision makers for people with Alzheimer's disease and reported on the surrogate decision makers self-perceived lack of medical knowledge as a barrier to shared decision making:<br>• *"...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"*<br><br>A further study of palliative community nursing staff in the UK[87,88] also reported patient's lack of knowledge about the course and outcomes of common life-limiting conditions as a barrier to end of life discussions. | Limitations of evidence | Serious | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | No theme saturation | |
| Sub-Theme 3: Denial about prognosis | | | | | |
| 1 | One interview | One study interviewed primary care physicians in Canada[93,94] who reported denial about the prognosis as being a barrier to being involved in shared decision making in the last days of life:<br>• *"The wife wasn't really grasping it and probably in* | Limitations of evidence | No limitations | MODERATE |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme | Saturated | |

| Study design and sample | | Themes and findings | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | | **Criteria** | **Rating** | **Overall** |
| | | *some denial… so she was sort of saying 'can we do this? Can we do this? Can we do more?'"*<br>• *"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…"* | saturation/sufficiency | | |
| Sub-Theme 4: Competing responsibilities | | | | | |
| 1 | One interview | One study interviewing surrogate decision makers in the USA reported competing responsibilities preventing them from taking part in shared decision making.[100] Examples reported included other family members the surrogate cares for, or the surrogates own health. | Limitations of evidence | No limitations | MODERATE |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Saturated | |
| Sub-Theme 5: Previous decision making experience | | | | | |
| 2 | Two interviews | Two included studies interviewed surrogate decision makers in America who reported having previous decision making experience as a facilitator in involvement in shared decision making[81,100]:<br>• "*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*" | Limitations of evidence | Serious | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |
| | | | Theme saturation/sufficiency | Saturated | |
| Sub-Theme 6: Knowledge of the dying persons opinion | | | | | |
| 2 | Two interviews | Two studies both interviewed populations of surrogate decision makers and family members in the USA. One study[3] reported having discussed the dying persons wishes prior to death as a facilitator in shared decision | Limitations of evidence | Serious | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Applicable | |

| Study design and sample | | Themes and findings | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | | **Criteria** | **Rating** | **Overall** |
| | | making with family members:<br>• *"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"*<br>• "*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"*<br>A further study[100] described a case where knowledge about the dying persons wishes acted as a barrier to the involvement of surrogate decision makers in shared decision making, where for logistical or clinical reasons their wishes could not be met:<br>• *"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"* | Theme saturation/sufficiency | Unclear | |
| Sub-theme 7: Emotional burden | | | | | |
| 1 | 1 interview | One American study observed clinician-family meetings in ITU settings where discussion of withdrawal of life support were raised[43]. Family members reported on the emotional burden of perceiving 'killing the patient or allowing them to die'. The concern about killing the patient seemed to make family members hesitant or unwilling to withdraw or withhold life support. | Limitations of evidence | Serious | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | applicable | |
| | | | Theme saturation/sufficiency | unclear | |

**Table 35: Summary of evidence: Theme 3 – factors relating to patients**

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | | **Criteria** | **Rating** | **Overall** |
| Sub theme 1: Denial in prognosis | | | | | |
| 1 | 1 interview | One study in primary care in the UK interviewed patients, healthcare professionals, and family members about shared decision making.[6] From 1 trial both the patient and the healthcare professional reported denial in prognosis as a barrier in shared decision making:<br>• Patient - *" 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"*<br>• 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 of evidence | Serious | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Not applicable | |
| | | | Theme saturation/sufficiency | unclear | |
| Sub theme 2: Willingness to discuss | | | | | |
| 1 | 1 interview | One study interviewed patients, family members and healthcare professionals in the UK around end of life decisions.[6] Healthcare professionals identified the patients and family members initiative as a facilitator to involvement in shared decision making:<br>• *"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"*<br>They also commented on patients and family members | Limitations of evidence | Serious | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Not applicable | |
| | | | Theme saturation/sufficiency | unclear | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| No. of studies | Design | | Criteria | Rating | Overall |
| | | unwillingness to have conversations as a potential barrier to involvement in shared decision making:<br>*"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 say to you or indicate 'I know where you're going with this and I don't want to hear"* | | | |

**Table 36: Summary of evidence: Theme 4 – factors relating to available resources**

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| No. of studies | Design | | Criteria | Rating | Overall |
| Sub-theme 1: Private room for discussion | | | | | |
| 1 | 1 interview | One American study[3] interviewed family members who had had relatives die on ITU. They reported lack of private space for discussion and family conferences as a barrier to shared decision making:<br>"*There was a critical need for space for family conferences. There was 1 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 1 time because they were having a serious conversation and they clearly needed privacy and the waiting room was so tiny"* | Limitations of evidence | Serious | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | applicable | |
| | | | Theme saturation/sufficiency | Unclear | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | | **Criteria** | **Rating** | **Overall** |
| Sub-theme 2: Documentation tools | | | | | |
| 5 | 5 interviews | Five UK studies reported on the use of documentation tools in shared decision making such as the Preferred Priority's for Care (PPC) or advance care planning (ACP).[35,68,82,87,89,96] Health care professionals reported the PPC as a facilitator, opening discussion with the dying person and empowering healthcare professionals. They believe the PPC gave the dying person and relatives the opportunity to make informed choices and provided holistic care. Nurses believed the document promoted discussion at team meetings and boosted multiprofessional working. One health care professional commented:<br>*'"…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."'*<br><br>However, healthcare professions were concerned some patient and relatives viewed the PPC negatively feeling that it took away hope and was used as a tick box exercise. Nursing staff also reported that ACP documents can be difficult to store and access at appropriate times given the multiple locations some people are treated at. | Limitations of evidence | Serious | LOW |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Very applicable | |
| | | | Theme saturation/sufficiency | Unclear | |
| Sub-theme 3: Available equipment and staff | | | | | |
| 1 | 1 interview | One study[87,88] with a population of UK nursing staff working in the community highlighted a disparity | Limitations of evidence | Serious | LOW |
| | | | Coherence of findings | Coherent | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | | **Criteria** | **Rating** | **Overall** |
| | | between resources available and the dying persons' and family's expectations acting as a barrier to shared decision making. District nurses faced challenges when trying to prioritise their time to enable them to manage the patient dying at home in conjunction with their regular workload. They also reported having to wait for equipment. | Applicability of evidence | Very applicable | |
| | | | Theme saturation/sufficiency | No theme saturation | |

## 7.4 Economic evidence

### Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

## 7.5 Evidence statements

### Clinical

Qualitative evidence indicated several themes from healthcare professionals, family members and surrogate decision makers experiences, opinions and attitudes on the barriers and facilitators to shared decision making in the last days of life. Low quality evidence from 14 qualitative studies (n=497) reported several sub themes related to the healthcare professional that could act as facilitators or barriers to shared decision making. These included communication skills, a trusting relationship built with good rapport with the dying person and those important to them, adequate information provision, clinical experience and certainty in diagnosis.

Themes related to the dying person were also identified in low quality evidence from 2 qualitative studies (n=30), including denial about prognosis and an unwillingness to discuss end of life care acting as a barrier to shared decision making.

Eight qualitative studies (n=267) reported on low to moderate quality themes related to those important to the dying person including the negative impact of denial about prognosis, a lack of medical knowledge, family conflict or competing responsibilities can have on shared decision making. The same studies also reported on factors associated with those important to the dying person that can facilitate shared decision making including family support, previous decision making experience and knowledge of the dying person's opinions.

Low quality evidence from 6 qualitative studies (n=135) was identified for themes relating to available resources that can influence shared decision making including documentation tools, available equipment and staff, and private room availability for discussion.

### Economic

No relevant economic evaluations were identified.

## 7.6 Recommendations and link to evidence

| | |
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| **Recommendations** | **14. Establish the level of involvement that the dying person wishes to have and is able to have in shared decision-making, and ensure that honesty and transparency are used when discussing the development and implementation of their care plan.**<br><br>**15. As part of any shared decision-making process take into account:**<br>• **whether the dying person has an advance statement or an advance decision to refuse treatment in place, or has provided details of any legal lasting power of attorney for health and welfare**<br>• **the person's current goals and wishes**<br>• **whether the dying person has any cultural, religious, social or spiritual preferences.**<br><br>**16. Identify a named lead healthcare professional, who is responsible for** |

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| | **encouraging shared decision-making in the person's last days of life. The named healthcare professional should:**<br>• **give information about how they can be contacted and contact details for relevant out-of-hours services to the dying person and those important to them**<br>• **ensure that any agreed changes to the care plan are understood by the dying person, those important to them, and those involved in the dying person's care.**<br><br>**Providing individualised care**<br><br>**17. Establish as early as possible the resources needed for the dying person (for example, the delivery of meals, equipment, care at night, volunteer support or assistance from an organisation) and their availability.**<br><br>**18. In discussion with the dying person, those important to them and the multiprofessional team, create an individualised care plan. The plan should include the dying person's:**<br>• **personal goals and wishes**<br>• **preferred care setting**<br>• **current and anticipated care needs including:**<br>**-preferences for symptom management**<br>**-needs for care after death, if any are specified**<br>• **resource needs.**<br><br>**19. Record individualised care plan discussions and decisions in the dying person's record of care and share the care plan with the dying person, those important to them and all members of the multiprofessional care team.**<br><br>**20. Continue to explore the understanding and wishes of the dying person and those important to them, and update the care plan as needed. Recognise that the dying person's ability and desire to be involved in making decisions about their care may change as their condition deteriorates or as they accept their prognosis.**<br><br>**21. While it is normally possible and desirable to meet the wishes of a dying person, when this is not possible explain the reason why to the dying person and those important to them.**<br><br>**22. Ensure that shared decision-making can be supported by experienced staff at all times. Seek further specialist advice if additional support is needed.** |
| Relative values of different outcomes | The Committee agreed that the themes which highlighted the barriers and facilitators to shared decision making in the last days of life were crucial to this review. This was highlighted as an element of care of the dying adult that required improvement in the Neuberger review.[30] The Committee decided to focus the review on the experiences, opinions and attitudes of the dying person, those important to them, and the healthcare professionals involved in their care, as it was felt that each population would offer a unique and informative perspective on this topic. |

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| Trade-off between clinical benefits and harms | The evidence identified a number of barriers and facilitators to effective shared decision making. These were divided into factors relating to the dying person (including denial about prognosis), those important to them (including family support and conflict, and their current understanding of medical information), healthcare professionals (such as their communication skills, and their relationships and rapport with the dying person) and resources available (for example clinician or private room availability). They felt that involving the dying person and those important to them in shared decision making improved end of life care for the dying person. The Committee considered that many of these themes could inform recommendations to improve shared decision making to reduce anxiety of the dying person and those important to them. These recommendations would ensure that dying persons and those important to them are provided with the information needed to make decisions regarding end of life care. No harms were identified by the Committee. |
| Trade-off between net health benefits and resource use | No economic evaluations were identified that addressed this review question.<br>There could be some economic implications associated with shared decision making in terms of healthcare professional time and the availability of support out of normal working hours. However, it was the Committee's opinion that this should already be in place. No quantitative evidence was reviewed for this review question, but the Committee was convinced that these recommendations would improve patient care at a reasonable additional cost. |
| Quality of evidence | Qualitative studies were identified from the perspective of those important to the dying person, surrogate decision makers and healthcare professionals. There were no identified studies from the perspective of the dying person in the last days of life. This was understood by the Committee given the context, as enrolling and interviewing people in the last days of life may provoke unnecessary stress. Evidence was identified in dying people before this time point for the context of shared decision making in the last days of life and this was included in the review due to paucity of evidence but downgraded in quality for applicability to the review population. The quality of evidence ranged from moderate to low; this was due to limitations in the studies including risk of bias and the applicability of the findings given that some studies were conducted in other healthcare settings to the UK. The evidence reviewed also examined wider topics then barriers and facilitators to shared decision making. The recommendations were based on the evidence and the consensus opinion of Committee members. There were no additional themes the Committee could identify from their experience that were not picked up in the evidence review, and all of the included themes were felt to be relevant. |
| Other considerations | The Committee recognised that shared decision making is standard across all medical specialities, but is especially important to consider in the last days of life. It is important to involve the dying person in decisions about their care, if they so wish. Equally, care providers should respond, where possible to decisions the dying person has made about their care in the last days of life. They noted also that the dying person may not wish to be involved in shared decision making and, if so, this should also be respected.<br>When working in partnership with the dying person to support decision making, the Committee felt that it would be important to gather information on a number of areas, including the location of items listed in any advance statement or any advance decision to refuse treatment, and the dying person's cultural preferences or religious and spiritual requirements, or cognitive abilities. The committee also noted that people at the end of life may have already identified a person with Lasting Power of Attorney as part of an advance care planning process and this would be of relevance particularly if the person was unconscious or unable to take part in a shared-decision making process for any other reason.<br>The Committee discussed the importance of being aware of different faith groups within the local community and noted in some areas there are "faith forums" that can provide useful information. The Committee recognise that organ donation is |

important in end of life care planning and may be something discussed under personal goals and wishes. The Committee noted that there is existing NICE Guidance on Organ donation for transplantation (CG135).

They noted that if the formal legal test, as described in the 'best interests process' outlined by the Mental Capacity Act,[4] has been applied and a person is shown to lack mental capacity, then their views expressed in advance care plans and Advanced Directives should be honoured according to legal requirements. The Committee noted that people with reduced capacity defined in the Mental Capacity Act[4] may have other needs and requirements, and these too should be honoured.

The Committee felt it was important to consider assessing capacity in a dying person in the context of shared decision making, in view of concerns surrounding the use of the LCP that the person and those important to them were being excluded from decisions about their care. An adult is deemed to have capacity unless, having been given all appropriate help and support, it is clear that they cannot understand, retain, use or weigh up the information needed to make a particular decision or to communicate their wishes.[37]

Health care professionals have a statutory obligation to follow the principles of the MCA 2005[4] (outlined below) when assessing an individual's mental capacity:

The following principles apply for the purposes of this Act.

- A person must be assumed to have capacity unless it is established that he lacks capacity.
- A person is not to be treated as unable to make a decision unless all practicable steps to help him to do so have been taken without success.
- A person is not to be treated as unable to make a decision merely because he makes an unwise decision.
- An act done, or decision made, under this Act for or on behalf of a person who lacks capacity must be done, or made, in his best interests.
- Before the act is done, or the decision is made, regard must be had to whether the purpose for which it is needed can be as effectively achieved in a way that is less restrictive of the person's rights and freedom of action.

The MCA 2005[4] defines a lack of capacity as below:

"A person lacks capacity in relation to a matter if at the material time he is unable to make a decision for himself in relation to the matter because of an impairment of, or a disturbance in the functioning of, the mind or brain".

"A person is unable to make a decision for himself if he is unable

a) to understand the information relevant to the decision
b) to retain that information
c) to use or weigh that information as part of the process of making the decision, or to communicate his decision (whether by talking, using sign language or any means)."

The committee noted that they felt it was not the place for this guideline to make specific recommendations related to these issues but felt it helpful to re-iterate the legal imperatives as context here. Their review had served only to understand how the dying person, their loved ones and their multiprofessional team could best work together to ensure that decisions made considered and met (where possible) the dying person's wishes.

A dying person should be involved in shared decision making to the level that they wish (and are able) and practical steps should be taken to assist them to make decisions about their care, for example, using simple language and not jargon. The committee recognised that, although some people may be unconscious or confused in their last days of life, it should not be assumed that this would always be the case

and the principle that the dying person should always be involved in decision-making should prevail. They felt it important to note that capacity is decision specific, for example, a person may have capacity to decide if they want to drink either water or milk, but they may lack capacity to make more complex decisions about their treatment.

The GMC guidance on Treatment and care towards the end of life: good practice in decision making (2010)[37] also sets out decision making models for both patients with capacity to decide and patients who lack capacity to decide (sections 14 and 15) which would be applicable to people within the last few days of life.

Variations in the availability of equipment were identified as a potential barrier to initiating discussions about the needs and wants of the dying person. Professionals may be unhappy to enter into a conversation about needs and desires unless they were certain that the resources were available locally to make a request possible. The Committee noted that in transferring someone to their home to die, a fast track referral for continuing care may be required. The Committee discussed these issues in the context of shared decision making and felt it was important to ascertain what resources were available such as the delivery of meals, equipment, or care at night. This information should help guide appropriate shared decision making with the dying person. The particular needs of people who may be dying alone were discussed and the committee felt that their recommendation encompassed the need to establish support from voluntary agencies to enable the implementation of other recommendations.

The information gathered in this assessment should then inform any shared decision making discussions with the patient. This should include a discussion on preferred care setting, preferences for symptom management and anticipated care needs. The Committee noted that discussions with other members of the multidisciplinary team may be via telephone discussion, and not necessarily convening a meeting of relevant professionals.

The Committee agreed that this information should be captured within the dying person's individualised plan of care, and documented clearly within medical records to reflect that relevant discussions have taken place. It would be important to seek to ensure that the dying person is in agreement with the decisions captured as part of the discussion and permission to capture this information may be considered advisable where possible. The Committee considered that any healthcare professional delivering care was able to record such discussions in relevant care plans or medical records and that this documentation should also capture who had been involved in those discussions.

The Committee recognised that the dying person's wishes or requirements may change within the last days of life and earlier documentation should be updated as appropriate and shared with all members of the multiprofessional care team, including those that may be working on different shifts throughout the day or week.

When a person is recognised as being in the last few days of life, the Committee considered it important that an experienced clinician was available to make decisions in partnership with the dying person. Discussions about treatment on the medications and clinically assisted hydration provided should be undertaken within normal working hours, in conjunction with the wider multiprofessional team, the dying person and those important to them. The lack of availability of clinicians was highlighted frequently within the review; and frequent staff changes were also thought to increase confusion among family members, with regard to who to talk to about the dying person's care. The Committee considered this and felt that a lead clinician should be named, documented in the notes and the dying person informed of how to contact them. The Committee feel that this person may be a clinician or nurse or any relevant person delivering NHS care. They discussed that it is important that one care provider takes responsibility for leading the discussions linked to decision-making to avoid the situation of other providers thinking someone else had provided that function when, in reality, no-one had prioritised this issue. The

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| | Committee discussed how local policy or decision making may inform what the most suitable contact details to provide are.<br>The Committee discussed that staff with limited experience in the caring of people in the last days of life may require support from staff with experience in shared decision making and that this should be available at all times in all settings. They also acknowledged that in some situations shared decision making can be complex and difficult to formulate, and if so, additional support from specialist palliative care services should be sought.<br>The Committee noted that in response to changing personal needs requiring amendments to care, it would also be important to ensure that this process was available outside of normal working hours, for example, access to medication or withdrawal of treatments. It was also noted that the physical and psychological ability to look after the dying person may also be considered as the dying person's condition changes. This may have an impact on where the person dies, and that supporting those important to the dying person may prevent unnecessary hospital admission.<br>The Committee discussed the importance of cultural, religious, social or spiritual preferences in shared decision making. The Committee noted the NHS Chaplaincy Guidelines,[92] which provide a comprehensive description of good practice in chaplaincy care for the NHS in England.<br>The Committee felt that these recommendations should be relevant to the care of people in the last days of life regardless of setting. They did note that additional resources or support may be required for older people or those living alone to enable them to die at home.<br>The Committee felt it important to note that specialist advice should be sought if additional advice was required out of hours and chose to make a recommendation in this regard. The group considered specialist support to include any specialty who are able, because of their specialist experience, to aid shared decision making. |

# 8 Maintaining hydration

## 8.1 Introduction

Maintaining hydration at the end of life is both controversial and emotive. There was significant media coverage surrounding the Liverpool Care Pathway and relatives' concerns about people dying from dehydration and suffering with distressing symptoms as a result of inadequate fluid intake. Suspicion was also raised that fluids were withheld and even denied to dying persons in order to hasten death. Concerns raised in the More Care Less Pathway review[30] related to poor communication with the dying person and their relatives surrounding the issue of hydration. There was also the suggestion that not providing hydration (whether via the oral or parenteral route) caused more distress to dying people and their relatives than the person's lack of ability or desire to eat and drink.

Clinically assisted hydration refers to the practice of providing fluids in the form of a drip, usually either intravenously or subcutaneously (a process known as hypodermoclysis) or via a nasogastric tube or gastrostomy to prevent dehydration. It does not include assisting a person to drink via the oral route. The subcutaneous route has some advantages at the end of life as it can be administered in many different settings, including in the community without the need for staff trained in venous access but its efficacy is unclear.

Practice varies widely across the UK regarding the use of clinically assisted hydration at the end of life and decisions are often setting dependent and based on individual clinician preference and patterns in the person's medical history. The RCP National Care of the Dying Audit for hospitals[85] showed that artificial hydration was in place for 29% of people at the time of death. There is a lack of clear evidence based guidance on whether clinically assisted hydration is effective in improving symptoms in the dying process for those in the last few days of life. The Committee therefore posed a review question which sought to establish if quality of care could be improved by the use of this intervention.

## 8.2 Review question: In patients in their last days of life, is clinically assisted hydration effective in improving symptoms and general comfort?

For full details see review protocol in Appendix C.

**Table 37: PICO characteristics of review question**

| | |
|---|---|
| **Population** | Adult people in the last days of life who are not maintaining sufficient oral hydration. |
| **Interventions** | **Interventions**<br>Clinically assisted hydration:<br>• Enteral hydration (via nasogastric tube, gastrostomy or jejunostomy)<br>• Parenteral hydration (intravenously or subcutaneously) |
| **Comparisons** | **Comparison**<br>• Placebo, for example, clinically insignificant amounts of assisted hydration<br>• No intervention<br>• Oral hydration only |
| **Outcomes** | **Critical outcomes**<br>• Quality of life, pre and post intervention, using validated scales.<br>• Symptom improvement on rating scales pre and post intervention. |

| | |
|---|---|
| | **Important outcomes**<br>• Hydration status using both objective and subjective measures (for example, hydration of oral mucosa, measuring vital signs and skin turgor).<br>• Adverse events both procedural (phlebitis, or line infections, for example) and from positive fluid balance (for example, pleural oedema).<br>• Subjective ratings from informal carers on quality of care received.<br>• Biochemistry results including urea, creatinine and sodium. |
| **Study design** | • Randomised controlled trials or prospective observational studies and systematic reviews of the above. |

## 8.3 Clinical evidence

One Cochrane review was identified.[39] This was assessed for inclusion and fulfilled our criteria for this topic. It was therefore decided to include this as evidence using the GRADE approach and to conduct an update search for the inclusion of further studies that may have been published since the Cochrane review's search cut-off (April 2014). No additional papers were included from this search.

The Cochrane review identified 6 primary studies;[14,15,20,69,101,102] these are summarised in Table 38. Using the GRADE approach, the evidence from these studies is summarised in the clinical evidence profile below Table 38 and Table 39. See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, forest plots in Appendix K, GRADE tables in Appendix J and excluded studies list in Appendix L.

The following control comparisons were made:

- There were 3 randomised control trials comparing 1000 ml of subcutaneous fluid with a 100 ml placebo[14,15] or oral hydration alone.[20]
- The other 3 papers had a prospective controlled trial design and compared a control group given at least 1000 ml fluid per day with those given oral hydration alone.[69,70,102,101] The route of clinically assisted hydration included IV and subcutaneous. One paper added hyaluronidase to the subcutaneous fluid given in the experimental arm.[101]

Differences in outcome reporting across the studies meant that meta-analysis was inappropriate. The papers used different terminology to describe clinically assisted hydration, including medically assisted hydration, artificial hydration and parenteral fluids. For the purposes of clarity and consistency the term clinically assisted hydration will be used throughout this review. This reflects the language used by the General Medicine Council (GMC).

### 8.3.1 Summary of included studies

**Table 38: Summary of Cochrane review included in this report**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Good 2014[39] | Study types included:<br>RCT and prospective controlled studies.<br><br>Interventions: clinically assisted | • Palliative care participants who received clinically assisted hydration.<br>• People receiving palliative care whose prognosis was limited and the focus of care was quality of life.<br>• All conditions.<br>• Adults aged 18 years and | **Primary outcomes**<br>• Quality of life on any measure (including symptom assessment scales).<br>**Secondary outcomes**<br>• Survival.<br>• Adverse events. | Only narrative analysis. Did not include any forest plots or graphical results. Concluded that there was no evidence found to support a |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | hydration of non-nutritional fluids administered via the subcutaneous tissue, venous system or enterally.<br><br>Control: placebo, usual care and no intervention. | above, both male and female and in any setting, such as home, hospice or hospital.<br>• Not limited to the terminal phase of life.<br>• Excluded people who had fluids as part of a perioperative chemotherapy/radiotherapy procedure or for symptom relief from these. | | significant benefit in the use of clinically assisted hydration in people receiving palliative care. |

Table 39 provides a summary of the studies included in the Cochrane review. No further studies were identified.

**Table 39: Summary of studies included in the review**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Bruera 2005[15] | Intervention: 1000 ml each day for 2 days.<br>Control: 100 ml each day for 2 days. | Advanced cancer, reduced oral intake, and evidence of mild to moderate dehydration on examination or clinical blood tests.<br>(n=51)<br>USA | • Perceived global benefit rated by both the patient and physician.<br>• Numeric rating scale (NRS) for symptom assessment for sedation, fatigue, hallucinations, myoclonus, and mini mental status examination (MMSE) score for delirium.<br>• Data presented as % improved (defined improvement as a decrease >1 point from baseline- unclear whether this is statistical or clinical improvement). | Study terminated early due to recruitment difficulties. Variability in performance status (scale for general wellbeing) at baseline. |
| Bruera 2013[14] | Intervention: 1000 ml each day for 7 days.<br>Control: 100 ml 0.9% NaCl each day for 7 days. | Mild to moderately dehydrated people in a hospice with a life expectancy of 1 week.<br>(n=129)<br>USA | • Symptoms improvement using Edmonton symptom assessment system (ESAS) (pain, fatigue, nausea, depression, anxiety, drowsiness, dyspnoea, appetite, wellbeing, hallucinations, myoclonus).<br>• Quality of life measured with the functional assessment of chronic illness therapy – general scale (FACITG).<br>• Survival. | Well-designed control, double blinded control intervention. Study was terminated early due to funding limitations. |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | | • Delirium measured using both the nursing delirium screening scale (NuDESC), and memorial delirium assessment scale (MDAS).<br>• Hydration status using a dehydration assessment scale and survival.<br>• Biochemistry results. | |
| Cerchietti 2000[20] | Intervention: 1000 ml a day subcutaneous.<br>Control: Usual care (no subcutaneous fluids). | People with terminal stage advanced cancer unable to drink >50 ml a day. (n=50)<br>USA | • Symptom assessment scales for thirst, chronic nausea, delirium, and anguish and mood.<br>• MMSE was also undertaken as an outcome of delirium.<br>• Survival. | Data mainly presented as graphs, some of which did not match text description. |
| Morita 2005[69] | Intervention: >1 day both 1 week and 3 weeks before death.<br>Control: Oral hydration only. | Those with abdominal malignancy (excluding hepatic cancer with a life expectancy estimated to be <3 months).(n=226)<br>Japan | • Dehydration assessment, diagnosis of fluid retention, hyperactive delirium, myoclonus, bedsores, agitation and communication capacity.<br>• Biochemistry results. | Whilst a large multicentred study, the design of intervention/ control and assessment had limitations. A multivariable analysis was conducted accounting for stomatitis, drugs prescribed, location of metastases, pneumonia, intestinal obstruction, and oral intake of fluid. |
| Viola 1997[101] | Intervention: Subcutaneous fluids + hyaluronidase 750 units/litre titrated to need. Average approximately 1000 ml.<br>Control: Usual care. | People with advanced cancer in hospice settings at risk of existing fluid deficit. (n=66)<br>Canada | • Visual analogue scale (VAS) scores (by patients where possible) for pain, anxiety, depression, activity, drowsiness, appetite, sense of wellbeing, dyspnoea, weakness, thirst, dry mouth.<br>• General wellbeing outcome. | Multicentred study as part of an MSc thesis, with well-designed intervention and method of assessment. Limited as a small study the groups were not matched at baseline. |
| Waller 1994[102] | Intervention group: IV hydration 1-2/day<br>Control:<br>Oral hydration- volumes not specified. | People receiving palliative care admitted to hospice, for whom blood and urine | • State of consciousness.<br>• Biochemistry results. | Poorly reported study, no baseline characteristics provided and limited description of intervention/ |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | samples collected <48 hours before death. (n=68)<br>Israel | | control. |

Table 40 and Table 41 provide the clinical evidence summary of outcomes assessed using GRADE.

**Table 40: Clinical evidence summary: Clinically assisted hydration versus placebo**

| Outcomes | No. of participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with clinically insignificant amounts | Risk difference with clinically assisted hydration (95% CI) |
| Change in quality of Life FACT G<br>(Change in FACT G scale, range 0-108, high is good outcome) | 93<br>(1 study)<br>7 days | LOW[a,b]<br>due to risk of bias, imprecision | - | The mean quality of life in the control group was 2.6 (+/-16.7) | The mean change in quality of life in the intervention groups was 4.1 higher<br>(1.63 lower to 9.83 higher) |
| Wellbeing - self-reported NRS<br>(measured on 0-10 scale, 10= high is good outcome) | 49<br>(1 study)<br>2 days | LOW[a,b]<br>due to risk of bias, imprecision | - | The mean self-reported wellbeing in the control group was 0.8 (+/-3.1) | The mean wellbeing - self reported in the intervention groups was 0.2 higher<br>(1.1 lower to 1.5 higher) |
| Wellbeing - physician rated<br>NRS<br>(measured on 0-10 scale, 10= high is good outcome) | 49<br>(1 study)<br>2 days | VERY LOW[a,b]<br>due to risk of bias, imprecision | - | The mean self-reported wellbeing in the control group was 0.9 (+/- 2.7) | The mean wellbeing - physician rated. in the intervention groups was 0.3 higher<br>(1.66 lower to 2.26 higher) |
| Symptom improvement - anxiety<br>ESAS<br>(Change in ESAS scale 0-10, high is poor outcome) | 93<br>(1 study)<br>7 days | LOW[a,b]<br>due to risk of bias, imprecision | - | The mean anxiety in the control group was -1.5 (+/-3.9) | The mean symptom improvement - anxiety in the intervention groups was 1.36 higher<br>(0.1 lower to 2.82 higher) |
| Symptom improvement - dyspnoea<br>ESAS<br>(Change in ESAS scale 0-10, high is poor outcome) | 93<br>(1 study)<br>7 days | MODERATE[b]<br>due to risk of bias | - | The mean dyspnoea in the control group was -1.4 (+/-3.5) | The mean symptom improvement - dyspnoea in the intervention groups was 0.5 higher<br>(0.68 lower to 1.68 higher) |
| Symptom improvement - pain | 93<br>(1 study) | LOW[a,b]<br>due to risk of | - | The mean pain in the control group was -1.2(+/-2.6) | The mean symptom improvement - pain in the intervention groups was 1.1 higher |

| Outcomes | No. of participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with clinically insignificant amounts | Risk difference with clinically assisted hydration (95% CI) |
| ESAS<br>(Change in ESAS scale 0-10, high is poor outcome) | 7 days | bias, imprecision | | | (0.16 lower to 2.36 higher) |
| Symptom improvement - nausea<br>ESAS<br>(Change in ESAS scale 0-10, high is poor outcome) | 93<br>(1 study)<br>7 days | MODERATE[b]<br>due to risk of bias | - | The mean nausea in the control group was -1(+/-2.6) | The mean symptom improvement - nausea in the intervention groups was 0.1 higher<br>(1.05 lower to 1.25 higher) |
| Symptom improvement - sedation/drowsiness<br>ESAS<br>(Change in ESAS scale 0-10, high is poor outcome) | 93<br>(1 study)<br>7 days | LOW[a,b]<br>due to risk of bias, imprecision | - | The mean sedation/drowsiness in the control group was -1.4 (+/-3.6) | The mean symptom improvement - sedation/drowsiness in the intervention groups was 0.6 lower<br>(2.09 lower to 0.89 higher) |
| Symptom improvement - delirium<br>NuDESC<br>(Change in NuDESC scale 0-10, high is poor outcome) | 93<br>(1 study)<br>7 days | MODERATE[b]<br>due to risk of bias | - | The mean dyspnoea in the control group was 0(+/-3.48) | The mean symptom improvement - sedation/drowsiness in the intervention groups was 0.0 lower<br>(1.02 lower to 1.02 higher) |
| Symptom improvement - delirium<br>MDAS<br>(Change in MDAS scale 0-30, high is poor outcome) | 93<br>(1 study) | MODERATE[b]<br>due to risk of bias | - | The mean dyspnoea in the control group was 2.5 (+/-4.99) | The mean symptom improvement - sedation/drowsiness in the intervention groups was -0.5 lower<br>(2.37 lower to 1.37 higher) |
| Adverse events - local - pain at injection site<br>NRS<br>(Measured on 0-10 scale | 49<br>(1 study)<br>2 days | LOW[a,b]<br>due to risk of bias, imprecision | - | The mean dyspnoea in the control group was 1.75 (+/-2.55) | The mean adverse events- local - pain at injection site in the intervention groups was 0.35 higher<br>(1.19 lower to 1.89 higher) |

| Outcomes | No. of participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with clinically insignificant amounts | Risk difference with clinically assisted hydration (95% CI) |
| (High is poor outcome) | | | | | |
| Adverse events- Local - swelling at injection site NRS<br>(Measured on 0-10 scale (High is poor outcome) | 49<br>(1 study)<br>2 days | LOW[a,b]<br>due to risk of bias, imprecision | - | The mean dyspnoea in the control group was 1.41(+/-) | The mean adverse events- local - swelling at injection site in the intervention groups was 0.59 lower<br>(1.4 lower to 0.22 higher) |
| Hydration status dehydration assessment scale<br>(Change in dehydration scale- 0-7 (high is poor outcome) | 93<br>(1 study)<br>7 days | LOW[a,b]<br>due to risk of bias, imprecision | - | The mean hydration status in the control groups was -0.5 | The mean hydration status in the intervention groups was 0.5 lower<br>(1.13 lower to 0.13 higher) |
| Biochemistry creatinine at day 7<br>(Assumed measured in micromoles/litre) | 93<br>(1 study)<br>7 days | LOW[a,b]<br>due to risk of bias, imprecision | - | The median change in creatinine in the control group was -0.1 (interquartile range -0.1 to 0.1) | The median creatinine in the intervention group was -0.1 (interquartile range -0.2-0) |
| Biochemistry sodium at day 7<br>(Assumed measured in mEq/litre) | 93<br>(1 study)<br>7 days | LOW[a,b]<br>due to risk of bias, imprecision | - | The median change in sodium in the control group was 0.7 (+/-5) | The median urea in the intervention group was 1.2 (0.85 lower to 3.2 higher) |
| Biochemistry urea at day 7<br>(Assumed measured in mg/dl) | 93<br>(1 study)<br>7 days | LOW[a,b]<br>due to risk of bias, imprecision | - | The median change in urea in the control group was 2.0 (interquartile range -1 to 8) | The median urea in the intervention group was -2.0 (interquartile range -7-3) |
| Survival time to death<br>(days) | 93<br>(1 study)<br>7 days | LOW[a,b]<br>due to risk of bias, imprecision | - | The median survival in the control group was 15 days (interquartile range 12-18) | The median control in in the intervention group was 21 days (interquartile range 13-29). Unable to calculate the hazard ratio from data reported. |

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

**Table 41: Clinical evidence summary: Clinically assisted hydration versus oral hydration only**

| Outcomes | No. of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Usual care | Risk difference with clinically assisted hydration (95% CI) |
| Wellbeing - Self-reported VAS (measured on VAS 0-100, high is poor outcome) | 26 (1 study) 14 days | VERY LOW[a,b] due to risk of bias, imprecision | - | The mean self-reported wellbeing in the control group was 80 (+/-34.5) | The mean self-reported wellbeing in the intervention groups was 1.05 standard deviations lower (2.01 to 0.08 lower) |
| Symptom - Anxiety VAS (measured on VAS 0-100, high is poor outcome) | 26 (1 study) 14 days | VERY LOW[a,b] due to risk of bias, imprecision | - | The mean anxiety in the control group was 27.5 (+/-34.5) | The mean symptom - anxiety in the intervention groups was 10.5 lower (39.33 lower to 18.33 higher) |
| Symptom - Dyspnoea VAS (measured on VAS 0-100, high is poor outcome) | 27 (1 study) 14 days | VERY LOW[a,b] due to risk of bias, imprecision | - | The mean dyspnoea in the control group was 12.9(+/-24.8) | The mean symptom - dyspnoea in the intervention groups was 8 higher (13.17 lower to 29.17 higher) |
| Symptom - Pain VAS (measured on VAS 0-100, high is poor outcome) | 28 (1 study) 14 days | VERY LOW[a,b] due to risk of bias, imprecision | - | The mean pain in the control group was 29.4(+/-27.2) | The mean symptom - pain in the intervention groups was 9.4 lower (29.41 lower to 10.61 higher) |
| Symptom - Nausea VAS (measured on VAS 0-100, high is poor outcome) | 28 (1 study) 14 days | VERY LOW[a,b] due to risk of bias, imprecision | - | The mean nausea and vomiting in the control group was 21.3(+/-40.2) | The mean symptom - nausea in the intervention groups was 2.5 higher (26.44 lower to 31.44 higher) |
| Symptom - Sedation/drowsiness VAS (measured on VAS 0-100, | 27 (1 study) 14 days | VERY LOW[a,b] due to risk of bias, | - | The mean sedation in the control group was 48.6 (+/-28.4) | The mean symptom - sedation/drowsiness in the intervention groups was 18.6 lower (43.11 lower to 5.91 higher) |

| Outcomes | No. of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Usual care | Risk difference with clinically assisted hydration (95% CI) |
| high is poor outcome) | | imprecision | | | |
| Delirium (no. scoring >3 on MDAS) | 226 (1 study) 3 weeks | VERY LOW[a,b,c] due to risk of bias, imprecision | RR 1.52 (0.62 to 3.37) | Study population | |
| | | | | 78 per 1000 | 40 more per 1000 (from 30 fewer to 184 more) |
| Adverse events-fluid overload (no. of events requiring termination of intervention) | 42 (1 study) 2 days | LOW[a,b] due to risk of bias, imprecision | Not estimable | See comment | 0 events in either arm. |
| Adverse events- local (no. of events of phlebitis) | 42 (1 study) 2 days | LOW[a,b] due to risk of bias, imprecision | Peto odds ratio of 8.17 (0.16-413) | Study population | |
| | | | | 0 per 1000 | - |
| Adverse events- pleural effusion (pleural effusion scale 0-2, high is poor outcome) | 226 (1 study) 3 weeks | VERY LOW[a,c] due to risk of bias, indirectness | - | The mean pleural effusion in the control group was 0.31 (+/-0.63) | The mean pleural effusion in the intervention groups was 0.05 higher (-0.13 lower to 0.23 higher) |
| Adverse events- oedema (measured on oedema scale 0-21, high is poor outcome) | 226 (1 study) 3 weeks | VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness | - | The mean ascites in the control group was 0.52 (+/-0.52) | The mean ascites in the intervention groups was 0.9 higher (-0.91 lower to 2.71 higher) |
| Hydration status (measured on ad hoc dehydration scale 0-5 (high is poor outcome) | 226 (1 study) 3 weeks | VERY LOW[a,b,c] due to risk of bias, imprecision, | - | The mean hydration status in the control group was 2.7 (+/-1.6) | The mean hydration status in the intervention groups was 0.5 higher (0.05 lower to 0.96 higher) |

| Outcomes | No. of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Usual care | Risk difference with clinically assisted hydration (95% CI) |
| | | indirectness | | | |
| Biochemistry urea/creatinine 7 days before death (measured in mg/dl) | 93 (1 study) | VERY LOW[a,b,c] due to risk of bias, imprecision, indirectness | - | The mean urea in the control group was 39 (+/-20) | The mean urea in the intervention groups was 5.0 higher (-2.17 lower to 12.11 higher) |
| Biochemistry urea/creatinine 2 days before death (measured in mg/dl) | 68 (1 study) | VERY LOW[a,b] due to risk of bias, imprecision | - | The mean urea in the control group was 33 (+/-13.4) | The mean urea in the intervention groups was 0.5 higher (-7.67 lower to 8.67 higher) |
| Biochemistry sodium 2 days before death (measured in mEg/litre) | 68 (1 study) | VERY LOW[a,b] due to risk of bias, imprecision | - | The mean sodium in the control group was 139 (+/-7.3) | The mean sodium in the intervention groups was 9.5 higher (3.73 lower to 15.27 higher) |

*(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*

### 8.3.2 Narrative evidence

**Symptom sedation/drowsiness - Waller 1994**

Waller 1994 had consciousness level as a secondary outcome.[102] It was not possible to extract data from the paper; but the paper reports there was no statistical difference between the intervention and the control group.

**Adverse Events - Morita 2005**

Morita 2005 reported adverse events from positive fluid balance. The study reported bronchial secretion.[69] It was not possible to extract data from the paper; but the paper reports there was no statistical difference between the intervention and the control group.

**Survival - Cerchietti 2000**

Cerchietti 2000 reported survival between a hydration and usual care comparison.[20] It was not possible to extract data from the paper; but a narrative description reports that there was no significant difference in survival between groups.

## 8.4 Economic evidence

**Published literature**

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

**Unit costs**

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost effectiveness.

**Table 42: Cost of setting up subcutaneous assisted hydration**

| Resource item | Cost per item (£) | Source |
|---|---|---|
| 25 gauge winged butterfly needle | 2.15 | NHS Supply Chain Catalogue April 2014 |
| Standard giving set (single chamber - 20 drops per ml) | 4.14 | NHS Supply Chain Catalogue April 2014 |
| Cannula dressing IV | 1.08 | NHS Supply Chain Catalogue April 2014 |
| Alcohol swab | 0.16 | NHS Supply Chain Catalogue April 2014 |
| Gloves | 0.38 | NHS Supply Chain Catalogue April 2014 |
| Infusion solution NaCal 1 litre | 0.70 | Commercial Medicines Unit, DoH 2014 |
| Staff cost – only hospital setting | 5.67 | PSSRU 2013 (assuming 10 minutes of a ward nurse) |
| Staff cost – only community setting | 30.00 | PSSRU 2013 (assuming 30 minutes of community nurse, including travel time) |
| Total – hospital setting | £14.28 | |
| Total – community setting | £38.61 | |

**Table 43: Cost of setting up IV assisted hydration**

| Resource item | Cost per item (£) | Source |
|---|---|---|
| 10 ml Syringe | 0.09 | NHS Supply Chain Catalogue April 2014 |
| 10 ml flush of NaCl | 0.05 | Commercial Medicines Unit, DoH 2014 |
| IV cannula | 1.09 | NHS Supply Chain Catalogue April 2014 |
| Standard giving set (single chamber - 20 drops per ml) | 4.14 | NHS Supply Chain Catalogue April 2014 |
| Cannula dressing IV | 1.08 | NHS Supply Chain Catalogue April 2014 |
| Alcohol swab | 0.16 | NHS Supply Chain Catalogue April 2014 |
| Gloves | 0.38 | NHS Supply Chain Catalogue April 2014 |
| Infusion solution NaCal 1 litre | 0.70 | Commercial Medicines Unit, DoH 2014 |
| Tourniquet (disposable) | 0.27 | NHS Supply Chain Catalogue April 2014 |
| Staff cost – only hospital setting | 3.50 | PSSRU 2013 (assuming 10 minutes of a foundation house officer) |
| Total – hospital setting | £17.12 | |

The costs reported above do not include the cost of treating adverse events due to the intervention.

## 8.5 Evidence statements

### Clinical

#### Clinically assisted hydration versus placebo

There was moderate to very low quality evidence identified from 2 RCTs (n=129 and 51) conducted in hospice and home settings on a population of people with cancer who were not severely dehydrated. Both RCTs compared 1 litre subcutaneous fluid with a placebo of 100 ml subcutaneous fluid. The RCT's reported no clinical difference in clinically assisted hydration over placebo on quality of life of people, patient wellbeing, survival time or on relief of symptoms (including anxiety, dyspnoea, pain, nausea and sedation or drowsiness and delirium), between the groups.

#### Clinically assisted hydration versus usual care

Moderate quality evidence was identified in 1 small RCT comparing clinically assisted hydration titrated to need or oral hydration only in a population of people with cancer in the last days of life. They reported no increased adverse procedural events or over-hydration in people with clinically assisted hydration over usual care alone. There was also very low quality evidence from this study that there was no clinical difference in survival between the groups.

Low and very low quality evidence was identified from non-randomised control trials (NRCT). An observational study comparing subcutaneous fluids with hyaluronidase titrated to need to usual care (n=26) reported no clinical benefit of clinically assisted hydration over usual care on patient-reported wellbeing or symptom relief from anxiety, dyspnoea, pain, nausea, and sedation or drowsiness.

This was reflected in another large NRCT (n=226) that showed that clinically assisted hydration gave no clinical benefit in preventing delirium over oral hydration only. This NRCT also found no increased clinical risk of oedema, ascites or pleural effusions, no increased clinical benefit in hydration status or clinical difference in laboratory tests between hydration and usual care.

### Economic

No relevant economic evaluations were identified.

## 8.6 Recommendations and link to evidence

**23.Support the dying person to drink if they wish to and are able to. Check for any difficulties, such as swallowing problems or risk of aspiration. Discuss the risks and benefits of continuing to drink, with the dying person, and those involved in the dying person's care.**

**24.Offer frequent care of the mouth and lips to the dying person, and include the management of dry mouth in their care plan, if needed. Offer the person the following, as needed:**

- **help with cleaning their teeth or dentures, if they would like**
- **frequent sips of fluid.**

**25.Encourage people important to the dying person to help with mouth and lip care or giving drinks, if they wish to. Provide any necessary aids and give them advice on giving drinks safely.**

**26.Assess, preferably daily, the dying person's hydration status, and review the possible need for starting clinically assisted hydration, respecting the person's wishes and preferences.**

**27.Discuss the risks and benefits of clinically assisted hydration with the dying person and those important to them. Advise them that, for someone who is in the last days of life:**

- **clinically assisted hydration may relieve distressing symptoms or signs related to dehydration, but may cause other problems (see recommendation 31)**
- **it is uncertain if giving clinically assisted hydration will prolong life or extend the dying process**
- **it is uncertain if not giving clinically assisted hydration will hasten death.**

**28.Ensure that any concerns raised by the dying person or those important to them are addressed before starting clinically assisted hydration.**

**29.When considering clinically assisted hydration for a dying person, use an individualised approach and take into account:**

- **whether they have expressed a preference for or against clinically assisted hydration, or have any cultural, spiritual or religious beliefs that might affect this documented in an advance statement or an advance decision to refuse treatment**
- **their level of consciousness**
- **any swallowing difficulties**
- **their level of thirst**
- **the risk of pulmonary oedema**
- **whether even temporary recovery is possible.**

**30.Consider a therapeutic trial of clinically assisted hydration if the person**

| | |
|---|---|
| | **has distressing symptoms or signs that could be associated with dehydration, such as thirst or delirium, and oral hydration is inadequate.**<br><br>**31. For people being started on clinically assisted hydration:**<br>• **Monitor at least every 12 hours for changes in the symptoms or signs of dehydration, and for any evidence of benefit or harm.**<br>• **Continue with clinically assisted hydration if there are signs of clinical benefit.**<br>• **Reduce or stop clinically assisted hydration if there are signs of possible harm to the dying person, such as fluid overload, or if they no longer want it.**<br><br>**32. For people already dependent on clinically assisted hydration (enteral or parenteral) before the last days of life:**<br>• **Review the risks and benefits of continuing clinically assisted hydration with the person and those important to them.**<br>• **Consider whether to continue, reduce or stop clinically assisted hydration as the person nears death.** |
| **Relative values of different outcomes** | The Committee was most interested in wellbeing ratings as a proxy for quality of life and symptom control as a surrogate outcome for comfort. Adverse events, such as pain at injection site, local swelling and oedema, were also considered to be critical. The Committee also considered length of survival as an important outcome. Laboratory results, while discussed, were not prioritised as important outcomes in the protocol as these were excluded from the scope. |
| **Trade-off between clinical benefits and harms** | The clinical evidence identified showed no overall improvement in wellbeing and symptom control associated with clinically assisted hydration. Clinically assisted hydration did not lead to more frequent adverse events over placebo or usual care, and survival length did not increase or shorten when using clinically assisted hydration, but was of limited quality. Committee consensus was that some adverse events do occur in practice including cannula site discomfort, line infections and worsening oedema or heart failure when there is fluid overload. However, the Committee discussed the equivalence in efficacy between clinically assisted hydration and usual care or placebo.<br>The Committee was divided on whether or not the addition of another intervention in the last hours or days of life would be perceived as beneficial by the people important to the dying person. Some members of the Committee considered such a procedure to be invasive, whereas others thought that it could possibly alleviate distress.<br>They also noted that providing an intervention that was invasive and that was not likely to provide any clinical benefit could also add an element of discomfort for the dying person.<br>The experience of the Committee was that there is benefit in some circumstances, such as in the case of managing thirst or managing delirium caused by dehydration, but this was not captured by the evidence. |
| **Trade-off between net health benefits and resource use** | No economic evidence was identified for this question. The Committee considered the cost of providing clinically assisted hydration when making recommendations; this cost was dependent on the care setting (hospital or community) and more resources, especially in terms of staff time, are required for providing clinically assisted hydration in the community setting. Also, the cost was different between subcutaneous and IV assisted hydration due to the different equipment, staff level and time needed. |

| | |
|---|---|
| | Since the clinical evidence did not show any overall clinical benefit associated with clinically assisted hydration and, in addition, clinically assisted hydration may cause discomfort to the patient, the Committee considered that providing clinically assisted hydration could, in some cases, unnecessarily increase costs. However, some benefits of clinically assisted hydration may not have been captured in the clinical evidence, such as improvement in thirst or delirium or the psychological benefit to the relatives and those important to the dying person who could otherwise feel distressed should clinically assisted hydration not be provided. For this reason, the Committee considered that, in some circumstances, the cost of the intervention could be outweighed by its benefits. |
| **Quality of evidence** | Evidence for the reported outcomes varied from moderate to very low quality. The evidence from the RCTs was considered to be moderate and, as such, was given more weight in the discussion. The Committee questioned the overall validity of the evidence available due to risk of bias in study design in all papers and the imprecision of a large proportion of the outcome measurements. They noted that the RCTs were terminated early due to recruitment or financial problems and were therefore underpowered. Two of the identified studies only included participants diagnosed as having mild to moderate dehydration[15,20] and 2 studies excluded people with severe dehydration.[14,15] Three studies excluded participants with symptoms of fluid overload (for example, ascites or congestive heart failure).<br>Most of the observational studies identified did take account of possible confounding characteristics which may have influenced results. The studies were performed in settings outside of the UK, and the Committee raised that this may not be representative of the range of settings in which most dying persons within the scope of the Committee will enter their last days. The majority of evidence was obtained in cancer populations, which may not be representative of people dying from other causes. |
| **Other considerations** | Being able to eat and drink is a basic human right and need but often as death approaches, the desire and ability to take in food and fluids diminishes. Some people, if they are able, will want to continue to eat and drink right up until the point of death; others have a prolonged dying phase lasting several hours to days or even weeks when they may not be able to drink for various reasons such as reduced conscious level (possibly due to sedative drugs), dysphagia, nausea and vomiting or extreme weakness. They may develop symptoms of dehydration including dry mouth, thirst, confusion and agitation, particularly if there are associated conditions such as hypercalcaemia and opioid toxicity due to impaired renal clearance. This can cause considerable distress to the patient and those important to them particularly if hydration is not adequately assessed and managed.<br>In an unconscious or semi-conscious patient the Committee discussed a need for careful assessment of hydration status by experienced staff to establish if the dying person is distressed with symptoms of dehydration (for example, becoming agitated or restless especially if on high dose opioids) or fluid overload (for example, increasing breathlessness). The Committee felt this may be done in conjunction with those important to the dying person and a best interests decision should be made (as per MCA guidance), taking into account the dying person's previous stated preferences, as to whether clinically assisted hydration should be continued, stopped or commenced.<br>The Committee was also aware of the General Medical Council's guidance in 2010[37] on clinically assisted hydration and nutrition. Members of the Committee felt that this guidance is a good starting point for inexperienced practitioners as it provides general background information as well as helpful specific ethical guidance regarding people who lack capacity and people in a persistent vegetative state.<br>It is important to differentiate dying from dehydration that is potentially reversible, for example, drugs given for pain relief that may have a sedating effect, meaning that a person may be unable to maintain an adequate oral intake. In the case of dying with symptoms of dehydration from an irreversible disease process, the aim of |

treatment is to relieve symptoms of dehydration and associated distress as a comfort, rather than to prolong life.

The Committee discussed the role of blood tests to indicate hydration status in the last days of life as they were aware that this was setting dependent. The Committee felt that there was not always additional benefit to performing these tests in the last days of life. They agreed that the principle should be that these tests not be routinely undertaken as hydration status could be assessed clinically. However, if laboratory test results are present then they may guide decisions around clinically assisted hydration but no recommendation was made as this was outside the remit of this guideline.

Oral hydration

The Committee was keen to note that the management of hydration in the dying person should always be individualised and, wherever possible, be by oral means. They felt it important to make a recommendation that indicated that this should be encouraged. The Committee were aware of the risks of maintaining oral hydration at the end of life, when the swallowing reflex becomes progressively impaired. The Committee highlighted the need to assess the dying person for any problems with oral hydration, whilst being mindful of their preferences. The Committee felt that the decision to take oral fluids should be with the dying person where possible, but that clinicians or care providers should take steps to prevent aspiration. The Committee felt that it is often appropriate to continue to offer and assist a dying person with oral fluids if that is their wish, but some health care professionals may feel uncomfortable with managing the risk associated with this aspect of care. Offering oral fluids may include small sips of ice water or chips of ice; being ice cold may reduce the risk of this fluid being aspirated, causing distressing choking or coughing, as the dying person cannot forget it is there and inhale it. Supporting the dying person to drink may also include encouragement with a straw, a teaspoon, the right beaker or thickened fluids.

The Committee felt that if enteral tubes were already in situ they could be used to provide fluids. They noted that certain clinical conditions may prevent the oral route, such as dysphagia, but that taking fluids, as required, by drinking would be the least invasive approach to managing the symptoms associated with dehydration.

Care of the mouth and lips

The Committee agreed that encouraging those important to the dying person to be part of oral care was also relevant and considered it important to include a recommendation that ensured that professionals encouraged this directly with those important to the dying person where desired. The Committee discussed the importance of frequent mouth care, such as cleaning teeth or dentures if they wish too. In addition, the Committee discussed the unconscious dying person and that lip care for these people was important, particularly as visible dry, cracked or bleeding lips could be distressing to those important to the dying person.

The speech and language therapist co-opted expert advisor identified that good oral care is important. The availability of artificial saliva as part of the management of a dry mouth was considered by the Committee, and they were aware that certain products are pork based and therefore not appropriate for some populations. The Committee noted that the input of speech and language therapists could be beneficial in the management of oral care at the end of life, where specialist advice is required. The Committee considered the above points but as no evidence review was conducted in these areas, they chose not to make any specific recommendations.

The Committee noted that there has been an MHRA alert regarding the use of oral hygiene sponges (oral swabs with a foam head). Foam heads of oral swabs may detach from the stick during use and may present a choking hazard for patients. The

MHRA advice is to:

- follow the manufacturer's instructions for use (where available)
- to check that the foam head is firmly attached to the stick before use
- do not leave the swabs soaking in liquid prior to use as this may affect the strength of the foam head attachment
- if required moisten the swab immediately before use.

If the dying person is likely to bite down on the swab, consider using an alternative such as a small headed toothbrush with soft bristles.

The co-opted speech and language therapist noted that many trusts have issued this statement for use by their staff, rather than withdrawing the product all together. The problem is that there is no obvious alternative, and if they are not used, the risk to oral hygiene from not having oral care is higher than the risk associated with using the mouth care sponges.

Clinically assisted hydration

A recommendation was made to review the need for clinically assisted hydration in people in the last few days of life preferably daily. It was felt that an assessment of hydration should be occurring routinely as part of general nursing and medical care. However, the Committee wanted to emphasise that there should be on-going monitoring and review of the dying person's hydration status and that once a decision is made to give or not give clinically assisted hydration, it is not "set in stone". Any individual's hydration needs may change as their condition changes depending on their underlying disease and other factors, such as medications.

The Committee chose to make a recommendation to discuss the risks and benefits of clinically assisted hydration with the dying person and those important to them because many criticisms of the Liverpool Care Pathway made reference to the issue of hydration and concerns of dying slowly of dehydration, and there had been little or no communication from healthcare staff about providing fluids.

The Committee felt it was important to emphasise that clinicians weigh up the risks and benefits of clinically assisted hydration on a case by case basis for any dying person. They wanted to emphasise that open and honest discussions should take place around the decision making process, ensuring that the dying person and those important to them are aware of the uncertainty about its benefits and the effect on survival. The Committee felt this discussion alone may alleviate concerns (even if a decision is then made to not give clinically assisted hydration) as the dying person and those important to them will have a better understanding of hydration issues and the aims of care in the last few days of life.

It is important that the dying person and those important to them are aware that the benefits of giving assisted hydration are for relief of distressing symptoms of dehydration and that fluids are not being administered to prolong life, except when there is uncertainty about whether the person is dying or there is potential for recovery (for example, in a patient who has suffered a stroke). The dying person and those important to them should also be made aware of any potential harms of clinically assisted hydration, such as the need for intravenous cannulation or insertion of a subcutaneous needle, pooling of fluids in subcutaneous tissues, fluid overload causing increased respiratory secretions and the possibility of moving care setting if clinically assisted hydration cannot be provided in the community.

The Committee was aware from their clinical experience that family members may have preconceptions around the provision or 'withholding' of clinically assisted hydration in relation to the possibility of prolonging the dying process or hastening death. The Committee noted recent systematic reviews of the qualitative literature (Cohen et al., 2012;[25,26] del Rio et al. 2012,[28] and Gent et al., 2014,[38]) that report on the emotional, spiritual and comfort aspects of clinically assisted hydration. This literature also identifies similar key misconceptions amongst professionals as well as

lay people about clinically assisted hydration.[38]

The lack of clear evidence about the benefits of clinically assisted hydration in the last few days of life and effects on survival meant that the Committee was unable to make a clear recommendation about when to use it or not as all decisions should be made on a case by case basis after weighing up the risks, harms and benefits to the individual. They acknowledged that the issue of hydration is very emotive and influenced by cultural and societal beliefs. The Committee felt strongly that a dying person and those important to them should be made aware of the uncertainty surrounding the effects of clinically assisted hydration on survival due to the evidence showing equivocal results. The Committee was therefore keen to make a recommendation about advising the dying person and those important to them that there is uncertainty whether: a) giving clinically assisted hydration will prolong life or the dying process and b) not giving clinically assisted will hasten death. The Committee hope that through education and implementation of this recommendation, this will lead to a change in practice and dispel some of the misconceptions that withholding hydration will speed up death or giving hydration will improve survival and therefore prolong suffering, as neither of these statements is based on robust evidence.

The Committee noted that when reviewing the need for clinically assisted hydration, the wishes and preferences of the dying person and those important to them are respected, in order to capture discussions around culture and religion and any relevant decisions stated in the advance care plan. The Committee chose to state 'respected' to mean that in some cases it may not be possible, but that they would always be considered and taken into account.

The Committee discussed that the evidence in this area had limitations, but did show equivalence in efficacy between clinically assisted hydration and usual care or placebo. The Committee noted that the clinical evidence showed no increase or shortening in survival (that is, the provision of clinically assisted hydration is unlikely to prolong the dying process), but given the low quality, there is a high level of uncertainty. Moreover, the Committee did not feel, from their clinical experience, that withholding clinically assisted hydration would hasten death. The Committee recommended a therapeutic trial of clinically assisted hydration based on consensus using their expert knowledge. However, they felt it important that a full discussion of the harms and benefits of clinically assisted hydration took place with the dying person or those important to them, as appropriate, as part of holistic care and that any preconceptions and concerns are addressed before initiating clinically assisted hydration.

When considering who would benefit from clinically assisted hydration, the Committee discussed the following issues. They noted that existing comorbidities, such as heart failure, renal failure, or difficulties in swallowing, may influence a clinical decision to start or withdraw fluids. For example, a dying person with heart failure may become more breathless by administration of excessive fluid but not simply by parenteral fluids per se. The Committee also highlighted that people with cognitive disabilities (including those with dementia and learning difficulties) may find the intervention invasive and distressing. This point was re-enforced by the co-opted psycho-geriatrician expert and the Committee felt that this should be taken into consideration when starting clinically assisted hydration. On the other hand, acute delirium caused or aggravated by dehydration may benefit from hydration whether by oral or a clinically assisted hydration route. The principle of care would be to maintain adequate hydration in the dying person in the last days of life to minimise unwanted symptoms such as delirium.

The Committee was aware from their experience that some cultures and religions have specific beliefs about clinically assisted hydration (for example, whether it is seen as a medical intervention or not and therefore a life prolonging measure) and recommended that this should be taken into account when considering the role of

clinically assisted hydration.

The Committee discussed that, for those people who are thought suitable for clinically assisted hydration after a careful weighing of the above factors, a trial of clinically assisted hydration could be initiated if the dying person was experiencing symptoms associated with dehydration (such as thirst or delirium). The Committee felt that the dying person should then be monitored at least once a day for evidence of clinical harm from the intervention; or to determine whether the hydration provided was sufficient. Whilst clinically assisted hydration was not found to cause clinical harm in the evidence reviewed, from their clinical background the Committee acknowledged that adverse events do occur, and that monitoring would be important to prevent this. If there is evidence of clinical harm then the Committee felt that any clinically assisted hydration should be reduced or stopped and this should be discussed with the dying person and those important to them. Equally, if there is no evidence of clinical benefit from a therapeutic trial of clinically assisted hydration and, in discussion with the dying person and those important to them, it is felt that fluids are not beneficial, they should be withdrawn. The group discussed whether significant discomfort at the infusion site would be a reason to discontinue clinically assisted hydration, but felt that in some cases it may be appropriate to change the infusion site.

The Committee commented that, on occasion, parenteral fluids are given to relieve psychological distress of the dying person and those important to them despite no clear evidence of their effect on physical symptoms. This may be an acceptable indication, provided there are no harmful effects, but the Committee felt that it would be important to explore the dying person's beliefs and correct any misconceptions first. This was an area highlighted in the Neuberger report.[30]

The Committee noted from their experience that not providing clinically assisted hydration to the dying person may cause psychological distress to those important to them and that, often, clinically assisted hydration may be prescribed to alleviate distress of those important to the dying person, as well as to improve hydration in the person who is dying. They felt that this practice was acceptable especially if there was any concern that the dying person was distressed with symptoms of dehydration, provided that the dying person was not experiencing any harmful effects from administration of the fluids.

The Committee also discussed that in their clinical experience parenteral fluid does not necessarily need to be administered continuously but could be provided as an overnight intervention only. They noted that it may only be necessary to provide relatively small volumes of fluid a day (for example, 1 litre) in 24 hours to relieve symptoms of dehydration. Factors such as the person's height and weight, amount of time unable to take oral fluids and presence of electrolyte disturbances, if known, should also be taken into consideration.

It was also discussed that a trial of clinically assisted hydration should more readily be started when there is uncertainty that a person is dying and might recover but is currently unable to take oral fluids. This would be important to prevent death from dehydration in a potentially reversible condition.

The Committee discussed whether a person dying at home would require a move to hospital for clinically assisted hydration, but agreed that this was not necessary and that it is possible to provide clinically assisted hydration at home if there were appropriate available resources. The Committee discussed that setting was not a barrier to providing clinically assisted hydration, but that this may require additional resources for implementation.

Please also see the chapter on shared decision making which details the Mental Capacity Act.

# 9 Pharmacological interventions

Optimal symptom control in the last few days of life requires considerable skill and may be challenging for even an experienced palliative care clinician. There may be a number of concurrent clinical problems as well as an underlying desire to get the care right for the dying person and those important to them. Poorly controlled symptoms can lead to considerable distress as they interfere with the ability to engage in other important activities including saying goodbye to those important to the dying person and putting financial affairs in order. Many of the medications used to manage these symptoms may cause a degree of sedation, or other side effects.

As a person approaches the last few days of life changes in their physical condition, as a result of organ failure, muscle weakness and progression of cancer, may also lead to a change in, or emergence of some of these symptoms. Careful assessment is required, and possibly a review of medication with changes to drugs, including doses and routes of administration, even when symptoms have been previously well controlled.

A single pharmacological agent may be used to treat more than 1 symptom, for example, an antipsychotic agent can treat both nausea and agitation but high doses of medications in combination may also be required to achieve adequate symptom control. Healthcare professionals in community or hospital settings may lack experience in using pharmacological agents in managing these symptoms and have concerns about escalating opioids or other medications for fear of causing sedation or even precipitating death.

This chapter addresses the management of pain, breathlessness, nausea and vomiting, agitation, delirium, anxiety and noisy respiratory secretions at the end of life. The sequence in which these are reviewed and presented below does not reflect any implied order of importance or strength of evidence for the recommendations.

Pain and breathlessness are discussed first as these are 2 of the most common symptoms occurring in people in the last few days of life and are often greatly feared by the person that is dying and those important to them. Pain is a complex phenomenon including physical, psychological and spiritual elements and is a unique experience for every individual. Non-physical pain such as fear or existential distress may also become more prominent as death approaches and this is an important consideration as part of prescribing analgesia and other medications. Breathlessness in a dying person has a number of underlying causes and does not necessarily correlate with the degree of hypoxia. It is a subjective experience and may be exacerbated by progressive muscle weakness, fatigue and increasing anxiety as the person approaches death.

Nausea and vomiting are presented next because they are commonly experienced, not only as symptoms of advancing diseases, but may reflect side-effects of drugs used to manage other symptoms such as pain or breathlessness. They can have a profound negative effect on the dying process and can cause distress to those important to the dying person as well. However, inexpert pharmacological management of these symptoms can lead to adverse effects such as excessive sedation or dystonic movements in older people.

Anxiety, delirium and agitation are then presented. A common sequence observed in practice is anxiety leading to agitation if it is not resolved; alternatively delirium may develop into an agitated state. The order of presentation of these 3 problems in the recommendations below is alphabetical rather than representing an order of priority. The focus of treatment is to minimise harm to the dying person and reduce the distress of family members and carers in managing these symptoms. Levels of anxiety may rise in people approaching their death due to fear and uncertainty and this may manifest as agitation.

The pharmacological management of noisy respiratory secretions (sometimes called 'death rattle') concludes the chapter. By no means universal, this physical sign (rather than strictly speaking, a subjective 'symptom'), affects a substantial proportion of people dying and are thought to arise when mucus gathers in the upper airways, or saliva pools in the pharynx and hypopharynx. In either situation, if the dying person is unable to cough effectively to expel the mucus or saliva, it can lead to 'gurgly' or 'rattly' sounds.

As well as building on historical experience in caring for people with advanced cancer in the hospice setting, the UK current approach to symptom management at the end of life has developed from knowledge of managing these symptoms in other clinical situations. As symptom management is an essential part of caring for the dying adult, it is important that our current practice is reviewed. Guidance surrounding the use of medications for managing pain, breathlessness, agitation, anxiety and delirium, nausea and vomiting and noisy respiratory secretions, and the potential for harm at end of life, should be developed based on a robust review of the evidence specific to this time period. The Committee drafted a question to address this issue.

For each symptom, the evidence is presented followed by recommendations on the specific management of that symptom with an accompanying discussion. The chapter is concluded with a series of overarching recommendations for pharmacological management that should be considered best practice for the delivery of pharmacological interventions in the last days of life.

## 9.1 Review question: For people in the last days of life, which pharmacological agents are most effective in relieving pain, breathlessness, nausea and vomiting, anxiety, agitation, delirium and noisy respiratory secretions and what degree of sedation do they cause?

For full details see review protocol in Appendix C. Three separate protocols were developed and 3 search strategies conducted for this question to enable ease of sifting and abstracting and to incorporate different drugs. In addition a Cochrane systematic review was identified for noisy respiratory secretions that required updating. For simplicity the review questions and summary PICO characteristics (Table 44) have been combined. However, each symptom was considered individually by the Committee and separate recommendations made for each.

**Table 44: PICO characteristics of review question**

| | |
|---|---|
| **Population** | Adult people in the last days of life who are experiencing pain, breathlessness, anxiety, agitation or delirium, nausea and vomiting or noisy respiratory secretions |
| **Intervention(s)** | • 5HT3 Antagonists<br>• Anticholinergics<br>• Antimuscarinics<br>• Antipsychotics<br>• Atypical antipsychotics<br>• Benzodiazepines<br>• Corticosteroids<br>• Diuretics<br>• Dopamine Receptor Blockers<br>• Heliox<br>• NK1 Antagonists<br>• NSAIDS<br>• Opioids |

| | |
|---|---|
| | • Oxygen<br>• Paracetamol<br>• Somatostatin Analogue Anti- secretory |
| **Comparison(s)** | • Any of the above<br>• Placebo<br>• Usual care |
| **Outcomes** | • Adverse effects of treatment<br>• Control of specific symptoms (pain, breathlessness, anxiety, agitation and delirium, nausea, vomiting and noisy respiratory secretions) - as rated by doctor, the dying person or those important to them.<br>• Level of sedation either subjective (patient-rated, clinician-rated, carer-rated) or objective (Glasgow Coma Scale or equivalent scale of responsiveness)<br>• Length of survival<br>• Quality of life or patient wellbeing (as rated by doctor, the dying person or those important to them) |
| **Study design** | • Systematic reviews of RCTs<br>• RCTs<br>• Non-randomised comparative studies |

# Managing pain

## 9.2 Clinical evidence

Systematic reviews, randomised controlled trials or comparative observational studies were searched for that addressed pharmacological management of pain in the last days of a person's life.

One RCT[98] was included in the review; this is summarised in the table below. This study involved people crossing over to alternative treatments and serving as their own controls. Evidence from this study is summarised in the GRADE clinical evidence summary in Table 46. See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, forest plots in Appendix K, GRADE tables in Appendix J and excluded studies list in Appendix L.

**Table 45: Summary of included studies**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Twycross (1977)[98] | Intervention:<br>Diamorphine<br><br>Comparison:<br>Morphine<br><br>In both groups the dose was increased to achieve adequate analgesia for 4 hours<br><br>Both groups received interventions orally as a liquid and were also given anti-emetics<br>Cocaine was included in the formulation (10 mg/dose)<br>An oral potency ratio of 1.5:1 was used (diamorphine:morphine) to determine equianalgesic doses | n=699 (but only 146 crossed over)<br>People in a hospice with terminal cancer prescribed diamorphine for pain relief<br>Median survival of people admitted to the unit <2 weeks<br>UK | Pain change score before and after crossover (VAS 0-100)<br>Nausea change score before and after crossover (VAS 0-100)<br>Sleep change score before and after crossover (VAS 0-100) | Randomised, crossover study<br>Cross over after 2 days, measurements not taken on day 3 to act as washout period<br>Only 21% survived/continued to crossover (and only 61% of these were analysed as others had changes in adjuvant medication or opioid dose during the observation period)<br>Males and females were analysed separately owing to differences in effect seen with dihydrocodeine. |

#### 9.2.1.1 GRADE assessment

GRADE tables are divided by comparison. See below for reported outcomes in each of the comparisons.

### 9.2.1.2 Pain management

**Table 46: Clinical evidence summary: Diamorphine versus morphine**

| Outcomes | No. of participants (studies) Follow-up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Morphine | Risk difference with Diamorphine (95% CI) |
| Pain (VAS 0-100) | 89 (1 study) 2 days | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | - | Mean pain score in control group was not given | The mean pain in the intervention group was 6.41 higher (1.34 to 11.47 higher) |
| Nausea (VAS 0-100) | 89 (1 study) 2 days | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | - | Mean nausea score in control group was not given | The mean nausea in the intervention group was 2.36 higher (1.04 lower to 5.77 higher) |
| Night-time sleep quality (VAS 0-100) | 89 (1 study) 2 days | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | - | Mean sleep score in control group was not given | The mean night-time sleep quality in the intervention group was 7.77 lower (15.89 lower to 0.34 higher) |

*(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.*

## 9.3 Economic evidence

### Published literature

No relevant economic evaluations were identified. See also the economic article selection flow chart in Appendix F.

### Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix N to aid consideration of cost effectiveness.

## 9.4 Evidence statements

### Clinical

### Diamorphine versus morphine

There was very low quality evidence from 1 crossover RCT (n=89) in people in a hospice with terminal cancer demonstrating no clinical difference between diamorphine and morphine for pain, nausea or night-time sleep quality as assessed by the patient.

No evidence was found for the quality of life or length of survival outcomes.

### Economic

No relevant economic evaluations were identified.

## 9.5 Recommendations and link to evidence

| | |
|---|---|
| **Recommendations** | **33. Consider non-pharmacological management of pain in a person in the last days of life.**<br><br>**34. Be aware that not all people in the last days of life experience pain. If pain is identified, manage it promptly and effectively, and treat any reversible causes of pain, such as urinary retention.**<br><br>**35. Assess the dying person's level of pain and assess for all possible causes when making prescribing decisions for managing pain.**<br><br>**36. Follow the principles of pain management used at other times when caring for people in the last days of life, for example, matching the medicine to the severity of pain and, when possible, using the dying person's preferences for how it is given.**<br><br>**37. For a person who is unable to effectively explain that they are in pain, for example someone with dementia or learning disabilities, use a validated behavioural pain assessment to inform their pain management.** |
| **Relative values of** | The Committee considered the following critical outcomes for pain for decision |

| | |
|---|---|
| **different outcomes** | making: symptom control, sedation and quality of life. The Committee considered these to have the most influence on their decision making, but also prioritised adverse events and length of survival as important outcomes contributing to recommendation development as they may provide evidence of harm. |
| **Trade-off between clinical benefits and harms** | The Committee discussed the benefit of good pain management in the last days of life, which if done in an appropriate manner can result in the patient being pain free and conscious.<br>The Committee discussed the potential harm of over or undertreating people in the last days of life in terms of the risk of adverse effects, or the perception of hastening death. The Committee considered potential harms to include unwanted sedation, which can lead to the dying person not being conscious to engage with loved ones in last days of life. The Committee agreed that potential benefits and harms should be clearly communicated to the dying person and those important to them, and that patient preference should be respected. Potential harms should be minimised by considering the choice of pain management in light of medication already being administered. |
| **Trade-off between net health benefits and resource use** | No economic evaluations were identified.<br>Clinical evidence was limited to the comparison of morphine and diamorphine. Although the clinical evidence found morphine to be just as effective as diamorphine, at a lower cost, the Committee felt the evidence was not sufficient to conclude that diamorphine offered no clinical benefit. Therefore the cost-effectiveness surrounding diamorphine remains uncertain.<br>Unit costs of other relevant pharmacological agents were presented to the Committee for them to make economic considerations. The Committee noted that although cost differences were small between different agents without any clinical evidence 1 treatment could not be said to be any more effective, and therefore cost-effective, over another. Therefore the Committee decided not to recommend any specific drug for the management of pain. |
| **Quality of evidence** | No evidence was found for the quality of life or time-to-death outcomes. Night-time sleep quality was used as surrogate measure of sedation.<br>For the management of pain in the last days of life there was evidence from 1 crossover RCT. This study compared diamorphine with morphine given orally to people with terminal cancer in a hospice setting. The Committee discussed the limited applicability of this study as diamorphine is no longer given orally and cocaine was included in the formulation. There was also a very high rate of loss to follow-up, which increases the risk of bias. All of the outcomes (pain, nausea and sleep) showed no clinical difference between the interventions (morphine was as effective as diamorphine) and were rated as very low quality evidence. |
| **Other considerations** | The Committee noted that the dying person is not always in pain, but that when they are it is important to determine the degree and likely cause of the pain. The Committee discussed the different types of pain including physical and emotional pain, and spiritual and psychological distress. These factors may influence the decisions around pain management including non-pharmacological strategies or simple options such as listening techniques and providing information about what to expect.<br>The Committee discussed the importance of good pain assessment of people in the last days of life. They acknowledged specific populations, including people with dementia or people with communication difficulties. The Committee were particularly concerned that pain may be undertreated in a dying person who cannot effectively verbally communicate and that other signs and symptoms that may be a sign of pain, such as restlessness or groaning, may be treated inappropriately with sedatives rather than analgesics. An evidence review was not conducted on the use of pain assessment tools in the last few days of life; however, the Committee chose to make a consensus recommendation about their use based on their own clinical experience. The NICE clinical guideline on dementia,[75] notes that observational pain assessment tools can be used if thought to be helpful. This is important to consider |

when aiming for a personalised approach to pain assessment in the last days of life. Clinicians should be aware of the legal imperative for access to an Independent Mental Capacity Advocate (IMCA), which is a legal right for people over 16 who lack mental capacity and who do not have an appropriate family member or friend to represent their views.

The Committee were aware of a number of pain assessment tools, including numerical scales as well as scores that incorporate the use of non-verbal cues such as facial grimacing and behavioural changes. Some of these tools are unvalidated and may not be appropriate for use in the last few days of life however, there are tools that can be used in the palliative care setting in patients unable to self-report pain, for example, MPAT (Multidimensional Objective Pain Assessment Tool). The Abbey pain scale is another example of a validated pain assessment tool that can be used in people with cognitive impairment and could be adapted for use in the end of life setting.

The use of a validated pain assessment tool allows an objective measure of the effectiveness of an intervention, particularly when different staff are caring for a dying person. This guides on-going symptom management alongside good clinical judgement including the use of an analgesic trial when appropriate. The Committee also discussed that those important to the dying person may also be able to help assess their level of pain when they have lost the capacity to communicate.

The Committee noted that reversible causes of pain should be treated and that examples of this include urinary retention or constipation.

The Committee discussed whether a specific medication should be recommended for pain relief after an appropriate assessment. However, the limited evidence combined with a wide population and different needs prevented them from doing this. They recognised that there are several widely used pain management methods used in settings outside the last days of life, including the WHO pain ladder,[110] and suggested that a clinicians normal pain management approaches should be used as at any other time of the person's life. The key principle would always be to match the choice of medication to the severity and cause of pain.

The Committee noted that diamorphine is used in care of the dying adult in this country, but not in other countries. They agreed it may be used when a large dose is required, as the greater solubility of diamorphine reduces the volume to be injected subcutaneously or to be swallowed. However, the Committee is aware of occasional difficulties in the availability of diamorphine and the fact that it is more expensive than morphine. They chose not to make a recommendation about this due to the lack of evidence.

The Committee highlighted several areas around good prescribing of analgesics in the last days of life relating to route of administration, including the importance of not withdrawing patches used for transdermal delivery of analgesic drugs in people with pain unless there is evidence of harm such as opioid toxicity. They discussed the fact that the transdermal route may be unreliable at the end of life when peripheral circulation is poor and additional analgesia may be required. However, when initiating new pain management approaches, the possibility of the oral route should be considered first. Although noting that availability for these choices is setting-specific, the Committee agreed that the sub-cutaneous or intravenous routes could also be used. Patient preference should be considered when deciding on the route of administration, and pain at the drug delivery site should be considered and managed. Other than route of administration, pain management should not be any different from that in other settings.

The Committee noted the NICE guideline 140: Opioids in palliative care:[76] safe and effective prescribing of strong opioids for pain in palliative care of adults, which could be referred to for additional guidance. The Committee observed that often people associate the use of opioids with death and incorrectly conclude that commencing opioids will speed up the dying process and therefore decline their use.

The Committee discussed the use of nitrous oxide and oxygen in cancer populations and that it has a role when addressing incident and procedural pain, but there may

| | |
|---|---|
| | be practical difficulties in using this at the end of life as the dying person needs to have adequate strength to inhale the gas effectively. The Committee chose not to make recommendations on this as no evidence was identified.<br>The Committee's general pharmacological recommendations for prescribing in the last days of life can be found in section 9.34, but some of the discussions linked to those recommendations specific to the management of pain are also included below for ease of reference.<br>The Committee acknowledged the importance of seeking specialist pain management advice if needed and was aware that there is often under referral or late referral of people in the dying phase of their illness to pain specialists and that better pain control could be achieved by appropriate early referral before the last days of life. Additionally, the Committee noted the importance of people being reviewed every day and the availability of specialist palliative care advice, including at night and at the weekends. Options should be discussed with the person themselves and their choices should be respected, along with any advance care plan they have formulated.<br>The Committee commented that research in this area is predominantly in cancer populations. The Committee discussed the use of existing routes, such as a Hickmann line previously used for chemotherapy, and that they can be used for giving pain medication. The co-opted expert in pain management raised some points that the Committee also discussed, including maintaining existing pain management strategies to avoid the risk of withdrawal effect and potential agitation.<br>Where the dying person receives pain management was also discussed. This reflected the fact that one possibility would be transferring from hospice to hospital if additional pain management were required, but that the dying person's preferred place of death would also need to be taken into consideration. The Committee generally felt that such an intervention should be avoided at the time of dying and an appropriate shared decision made on balance.<br>The Committee discussed patients with chronic pain and renal impairment. Caution was advised in the use of opioids in renal impairment, especially where a drug or its active metabolites have significant renal elimination, and thus the potential for accumulation. The British National Formulary gives advice in this area. The Committee wanted to highlight the importance of taking into consideration other comorbidities and other medications the dying person is taking when making prescribing decisions. They chose not to make any specific recommendations about pain management in different patient groups, and suggested that clinicians should follow their normal prescribing practices as at any other time of life. |

# Managing breathlessness

## 9.6 Clinical evidence

The clinical question asked can be found in section 9.1. We searched for systematic reviews, randomised controlled trials or comparative observational studies that addressed pharmacological management of breathlessness in the last days of a person's life.

### 9.6.1 Three studies were included in the review, 2 RCTs[80,11] and 1 non-randomised these are summarised in the table below. Two of the studies[11,24] involved people alternative treatments and serving as their own controls. Only 1 study[80] had a clearly population matching our protocol. All studies addressed different comparisons and so data was possible. Evidence from these studies is summarised in the GRADE clinical summaries below (GRADE assessment

GRADE tables are divided by comparison. See below for reported outcomes in each of the comparisons.

Table 48-Table 54).GRADE tables are divided by comparison. See below for reported outcomes in each of the comparisons. See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, forest plots in Appendix K, GRADE tables in Appendix J and excluded studies list in Appendix L.

### 9.6.2 Summary of included studies

**Table 47: Summary of studies included in the review**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Booth et al. (1996)[11] | Intervention:<br>Oxygen<br><br>Comparison:<br>Air<br><br>Both groups received their breathing gas via a nasal cannula at 4 litres/minute | n=38<br>Hospice in people with advanced cancer and breathlessness at rest<br>Mean survival time 19 days<br>UK | Breathlessness:<br>Vertical 100 mm VAS<br>Modified Borg scale at 15 minutes<br>Adverse effects relating to study procedure | Randomised crossover study: No formal washout period. Duration of each treatment was 15 minutes in order to allow time for previously administered gas to wash-out before assessment<br>Subgroup data given for those with cardiopulmonary disease<br>At baseline, 6 people were hypoxic (SaO2 <90%) |
| Clemens et al. (2009)[24] | Intervention:<br>Oxygen ( litres/minute nasally)<br>Morphine/ hydromorphone (orally) | n=46<br>Palliative care in people with advanced terminal cancer or other terminal incurable | Dyspnoea intensity at rest (patient-rated 0-10 scale) | Non-randomised comparative study<br>People were prospectively followed and assessed. They |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Comparison:<br>Baseline – room air | disease and breathlessness at rest<br>Assessed in subgroups:<br>Hypoxic vs. non-hypoxic<br>Opioid pre-treated vs. naive<br>Mean (SD) survival 16.2 (11.9) days and 28.4 (22.4) days, for hypoxic and non-hypoxic groups, respectively<br>Germany | | were given interventions sequentially, first oxygen for 60 minutes then morphine<br>Unclear washout period<br>The choice of opioid (morphine or hydromorphone) was also based on dyspnoea intensity and performance status |
| Navigante et al. (2006)[80] | Intervention:<br>Midazolam<br>Morphine plus midazolam<br>Comparison:<br>Morphine<br><br>Midazolam was given 5 mg every 4 hours, morphine 2.5 mg every 4 hours if opioid naïve or 25% increment over daily dose if baseline opioids received<br><br>In all groups rescue medication was permitted for breakthrough dyspnoea, this was midazolam in the morphine group and morphine in the other groups<br><br>Psychological, spiritual, and non-pharmacological support (air therapy, breathing therapy, relaxation exercises) were offered.<br><br>People who received morphine were systematically pre-medicated with laxatives. | n=101<br>People with terminal advanced cancer, 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')<br>Life expectancy <1 week<br>Argentina | Intensity of dyspnoea (modified Borg scale)<br>Dyspnoea relief<br>Somnolence<br>Nausea/vomiting | Treatment was suspended for people who developed somnolence grade 3 (patient sleeping between 6 and 1 hours during the day) or more |

### 9.6.3 GRADE assessment

GRADE tables are divided by comparison. See below for reported outcomes in each of the comparisons.

**Table 48: Clinical evidence summary: Midazolam versus morphine**

| Outcomes | No. of participants (studies) Follow-up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with morphine | Risk difference with Midazolam (95% CI) |
| Dyspnoea relief - 24 hours | 55 (1 study) 24 hours | LOW[a,b] due to risk of bias, imprecision | RR 0.67 (0.41 to 1.08) | 690 per 1000 | 228 fewer per 1000 (from 407 fewer to 55 more) |
| Dyspnoea relief - 48 hours | 47 (1 study) 48 hours | LOW[a,b] due to risk of bias, imprecision | RR 0.84 (0.63 to 1.12) | 875 per 1000 | 140 fewer per 1000 (from 324 fewer to 105 more) |
| Dyspnoea intensity - 24 hours Measured on the modified Borg scale; range 0 (none) – 10 (maximal) | 68 (1 study) 24 hours | LOW[a,c] due to risk of bias | Median (IQR) Midazolam: 4 (2-6.2); Morph: 3 (2-5.5) | - | The median dyspnoea intensity at 24 hours was higher in the intervention group |
| Dyspnoea intensity - 48 hours Measured on the modified Borg scale; range 0 (none) – 10 (maximal) | 68 (1 study) 48 hours | LOW[a,c] due to risk of bias | Median (IQR) Midazolam: 2 (0-7); Morphine: 2 (0-4.7) | - | The median dyspnoea intensity at 48 was the same in both groups |
| Clinically relevant (grade 2 or above on CTC score) adverse events at 48 hours - Nausea/vomiting | 68 (1 study) 48 hours | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.27 (0.03 to 2.25) | 114 per 1000 | 83 fewer per 1000 (from 111 fewer to 143 more) |

| Outcomes | No. of participants (studies) Follow-up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with morphine | Risk difference with Midazolam (95% CI) |
| Clinically relevant (grade 2 or above) adverse events at 48 hours – Somnolence (3 or more hours sleeping during the day) | 68<br>(1 study)<br>48 hours | VERY LOW[a,b]<br>due to risk of bias, imprecision | RR 0.35<br>(0.08 to 1.63) | 171 per 1000 | 111 fewer per 1000<br>(from 158 fewer to 108 more) |

*(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 49: Clinical evidence summary: Morphine plus midazolam versus midazolam**

| Outcomes | No. of participants (studies) Follow-up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with midazolam | Risk difference with morphine plus midazolam (95% CI) |
| Dyspnoea relief - 24 hours | 51<br>(1 study)<br>24 hours | MODERATE[a]<br>due to risk of bias | RR 1.99<br>(1.3 to 3.07) | 462 per 1000 | 457 more per 1000<br>(from 138 more to 955 more) |
| Dyspnoea relief - 48 hours | 46<br>(1 study)<br>48 hours | LOW[a,b]<br>due to risk of bias, imprecision | RR 1.29<br>(1 to 1.67) | 739 per 1000 | 214 more per 1000<br>(from 0 more to 495 more) |
| Dyspnoea intensity - 24 hours<br>Measured on the modified Borg scale; range 0 (none) – 10 (maximal) | 66<br>(1 study)<br>24 hours | LOW[a,c]<br>due to risk of bias | Median (IQR)<br>Morphine plus midazolam: 3 (2-5); midazolam: 4 (2-6.2) | - | The median dyspnoea intensity at 24 hours was lower in the intervention group |
| Dyspnoea intensity - 48 hours<br>Measured on the modified Borg scale; range 0 (none) – 10 (maximal) | 66<br>(1 study)<br>48 hours | LOW[a,c]<br>due to risk of bias | Median (IQR)<br>Morphine plus midazolam: 2 (1-5); midazolam: 2 (0-7) | - | The median dyspnoea intensity at 48 hours was the same in both groups |
| Clinically relevant (grade 2 or above on CTC score) adverse events at 48 hours - | 66<br>(1 study) | VERY LOW[a,b]<br>due to risk of | OR 0.14<br>(0 to 6.82) | 30 per 1000 | 30 fewer per 1000<br>(from 110 fewer to 50 more)d |

| Outcomes | No. of participants (studies) Follow-up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with midazolam | Risk difference with morphine plus midazolam (95% CI) |
| Nausea/vomiting | 48 hours | bias, imprecision | | | |
| Clinically relevant (grade 2 or above) adverse events at 48 hours – Somnolence (3 or more hours sleeping during the day) | 66 (1 study) 48 hours | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.5 (0.27 to 8.4) | 61 per 1000 | 30 more per 1000 (from 44 fewer to 448 more) |

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

**Table 50: Clinical evidence summary: Morphine plus midazolam versus morphine**

| Outcomes | No. of participants (studies) Follow-up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with morphine | Risk difference with morphine plus midazolam (95% CI) |
| Dyspnoea relief - 24 hours | 54 (1 study) 24 hours | LOW[a,b] due to risk of bias, imprecision | RR 1.33 (1.02 to 1.75) | 690 per 1000 | 228 more per 1000 (from 14 more to 517 more) |
| Dyspnoea relief - 48 hours | 47 (1 study) 48 hours | LOW[a,b] due to risk of bias, imprecision | RR 1.09 (0.92 to 1.3) | 875 per 1000 | 79 more per 1000 (from 70 fewer to 262 more) |
| Dyspnoea intensity - 24 hours Measured on the modified Borg scale; range 0 (none) – 10 (maximal) | 68 (1 study) 24 hours | LOW[a,c] due to risk of bias | Median (IQR) Morphine plus midazolam: 3 (2-5); morphine: 3 (2-5.5) | - | The median dyspnoea intensity at 24 hours was the same in both groups |
| Dyspnoea intensity - 48 hours Measured on the modified Borg scale; range | 68 (1 study) | LOW[a,c] due to risk of | Median (IQR) Morphine plus | - | The median dyspnoea intensity at 48 hours was the same in both groups |

| | | | | | |
|---|---|---|---|---|---|
| 0 (none) – 10 (maximal) | 48 hours | bias | midazolam: 2 (1-5); morphine: 2 (0-4.7) | | |
| Clinically relevant (grade 2 or above on CTC score) adverse events at 48 hours - Nausea/vomiting | 68 (1 study) 48 hours | LOW[a,b] due to risk of bias, imprecision | OR 0.13 (0.02 to 0.97) | 114 per 1000 | 114 fewer per 1000 (from 230 fewer to 0 fewer)[d] |
| Clinically relevant (grade 2 or above) adverse events at 48 hours – Somnolence (3 or more hours sleeping during the day) | 68 (1 study) 48 hours | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.53 (0.14 to 1.95) | 171 per 1000 | 81 fewer per 1000 (from 147 fewer to 163 more) |

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

**Table 51: Clinical evidence summary: Oxygen versus air**

| Outcomes | No. of participants (studies) Follow-up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with air | Risk difference with oxygen (95% CI) |
| Dyspnoea Measured on the modified Borg scale; range 0 (none) – 10 (maximal) | 38 (1 study) 15 minutes | VERY LOW[a,b] due to risk of bias, indirectness | - | The mean dyspnoea on modified Borg scale in the control groups was 3.1 | The mean dyspnoea on modified Borg scale in the intervention group was 0.2 lower |
| Dyspnoea on VAS (follow-up 15 minutes; range of scores: 0-100 | 38 (1 study) 15 minutes | VERY LOW[a,b] due to risk of bias, indirectness | - | The mean dyspnoea on VAS in the control groups was 42 | The mean dyspnoea on VAS in the intervention group was 3 lower |
| Dyspnoea on VAS: subgroup with cardiopulmonary disease Scale from: 0 to 100. | 16 (1 study) 15 minutes | VERY LOW[a,b] due to risk of bias, imprecision | - | The mean dyspnoea on VAS in the control groups was 51 | The mean dyspnoea on VAS in the intervention group was 2 lower |
| Dyspnoea on VAS: subgroup without cardiopulmonary disease | 22 (1 study) | VERY LOW[a,b] due to risk of | - | The mean dyspnoea on VAS in the control groups was 47 | The mean dyspnoea on VAS in the intervention group was 6 lower |

| | | | | | |
|---|---|---|---|---|---|
| Scale from: 0 to 100. | 15 minutes | bias, imprecision | | | |
| Adverse events (relating to study procedure) | 38<br>(1 study)<br>30 minutes | LOW[a,b]<br>due to risk of bias, indirectness | Not estimable | No events recorded in either group | No events recorded in either group |

*(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 52: Clinical evidence summary: Oxygen versus morphine or hydromorphone**

| Outcomes | No. of participants (studies) Follow-up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with morphine or hydromorphone (NRS) | Risk difference with oxygen (95% CI) |
| Dyspnoea at rest<br>Measured on 0 (absent) – 10 (worst possible) scale | 46<br>(1 study)<br>120 minutes after opioid application | VERY LOW[a,b]<br>due to risk of bias, indirectness | - | The mean dyspnoea at rest in the control group was 1.5 | The mean dyspnoea at rest in the intervention group was 4.31 higher (3.63 to 4.98 higher) |

*(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 53: Clinical evidence summary: Morphine or hydromorphone versus room air**

| Outcomes | No. of participants (studies) Follow-up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with room air (NRS) | Risk difference with morphine or hydromorphone (95% CI) |
| Dyspnoea at rest<br>Measured on 0 (absent) – 10 (worst possible) scale | 46<br>(1 study)<br>120 minutes after opioid application | VERY LOW[a,b]<br>due to risk of bias, indirectness | | The mean dyspnoea at rest in the control group was 5.9 | The mean dyspnoea at rest in the intervention group was 4.39 lower (5 to 3.78 lower) |

*(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 54: Clinical evidence summary: Oxygen versus room air**

| Outcomes | No. of participants (studies) Follow-up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with room air (NRS) | Risk difference with oxygen (95% CI) |
| Dyspnoea at rest<br>Measured on 0 (absent) – 10 (worst possible) scale | 46<br>(1 study)<br>60 minutes | VERY LOW[a,b]<br>due to risk of bias, indirectness | | The mean dyspnoea at rest in the control group was 5.9 | The mean dyspnoea at rest in the intervention group was 0.13 higher (0.96 lower to 0.70 higher) |

*(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.*

## 9.7 Economic evidence

### Published literature

No relevant economic evaluations were identified. See also the economic article selection flow chart in Appendix F.

### Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix N to aid consideration of cost effectiveness.

## 9.8 Evidence statements

### Clinical

#### Morphine versus midazolam versus morphine plus midazolam

There was moderate and low quality evidence from 1 RCT (n=101) suggesting that the combination of morphine plus midazolam was clinically beneficial compared with either of the interventions alone for achieving relief from dyspnoea at 24 and 48 hours after initiation of the therapy regimen in people in a cancer institute (life expectancy of less than 1 week). The effect was less pronounced at the later time point when a larger proportion of the randomised people had died. However, low quality evidence suggested that there was no clinical difference between morphine plus midazolam and morphine alone for dyspnoea intensity measured on the modified Borg scale at 24 or 48 hours, although, the median score was higher in the midazolam group compared with the other groups at 24 hours. In the same study, low and very low quality evidence suggested a clinical benefit of morphine plus midazolam or midazolam alone compared with morphine alone for reducing clinically relevant (grade 2 or above) nausea or vomiting and somnolence.

No evidence was found for the quality of life or length of survival outcomes.

#### Oxygen versus air

There was very low quality evidence from 1 crossover RCT (n=38) in people with advanced cancer treated in 2 hospices (mean survival 19 days) suggesting that there was no clinical difference between oxygen and air given via a nasal cannula on dyspnoea intensity measured at the end of a 15-minute administration on the modified Borg scale. No study-related adverse events were reported in either group.

No evidence was found for the quality of life, sedation or length of survival outcomes.

#### Oxygen versus morphine or hydromorphone versus room air

There was very low quality evidence from 1 prospective, non-randomised study in palliative care unit in people with terminal incurable disease sequentially given different interventions (n=46) suggesting that the opioid (administered last in the sequence) was clinically beneficial compared with nasal oxygen insufflation or no intervention (baseline assessment breathing room air) for reducing dyspnoea at rest measured on a 0-100 scale. However, very low quality evidence from the same study suggested that there was no clinical difference between nasal oxygen insufflation and room air for the same outcome.

No evidence was found for the quality of life, sedation, adverse events or length of survival outcomes.

**Economic**

No relevant economic evaluations were identified.

## 9.9 Recommendations and link to evidence

| | |
|---|---|
| **Recommendations** | **38. Identify and treat reversible causes of breathlessness in the dying person, for example pulmonary oedema or pleural effusion.**<br><br>**39. Consider non-pharmacological management of breathlessness in a person in the last days of life. Do not routinely start oxygen to manage breathlessness. Only offer oxygen therapy to people known or clinically suspected to have symptomatic hypoxaemia.**<br><br>**40. Consider managing breathlessness with:**<br>• **an opioid[d] or**<br>• **a benzodiazepine[d] or**<br>• **a combination of an opioid[d] and benzodiazepine[d].** |
| Relative values of different outcomes | The Committee considered the following critical outcomes for breathlessness for decision making: symptom control, sedation and quality of life. The Committee considered these to have the most influence on their decision making, but also prioritised adverse events and length of survival as important outcomes contributing to recommendation development as they may provide evidence of harm. |
| Trade-off between clinical benefits and harms | The Committee commented on the distressing nature of breathlessness in the last days of life for both the person and those important to them. They emphasised in their discussion the importance of managing breathlessness, including the use of pharmacological agents.<br>The Committee discussed the potential harm of over-treating people in the last days of life in terms of the risk for adverse effects and hastening death, or the perception of hastening death. The Committee commented on the potential harms of using opioids to manage breathlessness if not prescribed appropriately. Harms discussed included over suppression of respiratory drive which could hasten death. They also commented on the use of oxygen therapy in those with COPD in the last days of life which, if not treated properly, can lead to loss of respiratory drive in these people. The Committee agreed that potential benefits and harms should be clearly communicated to the dying person and those important to them, and that patient preference should be respected. Potential harms should be minimised by considering the choice of management in light of medication already being administered, and other comorbidities. The Committee commented on the importance of monitoring for unwanted sedation and other side-effects that could impair the quality of the dying person's last days. Also, monitoring would minimise the risks of clinical harm in using these medications. |
| Trade-of between net health benefits and resource use | No economic evaluations were identified.<br>Cost of oxygen in England was not available from national published sources, but this is likely to be the more costly intervention among those available for managing |

[d] At the time of publication (December 2015), this medication did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

| | |
|---|---|
| | breathlessness. The clinical evidence showed that there was unlikely to be any clinical benefit of administering oxygen for breathlessness as opposed to room air, therefore the Committee felt that initiating oxygen for breathlessness would increase cost without improving health outcomes. The Committee noted that this was specific for the management of breathlessness and that this summary was not applicable to the cost-effectiveness of oxygen in general.<br>The clinical evidence also compared the effectiveness of opioids against benzodiazepines. This evidence showed that morphine was favoured over midazolam but a combination of both was more effective than either alone. The Committee noted the limitations of this data and, given the very small cost difference between the 3 alternatives, there was not a strong argument to be made for 1 treatment to be favoured from a cost-effectiveness point of view. |
| Quality of evidence | Evidence was not meta-analysed as it was inappropriate to pool the data given the difference in study design and outcomes reported.<br>No evidence was found for the quality of life or time-to-death outcomes. The most commonly reported outcome was control of breathlessness, while nausea and vomiting were reported as adverse effects.<br>For the management of breathlessness in the last days of life, there was evidence from 1 parallel RCT, 1 crossover RCT and 1 non-randomised comparative study. Low to moderate quality evidence for dyspnoea relief suggested that morphine may be clinically beneficial compared with midazolam and that the combination of both was clinically beneficial compared with either intervention alone. However, when assessing dyspnoea intensity using the modified Borg scale, there was no clinical difference. No clinical difference was apparent for dyspnoea intensity and no adverse events were recorded between air and oxygen delivered nasally to people with advanced cancer. One very low quality study compared nasally applied oxygen, oral opioids and baseline conditions breathing room air in people with a terminal incurable disease. It reported a large clinical benefit of the opioid compared with either oxygen or room air and no clinical difference between oxygen and room air for dyspnoea intensity at rest.<br>The Committee commented on several methodological flaws in the studies included. The use of indirect outcome measures was highlighted, including a scale for somnolence as an indirect measure for sedation which was criticised by the Committee. They also commented on the study design where concomitant treatment was not the same in both groups, and in the crossover studies there was an insufficient washout period between interventions. The Committee noted that the RCT comparing morphine, midazolam and their combination did not report on or take account of the different pharmacokinetics of the 2 drugs which may have had an impact on the outcomes. |
| Other considerations | The Committee discussed the importance of non-pharmacological methods, including facial fans and open windows, for controlling breathlessness which, although not formally reviewed, have in the Committee's experience been of benefit to people in the last days of life. In particular, they noted that the physiological effect of blowing cool air over the snout area of the face can reduce the sensation of breathlessness. This was felt by the Committee to explain the benefit seen with both air and oxygen to relieve dyspnoea.<br>The evidence review was unable to show whether oxygen was beneficial or not for the management of breathlessness in the last few days of life. However, the consensus of the Committee was that oxygen may be beneficial to people who are symptomatic with known or suspected hypoxia based on their clinical experience in other palliative care settings, and therefore should be offered in this situation. They were keen to emphasise that oxygen should not be routinely initiated in the last few days of life to manage breathlessness (as there is no evidence it is beneficial and it has potentially harmful effects) and therefore made a recommendation to this effect.<br>The Committee discussed that breathlessness is not always related to oxygen |

| | |
|---|---|
| | saturation and can, for example, be related to anxiety.<br>The Committee all agreed that oxygen should not be used purely on the basis of low oxygen saturations in the absence of symptoms or any beneficial effect. The Committee noted that oxygen is considered a drug and that, as for any medications used in the last few days of life, prescribing decisions should be made on a case by case basis, weighing up the risks and benefits for any given individual. Oxygen should be used alongside other interventions to help breathlessness in the last few days of life, including opioids and benzodiazepines and non-pharmacological management. The Committee discussed that measuring hypoxia (SaO2 ≤88-90%), was setting dependant and may not always be appropriate in a community or care home setting, but, where possible, noted that it can impact on decisions regarding management of breathlessness (for example, in ICU). The Committee noted that a person who is not hypoxic at rest may still desaturate on walking and may need ambulatory oxygen. Therefore, they noted that there is a need for trained part B HOOF (Home Oxygen Order Form) prescribers to be available 7 days a week to facilitate home oxygen where necessary. The Committee recognised that this element of service provision was outside the scope of this guidance and therefore did not make a recommendation. The Committee did note, however, the importance of staff working in the community being aware of the correct contact person to ensure that any changes in oxygen requirements are met efficiently.<br>The Committee believed that it was important to recognise that some people may already be on oxygen and a decision to continue or discontinue oxygen should be made on an individual basis balancing up the potential benefits (reduced breathlessness) and harms (dry nasal passages or friction sores).<br>The Committee noted that Heliox may be used for laryngeal stridor but chose not to make a specific recommendation as no evidence was identified supporting this.<br>The Committee discussed that if the dying person is not hypoxic but is breathless, then a trial of an opioid, benzopdiazepine or a combination of both may be appropriate. This reflected their clinical experience and the evidence identified. They noted the importance of choosing the correct medication for the patient and identified that this should be individualised, taking into account other symptoms and medications the person is currently taking. They commented that people whose breathlessness may be a result of anxiety or psychological distress may benefit from a benzodiazepine. Where the breathlessness is not associated with anxiety they agreed a trial of opioid would be more appropriate.<br>The Committee were aware that opioids and benzodiazepines were off license for the management of breathlessness in the last days of life, but in their clinical experience they are often used in this setting with effect. Further general pharmacological recommendations for prescribing in the last days of life can be found in section 9.3.4. |

# Managing nausea and vomiting

Nausea and vomiting can be debilitating and distressing for people in the last days of life and for those important to them. Aetiology may be multifactorial and it is essential to determine the underlying cause as this will guide choice of therapy. While there are non-pharmacological management options (for example, nasogastric tube or venting gastrostomy for vomiting in bowel obstruction), this chapter focuses on pharmacological treatment. Criticism of the Liverpool Care Pathway included concerns over injudicious use of medication particularly with regards to over-sedation. Episodes of nausea and vomiting may occur together or in isolation but as they are largely treated using the same pharmacological agents we have considered them together.

There are some important clinical considerations in managing nausea and vomiting at the end of life. In some cases, these symptoms may abate as the person approaches death owing to their decreased consciousness and consequent reduction in fluid and food intake. In others, sedation, which is a common side effect of some anti-emetics, may now confer benefit. The mode of administration is also important because oral anti-emetics may not be appropriate in a dying person. A change in route may therefore be indicated even in people previously well managed on regular oral anti-emetics to ensure continuity of symptom control.

There is no evidence-based guidance for best practice in the pharmacological management of nausea and vomiting in the last few days of life and current practice has been extrapolated from knowledge of treating these symptoms at other stages of illness in different diseases. There is concern that choice of anti-emetic is often based on convenience and familiarity rather than after a considered assessment of the cause of the nausea and vomiting and the patient's circumstances. An individualized approach to the management of nausea and vomiting is an essential part of caring for the dying adult.

There are certain causes of nausea and vomiting in the last few days of life that may require specific treatment, for example, brain metastases or bowel obstruction. Detailed management of these situations is outside the scope of this guideline.

## 9.10 Clinical evidence

The clinical question asked can be found in section 9.1. Systematic reviews, randomised controlled trials or comparative observational studies were searched for that addressed pharmacological management of nausea and vomiting in the last days of a person's life.

Three RCT studies were included in the review;[67,72,83] these are summarised in Table 55 below. Evidence from these studies is summarised in the GRADE clinical evidence profile below (Table 56).

The 3 RCTs[67,72,83] compared octreotide with hyoscine butylbromide for controlling nausea and vomiting in people with bowel obstruction secondary to terminal abdominal malignancy. The people included were all diagnosed as not suitable for surgical interventions and were not receiving active treatment for their primary diagnosis. The octreotide and hyoscine butylbromide were delivered using a continuous subcutaneous infusion in all studies, but at varying dose both within and between the studies. In all of the studies other adjuvant medications were given, including drugs with potential antiemetic effects, preventing the combining of data into a meta-analysis as they were not like-for-like comparisons. Two studies were included in this review despite these limitations, as they listed survival as an outcome and the majority of the participants died within 14 days from the start of the intervention.[67,83] The third RCT had a longer survival time, ranging from 7-61 days, but it was included after discussion with the Committee chair as the final time point was 1 day prior to death, which was decided relevant information for this review.[71,72]

There were no other comparisons found for the possible combinations listed in the protocol.

See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, forest plots in Appendix K, GRADE tables in Appendix J and excluded studies list in Appendix L.

### 9.10.1 Summary of included studies

**Table 55: Summary of studies included in the review**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Mystakidou 2002[71,72] | **Intervention:** Octreotide<br><br>**Comparison:** Hyoscine butylbromide<br><br>Both groups given chlorpromazine in addition.<br>Subcutaneous route used in both groups. | n=68<br>People with advanced cancer, and bowel obstruction, not suitable for surgical interventions. Survival time from start of study ranged from 7 days to 61 days.<br><br>If no vomiting control achieved at day 7 they were dropped out of study.<br><br>Greece | Nausea and vomiting scales used.<br><br>Survival time listed as an outcome but not presented individually between the groups. | Intervention started on average 60 days before death, so indirect from our protocol design, but the final outcome measurement was 1 day before death so included in review.<br><br>People were removed from the study at 72 hours if there was no nausea control and no intention to treat analysis was performed. A larger number in the hyoscine butylbromide arm dropped out (35%) compared within the octreotide arm (9%).Both groups had a marked initial improvement. |
| Ripamonti 2000[83] | Intervention: Octreotide<br><br>**Comparison:** Hyoscine butylbromide<br><br>Subcutaneous route used in both groups | n=17<br>People with advanced cancer with bowel obstruction not suitable for surgical interventions. Survival time from start of study ranged from 4 days to 17 days.<br><br>Setting: both hospitalised and home care people in each arm of the trial<br><br>Italy | Nausea, dry mouth, and drowsiness taken at day 3.<br><br>Survival time listed in methods but not presented individually between the groups. | Small study<br><br>Factors including clinically assisted hydration were not controlled between settings and people treated in hospital received more clinically assisted hydration then those at home in both arms of the study. |
| Mercadante 2000[66,67] | **Intervention:** Octreotide | n=15<br>People with | Episodes of vomiting, numerical | Poorly reported paper, with limited |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | **Comparison:**<br>Hyoscine butylbromide<br><br>Subcutaneous route used in both groups.<br><br>Both groups: Clinically assisted hydration given depending on setting/need. Both groups had morphine and haloperidol also given alongside intervention. | advanced cancer in both a hospital and home care setting.<br><br>Italy | rating scale for drowsiness, nausea and dry mouth.<br><br>Survival time listed in methods but not presented individually between the groups. | information on recruitment and inclusion and exclusion criteria.<br><br>Haloperidol given to both groups in addition to intervention. Multivariate analysis used to control for some variables introduced by design including volume of hydration given. |

The evidence was not combined in meta-analysis due to the differences in study designs, particularly the wide difference in concomitant treatments which are shown in Table 55.

**Table 56: Clinical evidence profile: Octreotide versus hyoscine butylbromide**

| Outcomes | No. of participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with octreotide vs. hyoscine butylbromide 72 hours (95% CI) |
| Nausea - day 3<br>Measured on a 4 point numeric rating scale (NRS) for nausea. | 15<br>(1 study)<br>3 days | VERY LOW[a,d]<br>due to risk of bias, imprecision | | 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) |
| Nausea - day 3<br>Measured on a 4 point NRS scale for nausea. | 7<br>(1 study)<br>3 days | VERY LOW[a ,f]<br>due to risk of bias, imprecision | | No clinical difference nausea ratings in those people cared for in hospital reported narratively in the study (no effect size given). [e] | |
| | 10<br>(1 study)<br>3 days | VERY LOW[a ,f]<br>due to risk of bias, imprecision | | Clinical benefit of octreotide in people cared for at home reported narratively in the study (p=0.05, no effect size given) [e] | |
| Vomiting - day 3<br>Number of episodes in 24 hours | 15<br>(1 study)<br>3 days | VERY LOW[a,d,]<br>due to risk of bias, imprecision | | The mean vomiting in the control groups was 1.6 | The mean vomiting in the intervention groups was 1.40 lower (2.08 to 0.72 lower) |
| Sedation - day 3<br>Measured on a 4 point NRS scale for drowsiness. | 15<br>(1 study)<br>3 days | VERY LOW[a,b,d]<br>due to risk of bias, indirectness, imprecision | | The mean sedation-drowsiness in the control groups was 1.6 | The mean sedation - drowsiness in the intervention groups was 0.4 higher (0.05 lower to 0.85 higher) |
| Sedation - day 3<br>Measured on a 4 point NRS scale for drowsiness. | 17<br>(1 study)<br>3 days | VERY LOW[a,b,f]<br>due to risk of bias, indirectness, imprecision | | No clinical difference reported narratively in the study (no effect size given)[e] | |
| Vomiting - 1 day before death.<br>Number of episodes in 24 hours. | 53<br>(1 study)<br>1-61 days | VERY LOW[a,c,d]<br>due to risk of bias, indirectness, imprecision | | 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 - 1 day before death.<br>Measured on 3 point NRS and multiplied by the number of hours | 53<br>(1 study)<br>0-61 days | VERY LOW[a,c,d]<br>due to risk of bias, indirectness, | | 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) |

| Outcomes | No. of participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with octreotide vs. hyoscine butylbromide 72 hours (95% CI) |
| on that day it occurred. | | imprecision | | | |
| Quality of life | 0<br>(0 studies) | No evidence found. | | | |
| Adverse event - dry mouth.<br>Measured on a 4 point NRS scale for dry mouth. | 15<br>(1 study)<br>3 days | VERY LOW[a,d]<br>due to risk of bias, imprecision | | The mean dry secretions in the control groups was<br>1.6 | The mean vomiting in the intervention groups was 0.1 higher<br>(0.35 lower to 0.55 higher) |
| Adverse event - dry mouth.<br>Measured on a 4 point NRS scale for dry mouth. | 17<br>(1 study)<br>3 days | VERY LOW[a,f]<br>due to risk of bias, imprecision | | No clinical difference reported narratively in the study (no effect size given)[e] | |

*(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) The majority of the evidence included an indirect outcome (downgrade by 1 increment) or a very indirect outcome (downgrade by 2 increments).*
*(c) The majority of the evidence included an indirect outcome (downgrade by 1 increment) or a very indirect outcome (downgrade by 2 increments).*
*(d) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.*
*(e) It was not possible to extract the anticipated absolute effects from the study with the data reported.*
*(f) Downgraded by 1 increment for impression as data were not presented in sufficient detail.*

## 9.11 Economic evidence

### Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix D.

### Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix N to aid consideration of cost effectiveness.

## 9.12 Evidence statements

### Clinical

The review found very low quality evidence from 3 RCTs comparing hyoscine butylbromide and octreotide given subcutaneously in people with nausea and vomiting as a result of bowel obstruction secondary to advanced terminal cancer where surgery was not recommended. One small RCT (n=15) undertaken in hospital and home care settings showed increased clinical benefit of using octreotide at day 3 in reducing both nausea and frequency of vomiting at day 3 of the intervention. The same study reported no clinical difference in sedation or dry mouth outcomes. A further small RCT (n=17) undertaken in the same settings reported a clinical benefit of octreotide in managing nausea at day 3 in those people cared for at home, but no clinical difference in managing nausea in those cared for in hospital. The study also found no clinical difference in adverse symptoms of dry mouth and drowsiness between octreotide and hyoscine butylbromide.

A third RCT (n=68) reported on the same drug group comparison and population but only in the home care setting. The study was longer in nature with a range of 1-61 days, but the final time point of the day before death was included in the review as indirect evidence. The study reported no clinical difference between octreotide or hyoscine butylbromide in the effect on nausea or vomiting outcomes the day prior to death.

No clinical evidence was found for the critical outcome of quality of life.

### Economic

No relevant economic evaluations were identified.

## 9.13 Recommendations and link to evidence

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|---|---|
| **Recommendations** | **41. Assess for likely causes of nausea or vomiting in the dying person. These may include:**<br>• **certain medicines that can cause or contribute to nausea and vomiting**<br>• **recent chemotherapy or radiotherapy**<br>• **psychological causes**<br>• **biochemical causes, for example hypercalcaemia** |

| | |
|---|---|
| | • **raised intracranial pressure**<br>• **gastrointestinal motility disorder**<br>• **ileus or bowel obstruction.**<br><br>**42. Discuss the options for treating nausea and vomiting with the dying person and those important to them.**<br><br>**43. Consider non-pharmacological methods for treating nausea and vomiting in a person in the last days of life.**<br><br>**44. When choosing medicines to manage nausea or vomiting in a person in the last days of life, take into account:**<br>• **the likely cause and if it is reversible**<br>• **the side effects, including sedative effects, of the medicine**<br>• **other symptoms the person has**<br>• **the desired balancing of effects when managing other symptoms**<br>• **compatibility and drug interactions with other medicines the person is taking.**<br><br>**45. For people in the last days of life with obstructive bowel disorders who have nausea or vomiting, consider:**<br>• **hyoscine butylbromide[e] as the first-line pharmacological treatment**<br>• **octreotide[e] if the symptoms do not improve within 24 hours of starting treatment with hyoscine butylbromide[e].** |
| Relative values of different outcomes | The Committee considered the following critical outcomes for nausea and vomiting for decision making: nausea control, number of vomiting episodes, sedation and quality of life. The Committee considered these to have the most influence on their decision making, but also prioritised adverse events and length of survival as important outcomes contributing to recommendation development as they may provide evidence of harm. |
| Trade-off between clinical benefits and harms | The Committee noted that drugs used to manage these symptoms were generally well tolerated and effective from their experience in their use at other times outside of the last days of life. They noted that there are potential adverse side effects such as unwanted sedation with antipsychotic agents. However, consideration was also needed as to how prescribed medications interact with other concomitant medications being used to manage other symptoms in the last days of life. Combining certain medications could have a cumulative sedative effect potentially causing harm. No evidence was identified for adverse effects of treatment linked to extrapyramidal side effects, but the Committee discussed dystonia and that this is may occur, particularly in those that are neuroleptically naïve. |
| Trade-off between net health benefits and resource use | The unit costs of a variety of nausea medications were presented to the Committee. As the clinical evidence focused on the use of octreotide versus hyoscine butylbromide, the Committee focused on the comparative costs of these 2 treatments. The average daily cost of octreotide ranged from £27.09 - £54.18 assuming a daily dose between 250 mg – 1000 mg/ml. The average daily cost of hyoscine butylbromide ranged from £0.88 - £2.64 assuming a daily dose between 60 – 180 mg/ml. Therefore octreotide was the more expensive option. |

[e] At the time of publication (December 2015), this medication did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

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| | The clinical evidence showed that octreotide was more clinically effective than hyoscine butylbromide in 1 study but there was no clinical difference in another. The Committee noted that, of the 3 included RCTs, 2 were very small and therefore the results could be due to statistical bias and the other study suffered from a high attrition rate. As there was no clear evidence that octreotide was the more clinically effective option, yet it was considerably more expensive, the Committee decided to recommend its use only for when hyoscine butylbromide produced ineffective results. |
| Quality of evidence | No evidence was found for quality of life. Sedation, another critical outcome, was reported in 2 of the included studies but this was reported as a surrogate measure of drowsiness and fatigue. Dry mouth was reported as an adverse event.<br>There was evidence found from 3 RCTs, all concerning 1 strata specified in the protocol (bowel obstruction) in people with abdominal malignancy only. All outcomes extracted were rated as very low quality. They all compared hyoscine butylbromide with octreotide, but, owing to the different concomitant treatments and differing doses, combining data were not appropriate. One included study had an indirect population that focused on people not in the last days of life although followed them up until 1 day prior to death and so were included. There was concern from the Committee that 2 of the RCTs had very small study sizes, and the larger RCT had a high attrition rate.<br>The Committee noted that, even though the drugs had a considerable rate of improvement in the control of nausea and vomiting, it was inconsistent and therefore not directly supporting 1 recommendation over another. One study reported an improvement in nausea and vomiting in those treated with Octreotide, while another reported no clinical difference between the drugs. Moreover, there were no clinical differences in adverse effects, including sedation and dry mouth, between octreotide and hyoscine butylbromide found in 2 studies. |
| Other considerations | The Committee noted the paucity of evidence for the management of nausea and vomiting specific to the last days of life and drew on their experiences of managing these symptoms more broadly in terminally ill people when drafting their recommendations. The Committee commented on the focus of the evidence around the management of nausea and vomiting in bowel obstruction in the last days of life. They highlighted that nausea and vomiting secondary to bowel obstruction affected a minority of people in practice, but that it should be considered when assessing for likely causes.<br>The Committee commented that there was currently wide national variability in the management of nausea and vomiting in the last days of life. The Committee highlighted that a recent national audit of care of the dying adults in hospitals[85] found that cyclizine was the most commonly prescribed antiemetic given. In the Committee's consensus opinion, this drug had lower efficacy compared with others, was often poorly tolerated by people at the end of life, is incompatible with many other drugs in a syringe pump and is frequently associated with site reactions if administered subcutaneously. However, no evidence was identified for cyclizine and no recommendations were made.<br>The SPC (summary of product characteristics) from the manufacturer of cyclizine gives the following special warning and precaution for use: "Cyclizine should be used with caution in patients with severe heart failure or acute myocardial infarction. In such patients, cyclizine may cause a fall in cardiac output associated with increases in heart rate, mean arterial pressure and pulmonary wedge pressure." When prescribing anti-emetics for a dying person with severe heart failure, it may be prudent to avoid cyclizine to avoid precipitating symptoms (for example, breathlessness) that may occur due to fall in cardiac output and tachycardia. Despite the lack of evidence, in this situation it would seem sensible to use an anti-emetic with an alternative mechanism of action. Therefore, the Committee felt that clinicians should make a decision on the use of anti-emetics on a case by case basis, taking into consideration the cause of nausea and vomiting and weighing up the risks |

and benefits of the medication.

As in other chapters regarding the pharmacological management of specific symptoms, the Committee noted that non-pharmacological management options were available for the management of nausea and vomiting and made a consensus recommendation in this regard. The Committee commented that, in their practice, non-pharmacological management of such symptoms, such as the use of nasogastric tubes, could be successful in treating some people's nausea and vomiting in the last days of life if the primary cause was bowel obstruction. However, the Committee noted that this may be intolerable or very uncomfortable at the end of life. They noted that this was primarily applicable in a hospital or hospice setting.

The Committee discussed the general importance of assessing the dying person to determine the cause of nausea and vomiting as they were aware from their clinical practice that different medications have different efficacies in different causes. When assessing the person for these different causes, they felt it was important to examine the person and take a detailed history, paying attention to the drug history of the person, and stopping, where possible, medications that can cause nausea and vomiting as a side effect. Potential causes of nausea and vomiting that are relevant to the last days of life included iatrogenic causes, such as recent chemotherapy, radiotherapy, or general anaesthesia, concomitant opioid prescribing, psychological and biochemical causes, raised intracranial pressures and motility disorders, including constipation.

The Committee also noted the fact that even if a person is previously on antiemetics to control symptoms of nausea and vomiting, as they enter the dying phase their symptoms may change due to disease progression, reduced oral intake and they may require up or down titration of medications or switching to alternative agents or routes.

They discussed the importance of treating underlying problems that are reversible as a priority over treatment with antiemetic therapy. For example, they highlighted the importance of good practice around correct titration of opioids in preventing nausea and vomiting as a side effect.

The Committee discussed the sedating aspects of certain antiemetics and the importance of discussing these carefully with the dying person and those important to them, given the findings from the recent Neuberger review.[30] Through this discussion an informed and shared decision about which antiemetic to be started on can be reached. The Committee acknowledged that some people may benefit and prefer a drug with a sedative side effect. They also highlighted the importance of making the dying person and those important to them aware that the level of consciousness in a dying person can naturally alter in the last days of life independent of medication.

Other factors that the Committee felt important to be considered in choosing an antiemetic included assessing which other medications the dying person is on. This was for 2 reasons; if a single agent with a dual effect on other symptoms being experienced could be effective then this would be preferential. It was also important to consider how the drug would be administered. If it was to be delivered via a syringe pump then the antiemetic would have to be compatible with the other medications prescribed. As noted earlier in this discussion, cyclizine presents particular challenges in this regard.

The Committee reviewed the available evidence presented regarding the comparison of using octreotide versus hyoscine butylbromide in the management of people in the last days of life with bowel obstruction. In their clinical experience, the Committee found that both of these drugs work well in treating nausea and vomiting in this setting. Although not reflected in the evidence found, from their clinical experience, some Committee members reported that octreotide tends to be better tolerated then hyoscine butylbromide, giving less side-effects. They discussed the increased cost of using octreotide given that there is mixed evidence to show its benefit over hyoscine butylbromide.

The Committee also discussed that hyoscine butylbromide can be used for other

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| | indications that the patient may be experiencing such as terminal respiratory secretions. Hyoscine butylbromide is also more compatible with other drugs in syringe pumps and is available more readily from community pharmacies. They also noted that octreotide requires refrigeration which may be challenging in some settings. Because of these factors, it was decided that hyoscine butylbromide should be prescribed first line, and if symptoms do not improve within 24 hours then prescribe octreotide. The Committee felt that octreotide was generally only initiated by specialists and therefore specialist palliative care advice should be sought in complex cases of bowel obstruction. |

# Managing anxiety

## 9.14 Clinical evidence

The clinical question asked can be found in section 9.1. No evidence was found regarding the management of anxiety which is in line with a recent Cochrane systematic review[17] for a broader palliative care population which also found no or limited evidence for treatment of this symptom. Hand-searching references from this review, none of the retrieved articles matched our population. See also the study selection flow chart in Appendix E and excluded studies list in Appendix L.

## 9.15 Economic evidence

### Published literature

No relevant economic evaluations were identified. See also the economic article selection flow chart in Appendix F.

### Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix N to aid consideration of cost effectiveness.

## 9.16 Evidence statements

### Clinical

No evidence was identified.

### Economic

No relevant economic evaluations were identified.

## 9.17 Recommendations and link to evidence

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| **Recommendations** | **46. Explore the possible causes of anxiety or delirium, with or without agitation, with the dying person and those important to them. Be aware that agitation in isolation is sometimes associated with other unrelieved symptoms or bodily needs for example, unrelieved pain or a full bladder or rectum.**<br><br>**47. Consider non-pharmacological management of agitation, anxiety and delirium in a person in the last days of life.**<br><br>**48. Treat any reversible causes of agitation, anxiety or delirium, for example, psychological causes or certain metabolic disorders (for example renal failure or hyponatraemia).**<br><br>**49. Consider a trial of a benzodiazepine to manage anxiety or agitation.**<br><br>**50. Consider a trial of an antipsychotic medicine to manage delirium or** |

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| | **agitation.**<br><br>**51. Seek specialist advice if the diagnosis of agitation or delirium is uncertain, if the agitation or delirium does not respond to antipsychotic treatment or if treatment causes unwanted sedation.** |
| Relative values of different outcomes | The Committee considered the following critical outcomes for anxiety, with or without agitation, for decision making: symptom control, sedation and quality of life. The Committee considered these to have the most influence on their decision making, but also prioritised adverse events and length of survival as important outcomes contributing to recommendation development as they may provide evidence of harm. |
| Trade-off between clinical benefits and harms | The Committee commented on the distressing nature of these symptoms in the last days of life and the importance of managing these, including the use of pharmacological agents. The Committee discussed the overlap of these symptoms and how early management of both anxiety and delirium can, in some cases, prevent agitation from occurring.<br>The Committee discussed the potential harm of over-treating people in the last days of life in terms of the risk for adverse effects and hastening death, or the perception of hastening death. The Committee commented on the use of antipsychotics for managing these symptoms as these can cause extra pyramidal side effects such as dystonia, particularly in some patients groups, such as those with Parkinson's. The Committee agreed that potential benefits and harm should be clearly communicated to the dying person and those important to them, and that patient-preference should be respected. Potential harms should be minimised by considering the choice of management in light of medication already being administered. The Committee commented on the importance of monitoring for unwanted sedation and other side-effects that could impair quality of a person's last days to minimise the risks of clinical harm in using these medications. |
| Trade-off between net health benefits and resource use | No economic evaluations were identified.<br>As no clinical evidence was identified no formal analysis could be conducted that assessed the cost-effectiveness of different pharmacological agents used to treat anxiety, agitation or delirium. Unit costs of the relevant pharmacological agents were presented to the Committee for them to make economic considerations. The Committee noted that, although cost differences were small between different agents, without any clinical evidence 1 treatment could not be said to be any more effective, and therefore cost-effective, over another. Due to side-effects of treatments and the possibility to treat symptoms without the need of pharmacological intervention, the Committee felt that the involvement of a specialist, where necessary, was important in ensuring the best health outcomes and avoiding unnecessary interventions. |
| Quality of evidence | No evidence was found for the management of anxiety, agitation or delirium in the last days of life, which is in line with recent Cochrane systematic reviews for broader palliative care populations that also found no or limited evidence for treatment of these symptoms. |
| Other considerations | The Committee noted that agitation, anxiety and delirium can have multiple aetiologies and highlighted the importance of assessing for any potential causes as a first step in managing these symptoms. Reversible causes (such as pain, full bladder, fever and fear or psychological causes) should always be identified and any inappropriate monitoring or drugs that could be contributing to the symptoms should be discontinued.<br>The Committee discussed the importance of providing non-pharmacological support in addition to any medications required for the management of anxiety, agitation and delirium. Both pharmacological and non-pharmacological interventions are considered to be important and an appropriate balance between the 2 should be sought for each dying person. These symptoms should be handled holistically |

| | |
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| | (including, for example, an assessment of any spiritual, psychological and social factors that may be contributing to symptoms or may influence their management), dependent on the dying person and those important to them.<br>The current standard practice for managing these symptoms was noted to be a holistic approach, including administration of benzodiazepines and antipsychotic agents in titration with continued re-assessment. However, the input of a specialist should be sought if symptoms are unclear or do not resolve and the Committee highlighted that this should be done in a timely fashion as these symptoms, in their experience, can escalate quickly.<br>The Committee heard from a co-opted psycho-geriatrician and considered his thoughts when developing these recommendations. The psycho-geriatrician commented that dementia sufferers may be predisposed to delirium due to their pre-existing condition which should be taken into account. The Committee also noted that antipsychotics should be avoided in people with Parkinson's disease and Lewy body dementia due to the risk of extrapyramidal side effects and that antipsychotic agents may lower the seizure threshold in at risk people, for example, those with cerebral metastases.<br>The Committee felt it was important to note that agitation is not always associated with delirium or anxiety and vice versa although they are often managed with the same medications. Agitation can be either hyperactive or hypoactive and these 2 conditions will need to be managed separately (see NICE guidance on delirium[73] for more details).<br>In a dying person who lacks capacity, discuss with those important to them (and legal proxies or advocates) the role of sedatives to relieve distress. Make any decisions within the best interests of the dying person balancing up the risks and harms. The Committee noted the GMC guidance[37] on treatment at end of life, section 15 decision making tool for people who lack capacity and following principles of MCA.<br>In the clinical experience of the Committee, agitated delirium is often managed with an antipsychotic agent with or without the addition of a benzodiazepine as an additional sedating and anxiolytic measure, whereas benzodiazepines alone may be sufficient for the pharmacological management of anxiety or agitation without delirium. The Committee noted that benzodiazepines may exacerbate agitation and delirium and it would be important to regularly assess and review their effect. |

# Managing delirium

## 9.18 Clinical evidence

No evidence was found regarding the management of delirium which is in line with a recent Cochrane systematic review[16] for a broader palliative care population which also found no or limited evidence for treatment of this symptom. Upon hand-searching references from this review, none of the retrieved articles matched our population. See also the study selection flow chart in Appendix E, and excluded studies list in Appendix L.

## 9.19 Economic evidence

**Published literature**

No relevant economic evaluations were identified. See also the economic article selection flow chart in Appendix F.

**Unit costs**

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix N to aid consideration of cost effectiveness.

## 9.20 Evidence statements

**Clinical**

No evidence was identified.

**Economic**

No relevant economic evaluations were identified.

## 9.21 Recommendations and link to evidence

See 'anxiety' LETR in section 9.17.

## 9.22 Research recommendation

2. **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.**

# Managing agitation

## 9.23 Clinical evidence

The clinical question asked can be found in section 9.1. No evidence was found regarding the management of agitation. See also the study selection flow chart in Appendix E and excluded studies list in Appendix L.

## 9.24 Economic evidence

**Published literature**

No relevant economic evaluations were identified. See also the economic article selection flow chart in Appendix F.

**Unit costs**

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix N to aid consideration of cost effectiveness.

## 9.25 Evidence statements

**Clinical**

No evidence was identified.

**Economic**

No relevant economic evaluations were identified.

## 9.26 Recommendations and link to evidence

See 'anxiety' LETR in section 9.17.

# Managing noisy respiratory secretions

## 9.27 Clinical evidence

The clinical question asked can be found in section 9.1. We searched for systematic reviews, randomised controlled trials or comparative observational studies that addressed pharmacological management of respiratory secretions in the last days of a person's life.

Two systematic reviews[64,103] were identified and assessed for suitability to be updated. The systematic review by Lokker and colleagues (2014) had a wider remit assessing all aspects ranging from prevalence to management, but also included non-comparative studies. It therefore did not fully fit our inclusion criteria and was cross-checked for references only. The other systematic review was a Cochrane review which was deemed suitable for updating. However, the protocol for our review includes non-randomised comparative studies, such as cohort studies, which were excluded in the Cochrane review. Altogether, 8 primary studies and the Cochrane systematic review were included. There were 4 randomised controlled studies [23,57,58,107] in the Cochrane systematic review which were assessed for further relevant outcomes. Three cohort studies[9,44,45] were excluded by the Cochrane authors, but are now included here. The study by Hughes et al., (2006)[44] is referring to an earlier study (Kass and Ellershaw, 2003)[53] which describes the control group in detail. One further RCT[41] was identified in the update search.

The main characteristics of these are summarised in Table 57. Evidence from these studies is summarised in the GRADE clinical evidence summary tables below. See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, forest plots in Appendix K, GRADE tables in Appendix J and excluded studies list in Appendix L.

For a number of possible comparisons no studies were identified. Please refer to Table 58 for a summary of comparisons that were or were not addressed by the evidence.

### 9.27.1 Summary of included studies

**Table 57: Main characteristics of studies included in the review**

| Study | Population | Intervention and comparison | Outcomes | Comments |
|---|---|---|---|---|
| Included Cochrane systematic review | | | | |
| Wee and Hillier, 2008[103] | People of all ages at the end of life, but only studies with adults were identified. | Any interventions including non-pharmacological or placebo. | Subjective or objective change in noise intensity (using validated scales).<br>Complete cessation of noise.<br>Number of different types of interventions.<br>Number of times intervention is repeated.<br>Measureable documented reduction in relatives' and | 4 RCTs included (see below)<br>Evidence reported as a narrative (not pooled) due to insufficient analysable data<br>Conclusion reached in the Cochrane review:<br>'….there is no evidence that any intervention, be it pharmacological or non-pharmacological was superior to placebo in the treatment of noisy breathing.' |

| Study | Population | Intervention and comparison | Outcomes | Comments |
|---|---|---|---|---|
| Included Cochrane systematic review | | | | |
| | | | patient's distress. | |
| Randomised controlled trials included in the Cochrane systematic review | | | | |
| Clark et al., 2008[23] | All participants had advanced cancer (n=10: n=6 gastrointestinal, n=2 haematological, n=1 breast, n=1 prostate), median age 79 (63-88). All participants remained unconscious for the duration of the study.<br><br>Australia | Hyoscine hydrobromide 400 micrograms subcutaneously.<br>Octreotide 200 micrograms subcutaneously. | Subjective rating of noisy breathing on a 5 point scale (none to very severe).<br>Duration of effect of medication in relief of subjective distress.<br>Side effect profile (patient comfort, level of consciousness, state of skin at site of injection, incidence of vomiting).<br>Relationship between hydration status and activity of the medication. | Pilot cross-over study; n=21 but only 10 received the intervention (the other 11 either died before medication was administered or respiratory secretion settled), no wash-out period before the cross-over (that is, change in drugs). |
| Likar et al., 2002[57] | People with advanced terminal cancer with life expectancy of less than 3 days (n=31). Fully conscious people were excluded from the study. Average time from first drug administration to death was < 16 hours.<br><br>Germany | Hyoscine hydrobromide 0.5 mg (in 1 ml saline) IV or subcutaneous.<br>Normal saline 1 ml intravenous or subcutaneous. | Subjective rating of noisy breathing on a 5 point scale (none to very severe).<br>Pain rated on a 3 point scale (mild to severe).<br>Restlessness rated on a 3 point scale (mild to severe).<br>Interval between start of treatment and death. | Description of study design, such as randomisation and allocation concealment, lacks detail.<br>Only percentages reported in adverse outcomes (unclear how it corresponds to the scale that is used) and do not match with the total number in each group. |
| Likar et al., 2008[58] | People with advanced terminal cancer with life expectancy of less than 3 days (n=13). Fully conscious people were excluded from the study. Average time from first drug administration to death <20 hours.<br>Germany | Hyoscine hydrobromide 0.5 mg every 6 hours intravenously.<br>Glycopyrronium bromide 0.4 mg every 6 hours intravenously. | Subjective rating of noisy breathing on a 5 point scale (none to very severe).<br>Pain rated on a 3 point scale (mild to severe).<br>Restlessness rated on a 3 point scale (mild to severe).<br>Interval between start of treatment and death. | Pilot study. Description of study design, such as randomisation and allocation concealment, lacks detail.<br>Restlessness data only presented graphically and raw numbers could not be extracted. Pain data were not provided (just described as non-significant). |

| Study | Population | Intervention and comparison | Outcomes | Comments |
|---|---|---|---|---|
| Included Cochrane systematic review | | | | |
| Wildiers et al., 2009[107] | People at the end of life with noticeable death rattle (n=333; n=316 cancer, n=17 non-cancer). Level of consciousness was not an exclusion criterion.<br><br>Belgium | Scopolamine (hyoscine hydrobromide) 0.25 mg subcutaneous bolus, followed by 1.5 mg/24 hours.<br>Hyoscine butylbromide 20 mg subcutaneous bolus, followed by 60 mg/24 hours).<br>Atropine 0.5 mg subcutaneous bolus, followed by 3 mg/24 hours. | Subjective rating of noisy breathing on a 4 point scale (none to very severe).<br>Side effects (consciousness, confusion).<br>Interval between start of treatment and death. | Open-label phase III trial. From the trial profile it looks like randomisation was carried out before assessment of inclusion criteria and consent. |
| Cohort studies excluded in the Cochrane systematic review but are-included here | | | | |
| Back et al., 2001[9] | People with terminal advanced cancer (mean time to death was 22 hours in 1 group and 27 hours in the other). Level of consciousness was not an exclusion criterion.<br>(n=191)<br><br>UK | Scopolamine (hyoscine hydrobromide) 0.4 mg subcutaneous bolus, repeated after 30 minutes if noisy breathing persisted.<br>Glycopyrronium bromide 0.2 mg subcutaneous bolus, repeated after 30 minutes if noisy breathing persisted. | Subjective rating of noisy breathing on a 4 point scale (none to very severe). | Prospective study conducted before and after a change in prescribing guidelines. This paper is UK based and reports some, though very limited, economic data. |
| Hugel et al., 2006[44] (and Kass and Ellerschaw, 2003[53]) | People with terminal advanced cancer who were managed using the Liverpool Care Pathway (number analysed n=72). Median time from onset of noisy breathing to death was 12 hours in the hyoscine hydrobromide group and 24 hours in the glycopyrronium group. Level of consciousness was not an exclusion criterion. Median time from onset of | Hyoscine hydrobromide 0.4 mg subcutaneously, followed by 1.2 mg/24 hour period continuous subcutaneous injection.<br>Glycopyrronium bromide 0.2 mg subcutaneous followed by 0.6 mg/24-hour continuous subcutaneous injections. | 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.<br>Agitation (number of episodes as a proportion of all episodes). | People matched for age, gender and diagnosis. However, the matching process is not described and characteristics not provided in a table. Baseline noisy breathing severity not provided.<br>The outcome seems to be somewhat arbitrarily defined. |

| Study | Population | Intervention and comparison | Outcomes | Comments |
|---|---|---|---|---|
| Included Cochrane systematic review | | | | |
| | respiratory secretions to death ≤ 24 hours<br><br>UK | | | |
| Hughes et al., 2000[45] | 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. (n=111)<br><br>UK | Hyoscine hydrobromide 0.4 mg subcutaneously stat, followed by 0.6 mg stat and 2.4 mg/24 hour by syringe pump.<br>Hyoscine butylbromide 20 mg subcutaneously stat, followed by 20 mg stat and 20 mg/24 hour by syringe pump.<br>Glycopyrronium bromide 0.2 mg subcutaneously stat, followed by 0.4 mg stat and 0.6 mg/24 hour by syringe pump. | Intensity of the noise of secretion on a 6 point scale (absent, much better, slightly better, same, slightly worse, or much worse).<br>Relatives' distress using the same 6 point scale. | Prospective comparative audit (convenience sample), groups described as similar in age, gender, initial severity of secretions and level of relatives' distress in each audit. However, no data for these were provided. |
| Randomised controlled trial identified in the update search | | | | |
| Heisler et al., 2013[41] | Terminally ill adults in a hospice, who had developed audible respiratory tract secretion (43% cancer). Level of consciousness was not an exclusion criterion.<br>n=137<br><br>USA | The study drug was administered as a one-time dose sublingually.<br>Two drops of atropine (1 mg).<br>Two drops of placebo (saline). | Subjective rating of noisy breathing on a 4 point scale (none to very severe).<br>Time to death. | Trial was stopped prematurely after second interim analysis because of futility (according to pre-planned criteria). Intervention time and trial follow-up was restricted to 4 hours. |

There are 3 points that can be highlighted from the main characteristics in Table 13.

The outcomes for all studies included a subjective rating of noisy breathing with the intensity most often rated on a 5 point scale by health care staff. An improvement was then usually classified as at least a 1 point difference in intensity.

All, apart from the RCT identified in the update search, focused exclusively or mainly on people with terminal cancer (in 1 other study 17 out of 333 were non-cancer participants).

In 4 of the 8 studies, participants were either unconscious or being 'fully conscious' was an exclusion criterion, whereas consciousness was not part of the inclusion or exclusion criteria in the remaining 4 studies.

The following 8 different drug comparisons were investigated in the studies.

**Table 58: Grid of the 8 pharmacological comparisons (darker shaded cells indicate comparisons for which no evidence was identified).**

| | Glycopyrronium bromide | Hyoscine butylbromide | Atropine | Octreotide | Placebo |
|---|---|---|---|---|---|
| **Hyoscine hydrobromide (scopolamine)** | Back et al. (2001)[9]<br>Hugel et al. (2006)[44]<br>Likar et al. (2008)[57]<br>Hughes et al. (2000)[45] | Wildiers et al. (2009)[107]<br>Hughes et al. (2000)[45] | Wildiers et al. (2009)[107] | Clark et al. (2008)[23] | Likar et al. (2002)[57] |
| **Glycopyrronium bromide** | | Hughes et al. (2000)[45] | | | |
| **Hyoscine butylbromide** | | | Wildiers et al. (2009)[107] | | |
| **Atropine** | | | | | Heisler et al. (2013)[41] |

### 9.27.1.1 GRADE assessment

GRADE tables are divided by comparison. See below for reported outcomes in each of the 8 comparisons.

**Table 59: Clinical evidence summary: Glycopyrronium bromide versus hyoscine hydrobromide**

| Outcomes | No. of participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with hyoscine hydrobromide | Risk difference with glycopyrronium bromide (95% CI) |
| Improvement in noise intensity – from baseline up to 12 hours | 13 (1 study) | VERY LOW[a,b] due to risk of bias, imprecision | N/A | Could not be extracted – only presented in graphical format. Therefore downgraded for imprecision. | It is described that there was a trend for the noise intensity to decrease more with glycopyrronium with statistically significant differences at 2 (p=0.029) and 12 hours (p=0.030). |
| Improvement in noise intensity initial vs. 1 hour | 158 (1 study) | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.7 (0.49 to 1.01) | 573 per 1000 | 172 fewer per 1000 (from 292 fewer to 6 more) |
| Improvement in noise intensity initial vs. final (median < 2 hours before death) | 160 (1 study) | VERY LOW[a,b] due to risk of bias, imprecision | RR 0.94 (0.65 to 1.37) | 447 per 1000 | 27 fewer per 1000 (from 156 fewer to 165 more) |
| Secretions relieved at death (prospective audit) | 74 (1 study) | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.2 (0.82 to 1.75) | 541 per 1000 | 108 more per 1000 (from 97 fewer to 405 more) |
| Response to drug (time from first observation until first observation of absent symptoms) – Immediate | 72 (1 study) | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.18 (0.61 to 2.28) | 306 per 1000 | 55 more per 1000 (from 119 fewer to 391 more) |
| Response to drug (time from first observation until first observation of absent symptoms) – Late | 72 (1 study) | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.3 (0.66 to 2.57) | 278 per 1000 | 83 more per 1000 (from 94 fewer to 436 more) |
| Response to drug (time from first observation until first observation of absent symptoms) – Transient | 72 (1 study) | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.43 (0.61 to 3.34) | 194 per 1000 | 84 more per 1000 (from 76 fewer to 455 more) |

| Outcomes | No. of participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with hyoscine hydrobromide | Risk difference with glycopyrronium bromide (95% CI) |
| Improvement in relatives' distress (prospective audit) | 54 (1 study) | VERY LOW[a] due to risk of bias | RR 0.95 (0.79 to 1.13) | 931 per 1000 | 47 fewer per 1000 (from 196 fewer to 121 more) |
| Length of survival (hours) | 13 (1 study) | LOW[a,b] due to risk of bias, imprecision | | The mean length of survival (hours) in the control groups was 19.5 hours | The mean length of survival (hours) in the intervention groups was 6.7 lower (21.12 lower to 7.72 higher) |
| Adverse event – restlessness from baseline up to 12 hours | 13 (1 study) | VERY LOW[a,b] due to risk of bias, imprecision | N/A | Could not be extracted – only presented in graphical format. Therefore downgraded for imprecision. | It is described that there was no statistically significant difference between the 2 groups in percentage of people experiencing restlessness. |

*(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 starting 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 60: Clinical evidence summary: Hyoscine butylbromide versus hyoscine hydrobromide**

| Outcomes | No. of participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with hyoscine hydrobromide | Risk difference with hyoscine butylbromide (95% CI) |
| Improvement in noisy breathing (score of 0-1 defined as effective reduction) – At 4 hours | 179 (1 study) | LOW[a,b] due to risk of bias, imprecision | RR 1.16 (0.86 to 1.55) | 468 per 1000 | 75 more per 1000 (from 66 fewer to 257 more) |
| Improvement in noisy breathing (score of 0-1 defined as effective reduction) – At 12 hours | 138 (1 study) | LOW[a,b] due to risk of bias, imprecision | RR 0.9 (0.66 to 1.22) | 571 per 1000 | 57 fewer per 1000 (from 194 fewer to 126 more) |
| Improvement in noisy breathing (score of 0-1 defined as effective | 100 (1 study) | LOW[a,b] due to risk of bias, | RR 0.88 (0.65 to 1.18) | 679 per 1000 | 82 fewer per 1000 (from 238 fewer to 122 more) |

| Outcomes | No. of participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with hyoscine hydrobromide | Risk difference with hyoscine butylbromide (95% CI) |
| reduction) – At 24 hours | | imprecision | | | |
| Secretions relieved at death (prospective audit) | 74 (1 study) | VERY LOW[b] due to risk of bias, imprecision | RR 1.2 (0.82 to 1.75) | 541 per 1000 | 108 more per 1000 (from 97 fewer to 405 more) |
| Improvement in relatives' distress (prospective audit) | 56 (1 study) | VERY LOW[a] due to risk of bias | RR 0.95 (0.81 to 1.13) | 931 per 1000 | 47 fewer per 1000 (from 177 fewer to 121 more) |
| Worsening in level of consciousness – At 12 hours | 134 (1 study) | LOW[a,b] due to risk of bias, imprecision | RR 0.47 (0.27 to 0.79) | 456 per 1000 | 242 fewer per 1000 (from 96 fewer to 333 fewer) |
| Worsening in level of consciousness – At 24 hours | 97 (1 study) | LOW[a,b] due to risk of bias, imprecision | RR 0.51 (0.28 to 0.91) | 481 per 1000 | 236 fewer per 1000 (from 43 fewer to 346 fewer) |
| Improvement in confusion (for those with sufficient level of consciousness to assess) – At 12 hours | 14 (1 study) | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 4.56[c] (0.19 to 111.03) | 0 per 1000 | 333 more per 1000 (from 160 fewer to 830 more)[c] |
| Improvement in confusion (for those with sufficient level of consciousness to assess) – At 24 hours | 13 (1 study) | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 4.24[c] (0.06 to 296.2) | 0 per 1000 | 111 more per 1000 (from 230 fewer to 450 more)[c] |

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

**Table 61: Clinical evidence summary: Atropine versus hyoscine hydrobromide**

| Outcomes | No. of participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with hyoscine hydrobromide | Risk difference with atropine (95% CI) |
| Improvement in noisy breathing (score of 0-1 defined as effective reduction–) - At 4 hours | 186 (1 study) | LOW[a,b] due to risk of bias, imprecision | RR 1.07 (0.79 to 1.44) | 468 per 1000 | 33 more per 1000 (from 98 fewer to 206 more) |
| Improvement in noisy breathing (score of 0-1 defined as effective reduction–) - At 12 hours | 135 (1 study) | LOW[a,b] due to risk of bias, imprecision | RR 1.24 (0.96 to 1.6) | 571 per 1000 | 137 more per 1000 (from 23 fewer to 343 more) |
| Improvement in noisy breathing (score of 0-1 defined as effective reduction–) - At 24 hours | 107 (1 study) | LOW[a,b] due to risk of bias, imprecision | RR 1.12 (0.88 to 1.42) | 679 per 1000 | 82 more per 1000 (from 82 fewer to 285 more) |
| Worsening in level of consciousness - At 12 hours | 130 (1 study) | LOW[a,b] due to risk of bias, imprecision | RR 0.64 (0.4 to 1.02) | 456 per 1000 | 164 fewer per 1000 (from 274 fewer to 9 more) |
| Worsening in level of consciousness - At 24 hours | 103 (1 study) | LOW[a,b] due to risk of bias, imprecision | RR 0.77 (0.49 to 1.22) | 481 per 1000 | 111 fewer per 1000 (from 245 fewer to 106 more) |
| Improvement in confusion (for those with sufficient level of consciousness to asses–) - At 12 hours | 7 (1 study) | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 4.06 (0.05 to 310.62) | 0 per 1000 | 200 more per 1000 (from 350 fewer to 750 more)[c] |
| Improvement in confusion (for those with sufficient level of consciousness to asses–) - At 24 hours | 10 (1 study) | MODERATE[a] due to risk of bias | N/A | No events | No events |

*(a) Downgraded by 1 increment if the majority of the evidence was at a high risk of bias or by 2 increments if the majority of the evidence was at a 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 MID.*

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

**Table 62: Clinical evidence summary: Atropine versus hyoscine butylbromide**

| Outcomes | No. of participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with hyoscine butylbromide | Risk difference with atropine (95% CI) |
| Improvement in noisy breathing (score of 0-1 defined as effective reduction) - At 4 hours | 177 (1 study) | LOW[a,b] due to risk of bias, imprecision | RR 0.92 (0.7 to 1.23) | 541 per 1000 | 43 fewer per 1000 (from 162 fewer to 124 more) |
| Improvement in noisy breathing (score of 0-1 defined as effective reduction) - At 12 hours | 133 (1 study) | LOW[a,b] due to risk of bias, imprecision | RR 1.37 (1.04 to 1.82) | 515 per 1000 | 190 more per 1000 (from 21 more to 422 more) |
| Improvement in noisy breathing (score of 0-1 defined as effective reduction) - At 24 hours | 101 (1 study) | LOW[a,b] due to risk of bias, imprecision | RR 1.27 (0.96 to 1.69) | 596 per 1000 | 161 more per 1000 (from 24 fewer to 411 more) |
| Worsening in level of consciousness - At 12 hours | 130 (1 study) | LOW[a,b] due to risk of bias, imprecision | RR 0.64 (0.4 to 1.02) | 456 per 1000 | 164 fewer per 1000 (from 274 fewer to 9 more) |
| Worsening in level of consciousness - At 24 hours | 103 (1 study) | LOW[a,b] due to risk of bias, imprecision | RR 0.77 (0.49 to 1.22) | 481 per 1000 | 111 fewer per 1000 (from 245 fewer to 106 more) |
| Improvement in confusion (for those with sufficient level of consciousness to assess) - At 12 hours | 7 (1 study) | VERY LOW[a,b] due to risk of bias, imprecision | Peto OR 4.06 (0.05 to 310.62) | 0 per 1000 | 200 more per 1000 (from 350 fewer to 750 more)[c] |
| Improvement in confusion (for those with sufficient level of consciousness to assess) - At 24 hours | 10 (1 study) | MODERATE[a] due to risk of bias | N/A | No events | No events |

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

**Table 63: Clinical evidence summary: Octreotide versus hyoscine butylbromide**

| Outcomes | No. of participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with hyoscine hydrobromide | Risk difference with octreotide (95% CI) |
| Improvement in noisy breathing intensity (from 1 hour after first dose to 6 hours after second dose) | 10 (1 study) | VERY LOW[a,b] due to risk of bias, imprecision | RR 1 (0.22 to 4.56) | 400 per 1000 | 0 fewer per 1000 (from 312 fewer to 1000 more) |

*(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.*

**Table 64: Clinical evidence summary: Atropine versus placebo**

| Outcomes | No. of participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with placebo | Risk difference with atropine (95% CI) |
| Improvement in noisy breathing (reduction of 1 point –r more) - At 2 hours | 137 (1 study) | LOW[a] due to imprecision | RR 0.92 (0.61 to 1.39) | 413 per 1000 | 33 fewer per 1000 (from 161 fewer to 161 more) |
| Improvement in noisy breathing (reduction of 1 point –r more) - At 4 hours | 128 (1 study) | MODERATE[a] due to imprecision | RR 0.77 (0.52 to 1.13) | 517 per 1000 | 119 fewer per 1000 (from 248 fewer to 67 more) |

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

**Table 65: Clinical evidence summary: Hyoscine hydrobromide versus placebo**

| Outcomes | No. of participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with placebo | Risk difference with hyoscine hydrobromide (95% CI) |
| Improvement in noise intensity - from baseline up to 10 hours | 31 (1 study) | LOW[a] due to risk of bias | N/A | Could not be extracted | It is described that there was no statistical difference between the drug and placebo (only graphically presented) |

| Outcomes | No. of participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with placebo | Risk difference with hyoscine hydrobromide (95% CI) |
| Restlessness | 31 (1 study) | VERY LOW[a,b] due to risk of bias, imprecision | RR 1.6 (0.75 to 3.41) | 375 per 1000 | 225 more per 1000 (from 94 fewer to 904 more) |
| Pain | 31 (1 study) | LOW[a] due to risk of bias | RR 6.93 (1.87 to 25.73) | 125 per 1000 | 741 more per 1000 (from 109 more to 1000 more) |
| Length of survival (minutes) | 31 (1 study) | VERY LOW[a,b] due to risk of bias, imprecision | | The mean length of survival (minutes) in the control groups was 611 minutes | The mean length of survival (minutes) in the intervention groups was 296 higher (51.81 lower to 643.81 higher) |

*(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.*

**Table 66: Clinical evidence summary: Glycopyrronium bromide compared with hyoscine butylbromide**

| Outcomes | No. of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with hyoscine butylbromide | Risk difference with glycopyrronium bromide (95% CI) |
| Secretions relieved at death (prospective audit) | 74 (1 study) | VERY LOW[a,b] due to risk of bias, imprecision | RR 1 (0.72 to 1.4) | 649 per 1000 | 0 fewer per 1000 (from 182 fewer to 259 more) |
| Improvement in 'relatives' distress (prospective audit) | 54 (1 study) | VERY LOW[a] due to risk of bias | RR 0.95 (0.79 to 1.13) | 931 per 1000 | 47 fewer per 1000 (from 196 fewer to 121 more) |

*(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.*

## 9.28 Economic evidence

### Published literature

No relevant economic evaluations were identified.

One economic evaluation relating to this review question was identified but was excluded due to a combination of limited applicability and methodological limitations.[9] This is listed in Appendix M, with reasons for exclusion given.

See also the economic article selection flow chart in Appendix F.

### Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix N to aid consideration of cost effectiveness.

## 9.29 Evidence statements

### Clinical

There was moderate to very low quality evidence from 5 RCTs (n=524) and 3 cohort studies (n=374) in people in the last days of life with advanced cancer (n=822) and non-cancer conditions (n=76) regarding pharmacological management of noisy respiratory secretions. The critical outcome of improvement of noisy respiratory secretions was reported in all 8 studies (n=898), which are summarised in Table 67. Four studies reported no difference in improvement of noisy respiratory secretions between medications, 1 study reported favouring placebo, 1 study favoured atropine, and 2 studies favoured glycopyrronium pyrronium. 1 RCT (n=130) reported that in people with advanced cancer, atropine was less sedating then hyoscine butlybromide or hyoscine hydrobromide. Other important outcomes are summarised in Table 68.

No evidence was found for the quality of life outcomes.

**Table 67: Grid of results by comparison and outcome – improvement in intensity of noisy breathing**

| | Glycopyrronium bromide | Hyoscine butylbromide | Atropine | Octreotide | Placebo |
|---|---|---|---|---|---|
| **Hyoscine hydrobromide (scopolamine)** | All rated as VERY LOW QUALITY evidence:<br>• Back et al. (2001)[9]: at 1 hour - favours HBrom; at final measure - no difference.<br>• Hugel et al. (2006)[44]: immediate - no difference; late - no difference; | • Wildiers et al. (2009)[107]: At 4 hours -no difference; at 12 hours - no difference; at 24 hours - no difference (all LOW QUALITY).<br>• Hughes et al., (2000)[45]: relieved at time of death - favours HyButyl (VERY LOW | • Wildiers et al. (2009)[107]: at 4 hours -no difference; at 12 hours - favours atropine; at 24 hours - no difference (all LOW QUALITY). | • Clark et al., (2008)[23]: from 1 hour after first dose to 6 hours after second dose - no difference (VERY LOW QUALITY). | • Likar et al. (2002)[57]: from baseline up to 10 hours - no difference (VERY LOW QUALITY). |

| | Glycopyrronium bromide | Hyoscine butylbromide | Atropine | Octreotide | Placebo |
|---|---|---|---|---|---|
| | transient - no difference.<br>• Likar et al. (2008)[57]: at 2 hours - favours Glyco; at 12 hours - favours Glyco.<br>• Hughes et al., (2000)[45]: relieved at time of death - favours Glyco. | QUALITY). | | | |
| **Glycopyrronium bromide** | | • Hughes et al., (2000)[45]: relieved at time of death - no difference (VERY LOW QUALITY). | | | |
| **Hyoscine butylbromide** | | | • Wildiers et al. (2009)[107]: at 4 hours -no difference; at 12 hours - favours atropine; at 24 hours - favours atropine (all LOW QUALITY). | | |
| **Atropine** | | | | | Heisler et al. (2013)[41]: at 2 hours - no difference; at 4 hours - favours placebo (LOW and MODERATE QUALITY). |

*Note: empty darker shaded cells indicate that no results were available for these comparisons*

**Table 68: Grid of results by comparison and outcome – all other outcomes**

| | Glycopyrronium bromide | Hyoscine butylbromide | Atropine | Octreotide | Placebo |
|---|---|---|---|---|---|
| **Hyoscine hydrobromide (scopolamine)** | All rated as VERY LOW QUALITY evidence:<br>• Likar et al. (2008)[57]: **Length of survival** - no difference.<br>• Hughes et al., (2000)[45]: **Improvement in relatives' distress** – no difference. | • Wildiers et al. (2009)[107]: **Worsening level of consciousness;** at 12 hours - favours HyBut; at 24 hours - favours HyBut (all LOW QUALITY). **Improvement in confusion;** at 12 hours - no clear difference; at 24 hours - no clear difference (all VERY LOW QUALITY).<br>• Hughes et al., (2000)[45]: **Improvement in relatives' distress** - no difference (VERY LOW QUALITY). | • Wildiers et al. (2009)[107]: **Worsening level of consciousness;** at 12 hours - favours Atropine; at 24 hours - favours Atropine (all LOW QUALITY). **Improvement in confusion**; at 12 hours - no clear difference; at 24 hours - no clear difference (all VERY LOW QUALITY). | | • Likar et al. (2002)[57]: **Restlessness** - favours placebo; **Pain** - favours placebo (BOTH LOW QUALITY). **Length of survival** - no difference (VERY LOW QUALITY). |
| **Glycopyrronium bromide** | | • Hughes et al., (2000)[45]: **Improvement in relatives' distress** – no difference (VERY LOW QUALITY). | | | |
| **Hyoscine butylbromide** | | | • Wildiers et al. (2009)[107]. **Worsening level of consciousness;** at 12 hours - favours Atropine; at 24 hours - favours Atropine (all LOW QUALITY). **Improvement in confusion;** at 12 hours - no clear difference; at 24 hours - no | | |

| | Glycopyrronium bromide | Hyoscine butylbromide | Atropine | Octreotide | Placebo |
|---|---|---|---|---|---|
| | | | clear difference (all VERY LOW QUALITY). | | |
| **Atropine** | | | | | |

*Note: empty darker shaded cells indicate that no results were available for these comparisons*

**Economic**

- No relevant economic evaluations were identified.

## 9.30 Recommendations and link to evidence

**Recommendations**

**52. Assess for the likely causes of noisy respiratory secretions in people in the last days of life. Establish whether the noise has an impact on the dying person or those important to them. Reassure them that, although the noise can be distressing, it is unlikely to cause discomfort. Be prepared to talk about any fears or concerns they may have.**

**53. Consider non-pharmacological measures to manage noisy respiratory or pharyngeal secretions, to reduce any distress in people at the end of life.**

**54. Consider a trial of medicine to treat noisy respiratory secretions if they are causing distress to the dying person. Tailor treatment to the dying person's individual needs or circumstances, using 1 of the following drugs:**

- **atropine[f] or**
- **glycopyrronium bromide[f] or**
- **hyoscine butylbromide[f] or**
- **hyoscine hydrobromide[f].**

**55. When giving medicine for noisy respiratory secretions:**

- **Monitor for improvements, preferably every 4 hours, but at least every 12 hours.**
- **Monitor regularly for side effects, particularly delirium, agitation or excessive sedation when using atropine or hyoscine hydrobromide.**
- **Treat side effects, such as dry mouth, delirium or sedation (see recommendations 24, 66 and 46).**

**56. Consider changing or stopping medicines if noisy respiratory secretions continue and are still causing distress after 12 hours (medicines may take up to 12 hours to become effective).**

**57. Consider changing or stopping medicines if unacceptable side effects,**

[f] At the time of publication (December 2015), this medication did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

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| | **such as dry mouth, urinary retention, delirium, agitation and unwanted levels of sedation, persist.** |
| **Relative values of different outcomes** | The Committee considered the following critical outcomes for noisy respiratory secretions for decision making: symptom control, sedation and quality of life. Important outcomes were adverse events and length of survival. Reduction of noise intensity was the most frequently reported outcome and was considered a critical outcome by the Committee as this may cause carer and family distress and, often the reason that drugs are initiated. Worsening level of consciousness was also given importance in the discussion with the caveat that this outcome was not very clearly reported. |
| **Trade-off between clinical benefits and harms** | The Committee discussed the value of treating noisy respiratory secretions pharmacologically. Often the dying person is unconscious and there was agreement between the Committee that noisy respiratory secretions are sometimes primarily treated to reduce distress in those important to the dying person. The Committee noted that there was a considerable rate of improvement (that is, reduction) in noise intensity reported by some of the studies. The Committee discussed that hyoscine hydrobromide was reported to lead to what was described in a study as worsening levels of consciousness compared with other drugs. However, it was noted that this could be an adverse or desired effect of this drug depending on other clinical symptoms unrelated to respiratory secretion. Other side effects that were not reported in the studies would also have implications for the management of the person taking these drugs. For example in instances when, antimuscarinic drugs lead to dry mouth and therefore require management to alleviate the secondary side effect (such as frequently moistening the mouth). Agitation and restlessness, which was reported by 1 study, can also be an adverse event, related particularly to hyoscine hydrobromide, that healthcare professionals and people important to the dying person should be aware of and monitor. It was noted that atropine, which is not commonly used in the UK, may share the same side-effect profile as hyoscine hydrobromide. Atropine is not a drug that is commonly used in the UK for respiratory secretions due to concerns about its cardiac effects, such as arrhythmias. However, in this review, the results of the largest randomised controlled study suggested that atropine was as, or even more effective than the more commonly UK used drugs.<br>Given the possible sedative effect of some of the medications used to treat this symptom, the Committee considered development of sedation an important outcome but were keen to note that, on occasion, this outcome could be considered beneficial. The Committee was aware that some medications could cause agitation which could also be distressing and so the Committee considered this an unwanted adverse effect together with dry mouth. |
| **Trade off between net health benefits and resource use.** | No economic evaluations were identified.<br><br>Unit costs were presented for a variety of drug treatments used for respiratory secretions. The Committee noted that, apart from octreotide, which was considerably more expensive, the unit costs were fairly similar amongst all treatments. As the clinical evidence also showed no evidence that indicated 1 treatment was more effective than another, the Committee decided to not recommend 1 drug over another. The Committee noted that, although more expensive than some of the other drugs, hyoscine hydrobromide is currently the only drug that is licenced. |
| **Quality of evidence** | Evidence that was presented to the Committee was low or, for the majority of outcomes, very low according to GRADE criteria. The Committee also noted that almost all of the studies reported on people who were dying from terminal cancer which was also a limitation of the evidence. It remains unclear whether the findings of these studies could be generalised to people with respiratory secretions who were dying from other conditions. The results from these studies were not pooled due to the differences in the descriptions of outcomes as well as variations in study design and follow-up times. |

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| | The validity of the scales that were used was also questioned by the Committee. In all studies the attending nurses rated the symptoms, but verbal anchors were often poorly described and the rating is very subjective and open to reporting or observer biases.<br>It was noted by the Committee that the comparison of drug dosages in 1 study was favouring atropine since the other drugs were given at a lower starting dose compared with usual UK practice.<br>More weight was given to the evidence from the 2 larger randomised controlled trials[41,107] because the study design was more robust. However, these 2 studies were quite different in the length of follow-up, drug dose and route of administration and results were therefore not directly comparable. Other evidence came from very small or pilot randomised controlled trials and a randomised study with a cross-over design without sufficient washout periods between drug changes. The observational studies were more applicable with regard to settings because all of them were conducted in the UK. However, they were using retrospective designs which are more likely to be biased and only 1 study used a matching process to account for possible selection biases leading to baseline differences between groups.<br>The Committee, on review of the evidence, considered that all drugs were of equal efficacy for symptom management of noisy respiratory secretions, and could not prioritise 1 drug over the other. |
| **Other considerations** | The Committee noted that respiratory secretions are frequently observed at the end of life and that this is also supported by the prevalence reported in reviews of the literature (see for instance Lokker and colleagues, 2014[63]). This is often distressing for relatives and the Committee noted that care given to the people important to the person who is dying is an important consideration in palliative practice.<br>The Committee discussed the cause of the noise, which could be related to pharyngeal secretions (pooled saliva), for example, in people with Motor Neurone Disease (MND), as well as respiratory secretions. Therefore the Committee chose to include the term 'pharyngeal' as well as 'respiratory' in the recommendation regarding non-pharmacological measures as it is important to include people with MND within this population.<br>It was noted that hyoscine hydrobromide and atropine are the only drugs which cross the blood brain barrier and therefore side effects, such as sedation, agitation or restlessness, would be more likely for these than for the others.<br>Atropine was seen by the Committee as useful in some people as it is available as ophthalmic drops which can readily be administered sublingually, and therefore recommended despite the Committee noting it was off license for noisy respiratory secretions.<br>Octreotide was not considered by the Committee to be a useful treatment for respiratory secretions and they did not endorse its use for this indication. They chose not to make a recommendation on this. It is also a more costly drug with a higher potential for a range of side effects and the 1 study where it was used had very low patient numbers and was low quality evidence.<br>The Committee chose to draft recommendations based on their clinical experience and focussed on the importance of discussing the experience of noisy respiratory secretions with the dying person and those important to them. From their clinical experience, they noted that the dying person is most often not aware of the noisy breathing accompanying this symptom but were aware that it was usually those important to them who were distressed by this 'death rattle'. They felt it important to state that this issue was clarified and discussed with the dying person and those important to them. They noted that, whilst this review had focussed on the pharmacological management of this symptom, there were other measures that could minimise the distress caused by respiratory secretions. These included re-positioning of the patient and, where appropriate, oropharyngeal suction. They felt that these basic nursing care management options would also be important to consider alongside any pharmacological management options. People with |

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| | tracheostomies often experience particularly troublesome and noisy secretions (not just at the end of life) and, in this situation, regular suction and tracheostomy care is an essential intervention. The Committee commented that this can be challenging, particularly in the community or non-specialist setting, especially when alleviating any concerns about airway obstruction. Tracheostomy care requires specialist nursing and is outside the scope of this guideline. The Committee agreed that specialist palliative care advice should be sought for people with problematic respiratory secretions with tracheostomies in the last few days of life.<br>The effectiveness of non-pharmacological treatments, such as repositioning or suction, was also considered. The Committee noted that some systematic reviews looking for evidence of their effectiveness had not identified any studies on the effectiveness of such measures (Lokker et al., 2014[63,64] and Wee and Hillier, 2008[103]). The Committee also noted that some non-pharmacological interventions may not be effective. For example, the use of suctioning and positioning do have the potential to worsen symptoms in some circumstances (such as when respiratory secretions are due to pulmonary oedema).<br>The Committee felt that any pharmacological management of this symptom should be accompanied by frequent preferably 4-hourly monitoring, but recognized that this may be dependent upon setting. They felt that, even if the person was dying outside of a hospital setting, monitoring should take place at least every 12 hours in order to ascertain whether symptoms were relieved or whether the administration of medication was having unwanted side effects. For example, increasing levels of sedation or agitation could signify an adverse pharmacological effect of hyoscine hydrobromide or atropine. Additionally, all antimuscarinics and octreotide can cause dry mouth and this may cause discomfort or be unpleasant for the dying person. On the other hand, reduction of bowel movements and of bladder tone could be beneficial in some situations.<br>The Committee was aware that all the drugs recommended were off license for the management of noisy respiratory secretions in the last days of life, but in their clinical experience they are often used in this setting with effect.<br>The Committee noted the findings liked to the outcome time frames of 4, 12 and 24 hours in the evidence reviewed and agreed that if a pharmacological treatment was not effective after 12 hours in managing the symptom, then an alternative should be tried. If the alternative also fails, it should be discontinued to minimise the unwanted burden of unnecessary or ineffective treatments. Equally, the Committee also considered it appropriate not to prescribe if there was considered no benefit or if family members were content with the management of noisy respiratory secretions, having had a full explanation of the nature of this symptom. |

## 9.31 Research recommendation

3. **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?**
   - **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.**

# General pharmacological considerations

## 9.32 Introduction

Having considered the clinical and economic evidence for each symptom, the Committee made several consensus recommendations to guide best practice in pharmacological management in the last days of life. The Committee used their clinical and practical experience in caring for dying people in developing these recommendations.

## 9.33 Evidence

The Committee made several consensus recommendations after considering the clinical and economic evidence for the individual symptom reviews.

## 9.34 Recommendations and link to evidence

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| **Recommendations** | **58. When it is recognised that a person may be entering the last days of life, review their current medicines and, after discussion and agreement with the dying person and those important to them (as appropriate), stop any previously prescribed medicines that are not providing symptomatic benefit or that may cause harm.**<br><br>**59. When involving the dying person and those important to them in making decisions about symptom control in the last days of life:**<br>• **Use the dying person's individualised care plan to help decide which medicines are clinically appropriate.**<br>• **Discuss the benefits and harms of any medicines offered.**<br><br>**60. When considering medicines for symptom control, take into account:**<br>• **the likely cause of the symptom**<br>• **the dying person's preferences alongside the benefits and harms of the medicine**<br>• **any individual or cultural views that might affect their choice**<br>• **any other medicines being taken to manage symptoms**<br>• **any risks of the medicine that could affect prescribing decisions, for example prescribing cyclizine to manage nausea and vomiting may exacerbate heart failure.**<br><br>**61. Decide on the most effective route for administering medicines in the last days of life tailored to the dying person's condition, their ability to swallow safely and their preferences.**<br><br>**62. Consider prescribing different routes of administering medicine if the dying person is unable to take or tolerate oral medicines. Avoid giving intramuscular injections and give either subcutaneous or intravenous injections.** |

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| | **63. Consider using a syringe pump to deliver medicines for continuous symptom control if more than 2 or 3 doses of any 'as required' medicines have been given within 24 hours.**<br><br>**64. For people starting treatment who have not previously been given medicines for symptom management, start with the lowest effective dose and titrate as clinically indicated.**<br><br>**65. Regularly reassess, at least daily, the dying person's symptoms during treatment to inform appropriate titration of medicine.**<br><br>**66. Seek specialist palliative care advice if the dying person's symptoms do not improve promptly with treatment or if there are undesirable side effects, such as unwanted sedation.** |
| **Relative values of different outcomes** | Not applicable. |
| **Trade-off between clinical benefits and harms** | These are general principles of good prescribing practice and minimal harms were identified. |
| **Trade-off between net health benefits and resource use** | These recommendations were not based on specific reviews of clinical and economic evidence but they reflect general principles of good prescribing practice.<br>The Committee concluded that they would not generate any considerable additional costs as these points should already constitute current practice. |
| **Quality of evidence** | No specific evidence was identified and these recommendations were made as a result of evidence identified elsewhere in this chapter. |
| **Other considerations** | The evidence review within this chapter had outcomes for several symptoms. Whilst discussing these individually with the Committee, several key areas around good prescribing for the end of life were identified. These overarching recommendations are now presented following consideration of the specific recommendations for each symptom considered as part of this guideline.<br>The Committee felt that several overarching recommendations were needed for the management of symptoms in the last days of life. Although evidence was identified for specific symptoms, such as pain and breathlessness, these recommendations are largely from Committee consensus, based on their expert opinion.<br>The Committee commented on the value of good symptom control in the last days of life, and noted that medication, along with non-pharmacological interventions, can be used to achieve this. However, many of the medications used for symptom relief in the last days of life can have side effects that can impact on the dying person's quality of life. The Committee agreed that it was important to inform the dying person and those important to them of the side effects of drugs given for symptom control, for example, benzodiazepines and antipsychotic agents may increase sedation (an area of concern highlighted in the Neuberger Report[104,105]). It was also noted that sedation may be desirable to the dying person and those important to them and that there could also be associated reduction in other distressing symptoms including pain, nausea and breathlessness, all of which should be discussed with the dying person and those important to them.<br>The Committee highlighted that these side effects, along with the benefits of the medication should be discussed with the dying person and those important to them in a balanced discussion, and their views sought. The Committee emphasised that |

the dying person should be involved in decision making as far as possible, and that their preferences should be respected, including those documented in any personalised care plan.

The Committee discussed the need to rationalise the dying person's medications and stop any regular medications that are not providing symptomatic benefit in the last days of life. They wanted to highlight the need to discuss this with the dying person and those important to them before rationalising medication, and explain which medications are not providing symptomatic relief. In their experience, there are some people who do not want to stop regular medications, and it is important to respect these wishes where possible. The Committee noted that polypharmacy may be prevalent for those at the end of life, placing them at high risk of drug-drug and drug-host interactions. Prescribing may also be driven by risk factors and disease guidelines. The medications that the dying person continues to take after rationalising their medication should be considered when prescribing for symptom relief. Please also see Chapter 7 on shared decision making which details the Mental Capacity Act,[4] which may be relevant if the dying person is unconscious or lacks capacity for decision making.

The Committee recognised that there are multiple routes for medications used for symptom relief in the last days of life. They stressed the importance of holding discussions with the dying person and those important to them, and considering the dying person's preferences, when deciding the most effective route for administering medicines in the last days of life .They also noted that the person's condition will also impact on choice, for example, they recognised that in those that can take oral medication this route should be prioritised. The Committee wanted to highlight that the intramuscular route should be avoided if alternative routes are possible, particular in those who are cachexic. The Committee also suggested that in some community settings, where prescribers are not available as readily, it might be of benefit to prescribe alternative routes for administration if, for example, the dying person loses the ability to take oral medication. In addition to subcutaneous or intravenous routes, the Committee discussed other applicable non-oral means, such as topical and sublingual, which may be of particular importance in community settings. In addition, intravenous access in the last days of life was discussed, and the Committee felt that, whilst this can be difficult and distressing to site cannulas in dying adults, if one was already in situ, or intravenous medication was deemed appropriate, this route should be considered.

The Committee also discussed the use of syringe pumps for continuous symptom control, but also noted that, whilst they should be considered, conversely there was discussion about their use "over medicalising" death, and also that some dying people are still able to take oral medication.

Cultural preferences were discussed that may impact on end of life decision making for symptom management, including accepted healthcare practices and remedies and accepted religious and spiritual beliefs. Recommendations on communication and shared decision making should also be taken into consideration, as detailed in Chapters 1 and 7.

Whilst some dying people will already be on medication for symptom control before the last days of the life, the Committee acknowledged that, in people who have not previously been given a medication before, it should be started at the lowest effective dose. The dose should be reviewed regularly and titrated as appropriate. The Committee noted that in these people it is usual practice to prescribe PRN or 'as required' medication, but wanted to highlight that if a dying person is requiring frequent PRN medication, a syringe pump for the medication to be delivered via the subcutaneous route should be considered and discussed with the dying person. The Committee agreed that a syringe pump should be considered if requiring more then 2 - 3 PRN doses within 24 hours.

The Committee also noted that there were contraindications in using some

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| | antiemetics, for example, the use of cyclizine in people with severe heart failure or prokinetics in people with mechanical bowel obstruction.<br>The Committee discussed the need for regular reassessment of a person's symptoms in the last days of life after initiating medication. This assessment should include looking for appropriate symptom control for unwanted sedation and other side effects, such as opioid toxicity. This information should aid the titration of the medication to allow the administration of an appropriate amount for symptom relief without causing unwanted side effects.<br>The Committee discussed engaging a specialist palliative care team early to gain specialist expertise if symptoms do not resolve. This may not require a face to face review but telephone advice may be available including outside of normal working hours. |

# 10 Anticipatory prescribing

## 10.1 Introduction

Uncertainty surrounds recognition of dying and, as with most chronic terminal illnesses, it is difficult to predict when and how death will occur (as discussed in the recognising dying chapter, [Chapter 5]). In all care settings however, it is important to prepare and anticipate symptoms that may arise in order to ensure that the dying person and those important to them do not experience undue distress. Symptoms that occur in the last few hours to days of life include pain, breathlessness, nausea and vomiting, anxiety, agitation, delirium and respiratory secretions. It can be difficult to predict whether an individual in the last few days of life will develop new or changing symptoms and over what period of time.

The need for anticipatory medications and any prescriptions would usually be made within normal working hours by a clinician who is familiar with the dying person. It is the practice of some clinicians to prescribe 4 or 5 medications and these will frequently be in injectable form, as the oral route may not be possible or effective as a person approaches death. They can be used as required or may be prescribed as a 24 hour continuous subcutaneous infusion via a syringe pump.

The anticipatory drugs that have been usually prescribed include:

- an analgesic (for example, morphine or diamorphine)
- an antiemetic or antipsychotic (for example, haloperidol or levomepromazine)
- an anxiolytic (for example, midazolam)
- an anti-secretory agent (for example, hyoscine butylbromide or glycopyrronium).

Other drugs and routes may also be prescribed depending on the person's underlying condition and likelihood of developing certain symptoms. For example, midazolam 10mg intramuscularly or intravenously is often prescribed for a person at risk of massive haemorrhage, tracheal stridor or status epilepticus in order to minimise distress and assist in providing a calm death.

If the person is being cared for in a community setting (for example, at home, in a residential or nursing home or in hospice), the drugs are frequently dispensed and stored nearby (sometimes called a "just in case box"). They are then readily available and can be administered at the bedside as soon as problematic symptoms arise. A nurse or trained carer can thus treat the person quickly in their current place of care without the need for a face-to-face medical review or transfer to a different setting or time lost in securing the prescription.

Although the practice of anticipatory prescribing is believed to have several benefits, the potential disadvantages (and indeed harms) need to be realised. Drugs are sometimes prescribed for ease in a blanket-like fashion on a pre-printed proforma or drug chart rather than being individualised to a person's needs.

One concern raised in the More Care Less Pathway review[30] was injudicious administration and prescription of medication by inexperienced staff, possibly unfamiliar with the person, who may use inappropriate doses or drugs or even incorrectly assess that the person is dying. This may cause harm either by undertreating symptoms or by causing detrimental side effects including hastening a person's death when potentially reversible conditions are missed. Once medications are started it can be difficult to stop them and may require advice from a health care professional experienced in end of life care. Another concern is the potential waste of drugs as any unused medications already dispensed in the community have to be discarded. It is also important to consider the psychological impact of a "just in case box" for the dying person and those important to them, which could be perceived either as anxiety provoking or reassuring depending on the explanation that is proffered by the responsible health care professional. There are undoubtedly risks that need to be weighed up

with the storage of controlled drugs and other drugs of abuse including the possibility of diversion and access and use by unauthorised individuals.

There is no uniform practice across the UK nor is there evidence based guidance about how and when anticipatory prescribing should be initiated, who should receive it, and what drugs should be used. In order to produce initial guidance on anticipatory prescribing in the last few days of life, the Committee felt it was essential to know about the experiences, opinions and attitudes of healthcare professionals, the dying person and those important to them regarding access to anticipatory prescribing.

## 10.2 Review question – quantitative: How effective is anticipatory prescribing at improving comfort in adults in the last days of life compared with prescribing at the bed side?

For this review question both quantitative as well as qualitative evidence was searched for. Information about the beliefs, experiences and opinions of the dying person, those important to them and health care professionals was felt to be important by the Committee. However, given that anticipatory prescribing will include cost implications a quantitative review was also undertaken. Information from this review would be of use to the Committee in considering the economic implications of anticipatory prescribing.

The main characteristics of the quantitative review are highlighted in Table 69. For full details see review protocol in Appendix C.

**Table 69: PICO characteristics of the quantitative review**

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| **Population** | Adults likely to be entering the last days of life, those important to them and healthcare professionals. |
| **Intervention** | Anticipatory prescribing of all necessary medications for symptom relief in the last days of life available in the home, sufficient for use over a weekend (plus bank holidays). |
| **Comparison** | Usual care, for example, prescribing at the bedside. |
| **Outcomes** | Critical outcomes:<br>• Quality of life (as rated by the dying person or those important to them or health care professional).<br>• Control of specific symptoms (agitation, terminal restlessness, breathlessness, pain, nausea and vomiting, respiratory secretions and anxiety).<br><br>Important outcomes:<br>• Subjective ratings from informal carers on quality of care received.<br>• The amount of medication prescribed that is administered.<br>• Incidence of prescribed medication misused<br>• Admissions to hospitals for symptom management. |
| **Study design** | Systematic reviews, randomised controlled trials, non-randomised comparative studies. |

## 10.3 Review question – qualitative: What are the experiences, opinions and attitudes of healthcare professionals, the dying person and those important to them regarding access to anticipatory prescribing?

A summary of the characteristics of the qualitative protocol is provided in Table 70. For full details see review protocol in Appendix C.

**Table 70: Summary of characteristics of the qualitative review question**

| | |
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| **Population and setting** | Healthcare professionals, the dying person and those important to them. |
| **Topic of interest** | Access to anticipatory prescribing of pharmacological treatments for the last days of life. |
| **Context** | **Context**:<br>Anticipatory prescribing in all settings in which NHS care is provided<br><br>**Outcomes**:<br>Themes will be identified from the literature found. |
| **Review strategy** | Study designs to be considered: qualitative studies (for example, interviews, focus groups, observations). A thematic analysis of the data will be conducted and findings presented.<br><br>If any studies include information on advance directives we will extract this information for discussion with the Committee. |

## 10.4 Clinical evidence – quantitative

Comparative quantitative studies were looked for on the effectiveness of anticipatory prescribing compared with usual care (for example, prescribing at the bedside). No studies were identified.

## 10.5 Clinical evidence – qualitative

Qualitative studies were looked for that explore views and experiences of anticipatory prescribing. These could be expressed by the person who is dying or those important to them, as well as by healthcare professionals.

Two studies[34,109] were identified; these are summarised in Table 71 below. All study participants were healthcare professionals. No studies that explored the views of dying people or those important to them were identified.

One study explored the views of a range of healthcare professionals that have experience of caring for dying people in the home setting[34] and 1 study interviewed nurses in both nursing home and community settings.[109] Both studies were set in the UK[34,109] and reported themes relating to barriers and facilitators to access to anticipatory prescribing. Neither study reported themes related to when anticipatory prescribing should be initiated and who should take responsibility for it.

Key findings from these studies are summarised in the clinical evidence summary below. See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, and excluded studies list in Appendix L.

### 10.5.1 Summary of included studies

Table 71 provides a brief summary of the included studies. For further details please refer to Appendix E.

**Table 71: Summary of studies included in the review**

| Study | Design | Population and setting | Research aim | Comments |
|---|---|---|---|---|
| Qualitative studies (including 1:1 interviews, focus groups, partner interviews, semi-structured interviews) | | | | |
| Faull et al., (2013)[34] | Focus groups and individual interviews. | District nurses (n=16), Marie Curie nurses (n=5), GPs (n=22), 'Hospice at Home' nurses (n=4), pharmacists (n=3), community matrons (n=4), specialist palliative care nurse (n=1), nursing home nurse (n=1)<br>UK – Leicestershire, Leicester and Rutland (City Primary Care Trusts, n=7; County Primary Care Trusts, n=47). | To explore the challenges encountered by primary and community health professionals related to anticipatory prescribing when caring for terminally ill people who wish to remain at home to die. | Even though the study focuses on challenges inferences can be made about possible facilitators from the identified themes. |
| Wilson et al., (2015)[109] | Ethnographic study using both 'real life' observations and interviews (individual and small group). | Nurses from 4 community nursing teams (n=42 interviews; and n=43 observations) and nurses from 4 care home teams (n=19 interviews; and n=40 observations)<br>Two UK areas: Lancaster and Cumbria, and Midlands. | To examine nurses' decisions, aims and concerns when using anticipatory prescribing. | Rather than exploring the whole process of anticipatory prescribing the study focusses on the administration of the medication, that is, when the decision has already been made. However, this is directly applicable since it identifies concerns about when to use such medications. |

## Evidence

### 10.5.1.1 Themes and sub-themes derived from the evidence

**Table 72: All themes as reported in the included studies**

| Main theme | Sub-themes |
|---|---|
| Perceived resourcing problems | • Concerns about medication waste<br>• Limited availability of drugs<br>• Lack of syringe pumps |
| Reflections on expertise and experience | • Difficulty in recognising dying<br>• Non-cancer conditions<br>• Knowing what to prescribe<br>• Concerns about accountability |
| Patient factors | • Inability to take oral medication |
| Patient-professional relationship | • Patient-professional relationship |
| Inter-professional relationship | • Relationship between out-of-hours care and usual care<br>• Relationship between community and hospital professionals<br>• Relationship between specialist and generalist teams |
| Concerns about medication | • Range of medication prescribed<br>• Belief anticipatory prescribing hastens death |

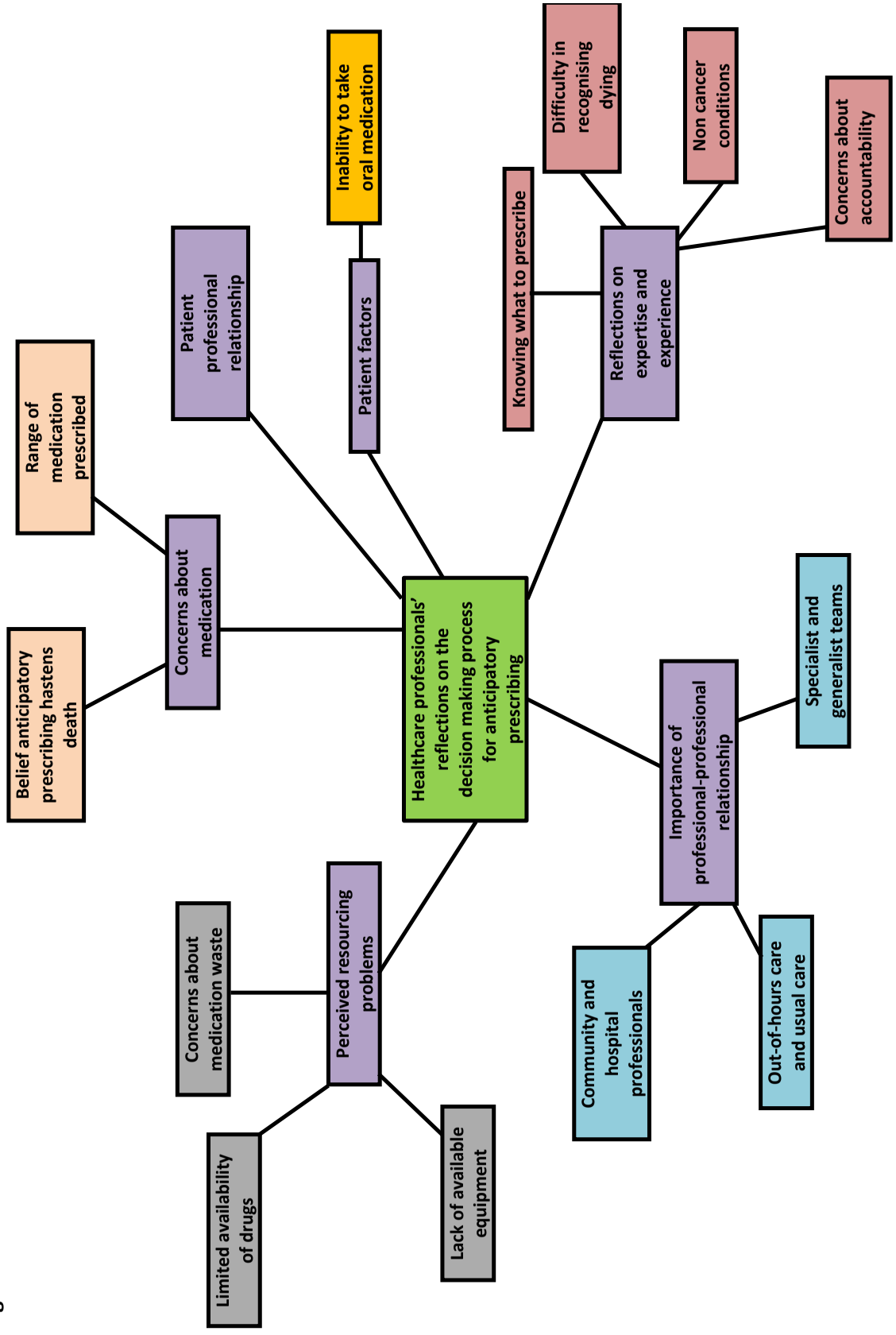


**Figure 6: Themes**

### 10.5.1.2 Evidence summary

**Table 73: Summary of evidence: Theme 1: perceived resourcing problems**

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | | **Criteria** | **Rating** | **Overall** |
| Sub-theme 1:Concerns about medication waste | | | | | |
| 1 | 1 focus group and interview<br>1 ethnographic study | One study[34] interviewed community healthcare professionals in the UK and reported concerns about medication waste that acted as a barrier to access anticipatory prescribing for some dying adults. This was based on their previous experience where previous participants did not require prescribed medications and despite being unused they had to be disposed, creating waste.<br>*"... I personally don't pre-emptively prescribe for every patient. I don't like that policy of 'any patient who you think is in their last few weeks, write them out a prescription for ABCD', you know, because I think it gives rise to a lot of waste because most of them don't need most of the things…"* | Limitations of evidence | No limitations | HIGH |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Very applicable | |
| | | | Theme saturation/sufficiency | Saturated | |
| Sub-theme 2: Limited availability of drugs | | | | | |
| 1 | 1 focus group and interview<br>1 ethnographic study | One study[34] interviewed community healthcare professionals in the UK and reported the difficulty of dispensing medication in the community due to the limited availability of drugs in pharmacies as a barrier to access anticipatory prescribing. One nurse commented this was impacted on by the local PCT not funding a palliative care formulary.<br>*"...every single time I've had to take prescriptions to my local chemist's it's 'next day'- or you can phone round and you have to split the prescription… it can take you hours and hours to sort it out, days even."* | Limitations of evidence | No limitations | HIGH |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Very applicable | |
| | | | Theme saturation/sufficiency | Saturated | |
| Sub-theme 3: Lack of syringe drivers | | | | | |
| 1 | 1 focus group and interview<br>1 ethnographic | One study interviewed[34] community healthcare professionals in the UK and reported lack of equipment, such as syringe pumps, as a barrier to accessing anticipatory prescribing in the community. | Limitations of evidence | No limitations | HIGH |
| | | | Coherence of findings | Coherent | |

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| | study | *"We've been in before where we've actually got pre-emptive drugs in, and gone in and pinched the syringe driver back out and taken it somewhere else because we need it. You know, it's difficult"* | Applicability of evidence | Very applicable | |
| | | | Theme saturation/sufficiency | Saturated | |

**Table 74: Summary of evidence: Theme 2: reflections on expertise and experience**

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | | **Criteria** | **Rating** | **Overall** |
| Sub-theme 1: Difficulty in recognising dying | | | | | |
| 2 | 1 focus group and interview<br>1 ethnographic study | Two UK studies[34,109] with populations of community healthcare professionals reported on the difficulty in recognising dying as a barrier to access anticipatory prescribing. This uncertainty from both nursing staff and GP's was implicated when they initiated anticipatory prescribing and from concerns that this led to some people being under medicated. One GP said:<br>*"… we have talked about how you predict these people, actually there isn't- well if there is we don't know about it- a formula to predict these people, but there just isn't, so it is gut feel."*<br><br>One nurse commented:<br>*"I've been involved in a few cases where… I'm covering the weekend and I've gone in and I've thought 'oh my god, look how ill this person is'. Maybe it was the district nursing team that was going in before or it was a junior nurse that went in a few days before, they can't recognise the signs, they don't realise how poorly these people are."* | Limitations of evidence | Serious limitations | MODERATE |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Very applicable | |
| | | | Theme saturation/sufficiency | Saturated | |
| Sub-theme 2: Non-cancer conditions | | | | | |
| 1 | 1 focus group and interviews | One study[34] interviewed community healthcare professionals in the UK and commented on people with non-cancer conditions being less likely to have access to anticipatory prescribing. They reported this was due to unfamiliarity with the end of life management of these conditions, as well as more uncertainty in recognising that these people were in the final days of life. One nurse commented:<br>*"GP's … accept that cancer patients are dying but with all the other (non-cancer, terminal conditions) the care just isn't there for them… I think it's just the fear of* | Limitations of evidence | No limitations | HIGH |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Very applicable | |
| | | | Theme | Saturated | |

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| | | *prescribing drugs that they don't prescribe that often for that group of patients."* | saturation/sufficiency | | |
| Sub-theme 3:Knowing what to prescribe | | | | | |
| 2 | 1 focus group and interview<br>1 ethnographic study | Two studies[34,109] of community healthcare professions in the UK commented on the uncertainty in knowing what to prescribe as a barrier to successful anticipatory prescribing. This was for a number of reasons including:<br>• inexperience or irregular encounters with anticipatory prescribing by GP's: *"…you know it's not something that is particularly easy, or straightforward to do. You do have to sit down and work it all out, don't you."*<br>• Nurses commented that GP's often focus on current symptoms rather than prescribing medication that will aid common symptoms experienced at the end of life, which can lead to the correct medication not being present at times of need.<br>• A pharmacist commented on uncertainty on what drugs were commonly prescribed, which if known would help with keeping appropriate levels in stock. | Limitations of evidence | Serious limitations | MODERATE |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Very applicable | |
| | | | Theme saturation/sufficiency | Saturated | |
| Sub-theme 4: Concerns about accountability | | | | | |
| 2 | 1 focus group and interview<br>1 ethnographic study | Two studies[34,109] of health care professionals in the UK commented on concerns about accountability acting as a barrier to access to anticipatory prescribing. This was for 2 reasons:<br>• Fear of misuse "*if it happens to be misused… who would take the responsibility? ... At the same time you try and do the best for the patient. Safety has to come first. So where do you draw the line? It's a difficult one!"*<br>• Legal accountability and fears of being accused of overdosing following the Harold Shipman murders *"There is a natural fear of… someone coming along and saying "you overdosed them and killed them!""* | Limitations of evidence | serious limitations | MODERATE |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Very applicable | |
| | | | Theme saturation/sufficiency | Saturated | |

**Table 75: Summary of evidence: Theme 3: patient factors**

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studie** | **Design** | | **Criteria** | **Rating** | **Overall** |

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|---|---|---|---|---|---|
| Sub-theme 1: Inability to take oral medication | | | | | |
| 1 | 1 ethnographic study | One UK study [109] interviewing community, hospice and care home nursing staff reported on the dying persons inability to swallow medication as being important in initiating anticipatory prescribing owing to the fact that anticipatory medications were usually injectable drugs for subcutaneous use. | Limitations of evidence | Serious limitations | MODERATE |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Very applicable | |
| | | | Theme saturation/sufficiency | Saturated | |

**Table 76: Summary of evidence: Theme 4: patient professionals relationship**

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | | **Criteria** | **Rating** | **Overall** |
| Sub-theme 1: Patient-professional relationship | | | | | |
| 2 | 1 focus group and interview<br>1 ethnographic study | Two studies[34,109] interviewing community healthcare professionals in the UK highlighted the patient-professional relationship as important in facilitating access to anticipatory prescribing. A study of nursing staff in multiple community settings commented that knowledge and familiarity with the particular patient and their condition enabled them to initiate anticipatory prescribing. A further study of healthcare professionals commented that having enough contact with people allowed them to develop longer term, trusting relationships which enabled sensitive communication surrounding anticipatory prescribing and provided a way of ensuring that past, present and future treatment was timely and coherent.<br><br>Both studies reported a lack of opportunity to build and maintain patient-professional links contributed to a failure to prescribe sufficiently in advance. A number of factors were mentioned including:<br>Increased concerns over the justification of prescribing decisions and the stress it caused professionals. *"It is very hard to prescribe for someone you don't know… you* | Limitations of evidence | Serious limitations | MODERATE |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Very applicable | |
| | | | Theme saturation/sufficiency | Saturated | |

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| | | *have got responsibilities to your patients, relatives, the GP whose patient is is…."*<br>GP's reported they felt they were less likely to admit their own patients to hospital than those of their colleagues, especially with the confidence that they could review the situation the next day.<br>Difficulty in communicating as unclear of what has previously been discussed with the patient *"It is very difficult to make big decisions about patient's sort of life and death when you have never met them before and you don't know anything about their history and you don't know what their GP has being saying to them and you don't know what the nurses have been saying to them."*<br><br>GP's also reported that an increased relationship with the patient had acted as a barrier to access to anticipatory prescribing as it had raised concerns about placing controlled drugs in a house where there were reasons to think they might be misused. | | | |

**Table 77: Summary of evidence: Theme 5: inter-professional relationship**

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | | **Criteria** | **Rating** | **Overall** |
| Sub-theme 1: Relationship between out-of-hours care and primary care | | | | | |
| 1 | 1 focus group and interview | One study[34] of UK community healthcare professionals reported on the relationship between out of hours care and primary care as a barrier or facilitator to access anticipatory prescribing. This was related to poor information hand over surrounding decision making and care planning which often led to people being admitted to hospitals unnecessarily. One GP reported:<br>*"…one of the issues is that the out of hours computer system is not linked to the normal GP notes, so you know nothing about the patient. What is really helpful is when GPs, if they have somebody with cancer, and they are getting to the terminal stages, is if the GPs actually send information to the out of hours system… because you have got a plan of action there in front of you and you know that's been sort of* | Limitations of evidence | No limitations | HIGH |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Very applicable | |
| | | | Theme saturation/sufficiency | Saturated | |

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| | | *agreed by the patient and their GP… and that nobody is going to come back at you and go 'why didn't you so something?'"*<br><br>However, another GP commented:<br>"*There's a form for general practitioners who know that somebody's nearing the end of life to send to (out of hours service) and it makes no difference."*<br><br>Nursing staff also commented on similar topics of information not being handed over correctly which led to poor patient outcome.<br><br>A trusting relationship between the GP and the nursing staff was also raised as important for access to successful anticipatory prescribing. When this trusting relationship was present, the GP was happier to prescribe larger ranges for the anticipatory prescribing giving nursing staff more flexibility in their administration. | | | |
| Sub-theme 2: relationship between community and hospital professionals | | | | | |
| 1 | 1 focus group and interview | One study[34] of UK community healthcare professionals reported on the relationship between community and hospital healthcare professionals as a challenge to anticipatory prescribing. This was often due to the person having a more 'trusted' relationship with the hospital provider which made it difficult for community providers to change the direction of care and prepare and plan with the patient and family for deterioration. | Limitations of evidence | No limitations | HIGH |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Very applicable | |
| | | | Theme saturation/sufficiency | Saturated | |
| Sub-theme 3: relationship between specialist and generalist teams | | | | | |
| 1 | 1 focus group and interview | One study[34] interviewed community healthcare professionals in the UK and reported on how a poor relationship between specialist and generalist teams in the community can act as a barrier to the access of anticipatory prescribing. They reported many occurrences where their specialist advice had been ignored by community nursing staff and GPs, which they believed was related largely to lack of trust. One nurse commented:<br>*"… the GP said to me 'what would this patient have in the syringe driver' and when I gave a suggestion he said 'I don't think we will go with that'. And he gave something, what I would say was inappropriate and the next day, which was a* | Limitations of evidence | No limitations | HIGH |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Very applicable | |
| | | | Theme saturation/sufficiency | Saturated | |

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| | | *Saturday, it was deemed necessary that this patient needed the drug that I had said the previous day and by the time we got it from the chemist, the patient had died. So it is them getting to know you, it is building up a relationship with your particular GP to the point that they actually trust you really well and trust your judgement. But their experience isn't as up to date probably as ours or the nurses that are using the drugs…"* | | | |

**Table 78: Summary of evidence: Theme 6: concerns about medication**

| Study design and sample | | Descriptors of themes | Quality assessment | | |
|---|---|---|---|---|---|
| **No. of studies** | **Design** | | **Criteria** | **Rating** | **Overall** |
| Sub-theme 1: Ranges of medication | | | | | |
| 2 | 1 focus group and interview<br>1 ethnographic study | Two studies[34,109] of healthcare professionals commented on the range of the medications prescribed and how this both acted as a barrier and a facilitator to successful anticipatory prescribing. Community nursing staff reported that the range of medication allowed them some discretion in providing an appropriate dose. However, some felt that this added a difficult additional responsibility, particularly when looking after a patient who was considered opiate naïve or frail, and that they would prefer to use the lower dose. One nursing staff commented:<br>"*[to err on the] side of caution, yeah, it not always the answer when somebody's needing relief from something, but I do think people absorb, obviously, drugs at different rate, and it's no good bombarding them. It's better to give a small dose and then go back a bit later and you can always give them another small dose and just see."*<br><br>A GP commented on a similar topic, concerned that prescribing a wide range although beneficial when the nursing staff were comfortable with using it, could act as a barrier to adequate analgesia being given:<br>*" …When you have a different nurse going in at night, they were very, very, reluctant to give the dose [of analgesia] that the patient had been having and they would tend to go to the lowest dose on the range, which causes difficulty with pain* | Limitations of evidence | serious limitations | MODERATE |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Very applicable | |
| | | | Theme saturation/sufficiency | Saturated | |

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| | | *control… not knowing the patient, not knowing the family, not knowing me, not knowing the team, and being asked to give what seemed to be a lethal dose of morphine.*" | | | |
| Sub-theme 2: Belief anticipatory prescribing hastens death | | | | | |
| 1 | 1 ethnographic study | One study[109] of UK community nursing staff reported concerns that anticipatory prescribing led to hastening death. This was surrounding the issue of people who are sedated being unable to take oral hydration or nutrition, as well as concern that the medication used to control pain and symptoms hastened death, particularly opioids. *"So I think not I think I don't want to give them too much [diamorphine] because am I hastening things. It's quite scary but you're on your own when you're making those decisions".* | Limitations of evidence | serious limitations | MODERATE |
| | | | Coherence of findings | Coherent | |
| | | | Applicability of evidence | Very applicable | |
| | | | Theme saturation/sufficiency | Saturated | |

## 10.6 Economic evidence

**Published literature**

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

### 10.6.1 Unit costs

Data on what medications should be included for anticipatory prescribing were derived from Lawton et al[55] and audit data taken from the Cambridgeshire Community Services NHS Trust. The medications that can be used for relieving the desired symptoms, shown below, are the ones most consistently used within the 2 studies. When there was an inconsistency as to which drug should be used the cheapest option was chosen. In the study by Lawton et al[55] they found the cost of anticipatory prescribing to be £22.12 per person.

Nurse time is not included in the estimate below as this cost will be incurred regardless of whether anticipatory prescribing is given to the patient.

The table below represents just an example of how much anticipatory prescribing medication could cost as opposed to a definitive estimate. Other medications could replace those shown below but, as shown in previous reviews, cost differences are not significant between drugs.

**Table 79: UK costs of 'Just In Case Boxes'**

| Drug | Use | Supply | Cost | % unused (Lawton) | % unused (CCS audit) | Cost of unused stock (additional cost of anticipatory prescribing) |
|---|---|---|---|---|---|---|
| Midazolam | Agitation and restlessness | 10 mg/2 ml x 5 | £0.80 | 69% | 42% | £0.45 - £0.73 |
| Hyoscine butylbromide | Respiratory secretions | 20 mg/1 ml x 5 | £1.46 | 74% | 94% | £1.08 - £1.37 |
| Morphine sulphate | Pain | 10 mg/1 ml x 5 | £4.68 | 60% | 36% | £1.68 - 2.81 |
| Levomepromazine | Nausea | 25 mg/1 ml x 5 | £10.07 | 75% | 69% | £6.95 - £7.55 |
| Water | Diluent for injections | 10 ml x 10 | £2.45 | 60% | NR | £1.47 |
| Syringe | | 10 ml x 10 | £5.30 | 70% | 60% | £3.19 - £3.68 |
| **Total** | | | **£25.02** | | | **£15.31 - £17.12** |

*Sources: NHS Drug Tariff; eMIT, Lawton (2012), CCS audit*

Below are examples of costs associated with potential unscheduled healthcare utilisation that would arise had the individual not been prescribed anticipatory medicine. The Committee noted that there would also be further costs associated with prescribing emergency medications out of hours.

**Table 80: Cost of unscheduled healthcare utilisation**

| Resource | Description | Cost | Source |
|---|---|---|---|
| GP visit | Based on average patient visit time of 11.7 minutes. Could vary depending on severity of symptoms. | £38 | PSSRU |

| Resource | Description | Cost | Source |
|---|---|---|---|
| Hospital admission | Inpatient specialist palliative care – single episode | £371 | NHS reference costs - 'Inpatient Specialist Palliative Care, 19 years and over' |

## 10.7 Evidence Statements

### Clinical

#### Quantitative review

No clinical evidence was identified comparing anticipatory prescribing with usual care for example, prescribing at the bed side when a symptom occurs.

#### Qualitative review

Qualitative evidence indicated several themes around healthcare professional's experiences, opinions and attitudes on the access to anticipatory prescribing. High quality evidence was identified in 1 qualitative study (n=56) surrounding perceived resourcing problems, including concerns about medication waste, limited availability of drugs, and lack of syringe pumps. Moderate to high quality evidence was obtained from 2 qualitative studies (n=117) reporting on reflections on expertise including difficulty in recognising dying, particularly in people with non-cancer conditions, knowing which drugs to prescribe, and concerns over accountability. Moderate quality evidence was identified in 1 qualitative study (n=61) on a person's inability to take oral medication as a facilitator to anticipatory prescribing. Two qualitative studies (n=116) of moderate quality also reported on the patients professional relationship as a theme and how this could both be a facilitator and barrier to anticipatory prescribing in different instances. High quality evidence from 1 qualitative study (n=56) described how inter-professional relationships can impact on access to anticipatory prescribing including between out of hours care and usual care, community and hospital professionals, and between specialist and generalist teams. Moderate quality evidence from 2 qualitative studies (n=116) was obtained regarding how concerns about anticipatorily prescribing medication, prevented access to it, this included the range of medication prescribed and a belief that the drugs used in anticipatory prescribing hasten death.

No evidence was obtained for the outcome of when anticipatory prescribing should be initiated or who should take responsibility for it. No evidence was obtained that explored the views of dying people or those important to them.

### Economic

- No relevant economic evaluations were identified.

## 10.8 Recommendations and link to evidence

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| **Recommendations** | **67. Use an individualised approach to prescribing anticipatory medicines for people who are likely to need symptom control in the last days of life. Specify the indications for use and the dosage of any medicines prescribed.**<br><br>**68. Assess what medicines the person might need to manage symptoms likely to occur during their last days of life (such as agitation, anxiety, breathlessness, nausea and vomiting, noisy respiratory secretions and** |

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| | **pain). Discuss any prescribing needs with the dying person, those important to them and the multiprofessional team.**<br><br>**69. Ensure that suitable anticipatory medicines and routes are prescribed as early as possible. Review these medicines as the dying person's needs change.**<br><br>**70. When deciding which anticipatory medicines to offer take into account:**<br>• **the likelihood of specific symptoms occurring**<br>• **the benefits and harms of prescribing or administering medicines**<br>• **the benefits and harms of not prescribing or administering medicines**<br>• **the possible risk of the person suddenly deteriorating (for example, catastrophic haemorrhage or seizures) for which urgent symptom control may be needed**<br>• **the place of care and the time it would take to obtain medicines.**<br><br>**71. Before anticipatory medicines are administered, review the dying person's individual symptoms and adjust the individualised care plan and prescriptions as necessary.**<br><br>**72. If anticipatory medicines are administered:**<br>• **Monitor for benefits and any side effects at least daily, and give feedback to the lead healthcare professional.**<br>• **Adjust the individualised care plan and prescription as necessary.** |
| **Relative values of different outcomes** | The Committee agreed that outcomes related to access to anticipatory prescribing in the last days of life were important to this review, particularly when anticipatory prescribing should be initiated and by whom, and concluded that a qualitative review would provide the information needed to answer these questions. The outcomes included the experiences, opinions and attitudes of the dying person, those important to them, and the multiprofessional team involved in their care, as it was felt each population would offer a unique and informative perspective on this topic.<br>The Committee also recognised the potential health economic implications regarding anticipatory prescribing, and felt a quantitative review would provide information to inform recommendations. Evidence regarding comparisons between anticipatory prescribing and reactionary or bedside prescribing was searched for. Critical outcomes included quality of life and control of specific symptoms. Other important outcomes included subjective ratings from informal carers on quality of care received, amount of medication prescribed, administered and misused, and admissions to hospitals for symptom management. These outcomes were agreed by the Committee to be useful in informing recommendations. |
| **Trade-off between clinical benefits and harms** | The qualitative evidence highlighted themes related to access to anticipatory prescribing. These included resourcing problems, expertise and experience, patient factors, patient-professional and inter-professional relationship factors and concerns about medication. There was no quantitative evidence identified. The benefits of good use of anticipatory prescribing were recognised, including facilitating symptom control for the dying person in any setting in a timely fashion. The Committee recognised from the review, potential harms associated with anticipatory prescribing being undertaken, such as over and under medication. They also recognised that not prescribing in advance can cause long waits for medications when the dying person is actively having symptoms that could be managed, requiring hospital admissions, which is often not the preferred place of death for the patient, and a burden on resources. In addition, the Committee noted that anticipatory prescribing is not only a |

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| | community issue; for people already dying in hospital, anticipatory prescribing may allow the multidisciplinary team to prescribe appropriately in-hours, and also reduce delays in getting both the drugs and a prescriber to the dying person when symptoms arise. |
| **Trade-off between net health benefits and resource use** | No economic evaluations were identified that assessed the cost-effectiveness of anticipatory prescribing.<br>Unit costs associated with anticipatory prescribing and the potential downstream cost savings were presented to the Committee. It was recognised that there are many drugs that could be prescribed anticipatorily, but reviews on pharmacological management showed that cost differentials between different drugs treating the same symptom remained mostly small. Therefore the cost of a sample package of anticipatory medication was presented to the Committee under the assumption that, although this wasn't necessarily accurate, the true cost would not be much different. This costing was supplemented by a study picked up in the clinical review search that used audit data to cost a 'just in case box'.<br>Although the cost of the anticipatory medication was found to only be £25.02, a significant portion of this was unused and therefore wasted according to audit data taken from a study by Lawton et al and an audit conducted by Cambridge CCG. The cost of this waste was estimated to be between £15 and £17.<br>The Committee considered potential cost savings that could arise from anticipatory prescribing which ranged from reduced administration time to prevented hospital admissions. The Committee recognised that anticipatory prescribing could potentially cut down time needed by various healthcare professionals including general practitioners and nurses. From a purely cost perspective, the Committee felt that anticipatory prescribing had a good chance of being cost-saving.<br>From a quality of life perspective, the Committee recognised the ways in which anticipatory prescribing could impact quality of life. With anticipatory prescribing the individual would have access to the medication as soon as needed. Without this, the individual would have to wait until they could get the needed medication prescribed. Therefore, there would be quality of life improvements that would arise from reduced time spent in discomfort. Conversely the Committee also recognised that having medication readily available may lead to over or unnecessary use and therefore an increase in adverse effects that can arise from some of the medications.<br>On a whole the Committee recognised that anticipatory prescribing was likely cost-effective but there were concerns about how it could be implemented in the most cost-effective manner, ensuring wastage and adverse outcomes were kept to a minimum. Therefore the Committee felt a research recommendation could help resolve these concerns. |
| **Quality of evidence** | Two qualitative studies identified a number of factors that acted as barriers and facilitators to accessing anticipatory prescribing. These were from the perspective of the healthcare professional only; no themes were identified from the dying person or those important to them. No information on the themes of when anticipatory prescribing should be initiated, and who should be responsible, were found. The quality of the evidence was rated from high to moderate quality; this was due to limitations in the study design. Both were recent UK studies and were direct in context and population to the study population. There were no themes the Committee could identify from their experience that were not picked up in the evidence review, and similarly none of the included themes were felt to be out of place.<br>No quantitative evidence was identified regarding anticipatory prescribing compared to reactive, or at bedside prescribing. No studies that explored the views of dying people or those important to them were identified.<br>The recommendations were based on the evidence identified and the consensus opinion of Committee members. |
| **Other considerations** | The Committee agreed that the appropriate timing for anticipatory prescribing would be at assessment, but highlighted the levels of uncertainty around recognising dying |

as a challenge.

The Committee considered that the drugs being prescribed anticipatorily may include either previous on-going prescriptions or newly prescribed drugs. In light of this, they were keen to ensure that the drugs being prescribed were, first and foremost, appropriate to the individualised anticipated needs of the dying person and not delivered using a proforma approach to prescribing. A proforma approach to prescribing was felt to lead to over medication of people. They recognised that this approach ran the risk that medications may not be available when needed, but overall, they felt that if all the key symptoms were considered around the time of clinical assessment, this risk could be mitigated. The Committee therefore recommended an individualised approach to prescribing.

The Committee discussed the value of having non-specialists or specialists lead prescribing for the dying person covering issues of both competence and confidence to prescribe. Both issues were identified as having an impact on health care professionals' willingness to anticipatorily prescribe medicines at the end of life. However, they chose not to make a recommendation about this, as it relates to service delivery and an evidence review was not conducted in this area.

Written clinical justification would be required as part of any anticipatory prescribing service, with information on the clinical indications for the medication clearly labelled. This was in line with good prescribing practice and, as such, did not form a separate recommendation.

When prescribing alternative routes of administration, the Committee thought it important for clinicians to consider appropriateness given that people may need support that may not be available at home (such as the IV route, which requires access to be inserted and maintained). Additionally, the Committee acknowledged that routes of administration and doses may vary across a person's different symptoms. The oral route would be ideal but is often not possible or effective at the end of life so drugs are usually prescribed in the subcutaneous route (or IV dependent on setting).

The Committee recognised that, potentially, issues could arise if multiple people are responsible for prescribing across 1 team, and also noted that multiple people would also be responsible for monitoring the dying person's drug use and reviewing prescriptions as appropriate to the care setting. The Committee felt that there should be a lead named clinician or a representative to have overall responsibility for prescribing decisions. The lead prescriber should be aware of any anticipatory drugs prescribed and also be informed when they have been administered. It was acknowledged that the prescriber may not necessarily be the lead named clinician, for example, when a person is discharged from hospital with anticipatory drugs, it would be important to inform the GP who may then assume the role of lead prescriber.

The Committee also acknowledged that anticipatory prescribing is a unique situation where the prescribing and administration of drugs are often separated in time and place and this may sit uncomfortably with both parties. It is therefore important that clear communication takes place around the practice of anticipatory prescribing. Because of this, the Committee felt it was important to make a recommendation about communicating changes with the lead healthcare professional to alleviate these concerns.

The Committee was aware of the risk of not having access to drugs when needed, and also the danger of not prescribing enough and failing to anticipate symptoms. They felt it was key to avoid situations where a person is experiencing unmet symptom control. The Committee commented on the difficulties of dispensing drugs from pharmacies, which was also highlighted in the evidence review. In their experience, when prescribing happens at the bed side, this has caused delays (particularly in rural communities) that have led to people being admitted to hospital for symptom management despite this not being their preferred place of death.

The risk of harm to the dying person due to inappropriate prescribing was also highlighted by the Committee. They were concerned that having medications available in the house can also lead to unnecessary administration of drugs that are

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| | sedating. They felt it was important to manage these risks by proper assessment of the dying person in their home.<br>The Committee voiced concerns about the management and monitoring of over-use of drugs, highlighting the possibility of over-medicating the dying. In contrast, other concerns around the under use of drugs were also considered. These anxieties were raised in the evidence review and were noted to act as a barrier to anticipatory prescribing.<br>The Committee recognised the need for feedback to be provided to the lead clinician regarding anticipatory prescribing changes, to ensure that prescribed medications were used in appropriate situations. They discussed the time frame needed for this feedback on the clinical condition to be provided, and decided a time point of daily (at least every 24 hours) was appropriate.<br>Concerns around the waste of medication and disposal of unused drugs were also raised. This causes issues of both resource loss as medication cannot be reissued to other people, as well as the need for pharmacists to dispose of the medication, both creating health economic implications. The Committee discussed how anticipatory prescribing would be monitored across different settings and, once initiated, what an 'exit plan' would entail.<br>The Committee noted some of the challenges when prescribing for opioid abusers or into homes where known opioid abusers also resided. It was felt that this was important to consider particularly when dispensing controlled drugs into the community as it was also noted in the qualitative evidence in the review. They recognised this as a barrier to anticipatory prescribing but felt, in their experience, this was a rare circumstance and as such did not require an individual recommendation. They believed these concerns could be addressed in the individualised decision to anticipatorily prescribe, with a view to minimising risk of controlled drug abuse and, as such, a recommendation was not made.<br>Prison settings were discussed from an equalities perspective as not all prisons include full hospitals and access to pharmacists. The Committee discussed whether separate recommendations for this group should be made. They concluded that all recommendations were applicable in this setting, as people in the last days of life in prison settings were likely to have access to medical care which should provide an individualised assessment, including risk assessment for any appropriate anticipatory prescribing.<br>The Committee discussed the use of anticipatory prescribing for homeless populations, but recognised that if someone was of no fixed abode then the dying person would likely be admitted to hospice or hospital care in the last days of life and, as such, would be engaged with health services.<br>It was discussed that whilst it can be reassuring for relatives and the dying person to have anticipatory drugs in the home setting, it can also be anxiety provoking, prompting concerns about when the drugs will be used and whether the trajectory of symptoms will progress. In this regard, communication with the dying person and carers was discussed and recognised as a key step in anticipatory prescribing being successful in the community. There were also concerns that informal carers may, in some instances, be responsible for administering medication to the dying person, which can cause anxiety. It was noted that injections would normally only be administered by trained nurses but some carers may be trained to administer certain drugs, for example, buccal midazolam in event of catastrophic haemorrhage. The Committee felt this would need to be managed on an individualised basis when formulating a management plan, and if informal carers are reticent, then options including district nursing and community palliative care services can be used.<br>The Committee felt that anticipatory medications for predictable, potentially terminal, events, such as catastrophic bleeds and seizures, should be guided by specialist advice. This includes the use of higher doses of opioids or midazolam intravenously or intramuscularly. The Committee also discussed non-pharmacological interventions (for example, a calming presence, dark towels in haemorrhage) and |

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| | their usefulness in this situation, as there is usually little time to draw up and administer medications. Specific advice should be sought from the relevant specialist. This was not in the scope for this guidance and therefore separate recommendations were not made. |

## 10.9 Research recommendations

4. **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?**
   - **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.**

# 11 Acronyms and abbreviations

| Acronym or abbreviation | Description |
|---|---|
| ACP | Advance care planning |
| ALS | Amyotrophic lateral sclerosis |
| BUN | Blood urea nitrogen |
| COPD | Chronic obstructive pulmonary disease |
| ECOG | Eastern Cooperative Oncology Group |
| ESAS | Edmonton symptom assessment system |
| FACT-G/FACITG | Functional Assessment of Cancer Therapy / Functional Assessment of Chronic Illness Therapy – General Scale |
| IMCA | Independent mental capacity advocate |
| ITU/ICU | Intensive care units |
| LCP | Liverpool care pathway |
| MCA | Mental Capacity Act http://www.legislation.gov.uk/ukpga/2005/9/contents |
| MDAS | Memorial Delirium Assessment Scale |
| MMSE | Mini mental status examination |
| NHSE | National Health Service England |
| NRS | Numeric Pain Rating Scale |
| NuDESC | Nursing delirium screening scale |
| PaP | Palliative prognostic score |
| PPC | Prepared Preferred priorities for care |
| PPI | Palliative prognostic index |
| PPS | Palliative performance scale |
| PSSRU | Personal Social Services Research Unit |
| RASS | Richmond Agitation Sedation Scale |
| VAS | Visual analogue scale |
| WHO | World Health Organisation |

# 12 Glossary

The NICE Glossary can be found at www.nice.org.uk/glossary.

**Clinical**

| Term | Definition |
|---|---|
| 5-HT3 antagonists | Drugs that bind to but do not activate serotonin 5-HT3 receptors, thereby blocking the actions of serotonin. |
| Advance care planning | A voluntary process of discussion about future care between an individual and their care providers, irrespective of discipline. If the individual wishes, their family and friends may be included. An ACP discussion might include:<br>• the individual's concerns and wishes<br>• their important values or personal goals for care<br>• their understanding about their illness and prognosis<br>• their preferences and wishes for types of care or treatment that may be beneficial in the future and the availability of these.<br>(www.endoflifecareforadults.nhs.uk) |
| Advance statement | A written statement that sets down an individual's preferences, wishes, beliefs and values regarding their future care. The aim is to provide a guide to anyone who might have to make decisions in an individual's best interest if they have lost the capacity to make decisions or to communicate them. |
| Advance decision to refuse treatment | An Advance Decision to Refuse Treatment is a set of instructions from an individual to their medical team. It sets out the specific circumstances in which they would:<br>• not want certain treatments<br>• want a particular treatment to be stopped.<br>It is a way of making sure that everyone knows what treatments an individual does not want or what treatments they would want stopped should there ever be a time when they can't make decisions for themselves. |
| Agitation | Excessive, purposeless cognitive and motor activity or restlessness, usually associated with a state of tension or anxiety. |
| Albumin | Water-soluble proteins found in blood, lymph, and other tissues and fluids. |
| Alzheimer's disease | A degenerative disease of the brain characterized by the insidious onset of dementia. Impairment of memory, judgment, attention span, and problem solving skills are followed by severe apraxias and a global loss of cognitive abilities. The condition primarily occurs after age 60, and is marked pathologically by severe cortical atrophy and the triad of senile plaques; neurofibrillary tangles; and neuropil threads. (From Adams et al., Principles of Neurology, 6th ed, pp1049-57) |
| Amyotrophic lateral sclerosis | A degenerative disorder affecting upper motor neurons in the brain and lower motor neurons in the brain stem and spinal cord. Disease onset is usually after the age of 50 and the process is usually fatal within 3 to 6 years. Clinical manifestations include progressive weakness, atrophy, fasciculation, hyperreflexia, dysarthria, dysphagia, and eventual paralysis of respiratory function. pathologic features include the replacement of motor neurons with fibrous astrocytes and atrophy of anterior spinal nerve roots and corticospinal tracts. (From Adams et al., Principles of Neurology, 6th ed, pp1089-94) |
| Analgesia | Medication that acts to relieve pain. |

| Term | Definition |
|---|---|
| Anorexia | The lack or loss of appetite accompanied by an aversion to food and the inability to eat. It is the defining characteristic of the disorder anorexia nervosa. |
| Anticipatory prescribing | Medication prescribed in anticipation of symptoms, designed to enable rapid relief at whatever time the patient develops distressing symptoms. |
| Anticholinergic | Drugs that bind to but do not activate cholinergic receptors, thereby blocking the actions of acetylcholine or cholinergic agonists. |
| Anti-emetics | Drugs used to prevent nausea or vomiting. |
| Antimuscarinic | Drugs that bind to but do not activate muscarinic receptors, thereby blocking the actions of endogenous acetylcholine or exogenous agonists. Muscarinic antagonists have widespread effects including actions on the iris and ciliary muscle of the eye, the heart and blood vessels, secretions of the respiratory tract, GI system, and salivary glands, GI motility, urinary bladder tone, and the central nervous system. |
| Antipsychotic agent | Agents that control agitated psychotic behaviour, alleviate acute psychotic states, reduce psychotic symptoms, and exert a quieting effect. They are used in conditions such as, schizophrenia; senile dementia; transient psychosis following surgery; or myocardial infarction. These drugs are often referred to as neuroleptics alluding to the tendency to produce neurological side effects, but not all antipsychotics are likely to produce such effects. Many of these drugs may also be effective against nausea, emesis, and pruritus. |
| Anti-secretory | Medicine that inhibits or decreases secretion, especially gastric secretion. |
| Antispasmodics | Agents that inhibit the actions of the parasympathetic nervous system. The major group of drugs used therapeutically for this purpose is the muscarinic antagonists. |
| Anuria | Absence of urine formation. It is usually associated with complete bilateral ureteral (ureter) obstruction, complete lower urinary tract obstruction, or unilateral ureteral obstruction when a solitary kidney is present. |
| Anxiety | Feeling or emotion of dread, apprehension, and impending disaster but not disabling as with anxiety disorders. |
| Anxiolytic sedative | A sedative with a direct effect upon anxiety. |
| Apnea | A transient absence of spontaneous respiration. |
| Atropine | A type of antispasmodic. |
| Atypical antipsychotics | Group of antipsychotic drugs used to treat psychiatric conditions. Like typical antipsychotics, they tend to block receptors to the brain's dopamine pathways but are less likely to cause extrapyramidal motor control disabilities. |
| Bicarbonate | Any salt containing the HCO3 anion. |
| Bilirubin | A bile pigment that is a degradation product of haem. |
| Breathlessness | Difficult or laboured breathing. |
| Cachexia | A state of severe weight loss and tissue wasting secondary to underlying disease, for AIDS, example terminal cancer, congestive heart failure or malnutrition. |
| Chemotherapy | The treatment of cancer with anticancer drugs. |
| Cheyne-Stokes respiration | An abnormal pattern of breathing characterized by alternating periods of apnea and deep, rapid breathing. The cycle begins with slow, shallow breaths that gradually increase in depth and rate and is then followed by a period of apnea. The period of apnea can last 5 to 30 seconds, then the cycle repeats every 45 seconds to 3 minutes. |

| Term | Definition |
|---|---|
| Chronic obstructive pulmonary disease | A disease of chronic diffuse irreversible airflow obstruction. Subcategories of COPD include chronic bronchitis and pulmonary emphysema. |
| Clinically assisted hydration | Refers to the practice of providing fluids in the form of a drip, usually either intravenously or subcutaneously (a process known as hypodermoclysis) or via a nasogastric tube or gastrostomy to prevent dehydration. (It does not include assisting a person to drink via the oral route). |
| Comorbidities | The presence of co-existing or additional diseases with reference to an initial diagnosis or with reference to the index condition that is the subject of study. Comorbidity may affect the ability of affected individuals to function and also their survival; it may be used as a prognostic indicator for length of hospital stay, cost factors, and outcome or survival. |
| Corticosteroids | An anti-inflammatory medicine prescribed for a wide range of conditions. They are a man-made version of hormones normally produced by the adrenal glands. Available as tablets, injections, inhalers, lotions, gels or creams. |
| Creatinine | Breakdown product of creatine phosphate in muscle, and is usually produced at a fairly constant rate by the body. |
| Cyanosis | A bluish or purplish discoloration of the skin and mucous membranes due to an increase in the amount of deoxygenated haemoglobin in the blood or a structural defect in the haemoglobin molecule. |
| Death Rattle | See noisy respiratory secretions. |
| Delirium | A disorder characterized by confusion; inattentiveness; disorientation; illusions; hallucinations; agitation; and in some instances autonomic nervous system over activity. It may result from toxic or metabolic conditions or structural brain lesions. (From Adams et al., Principles of Neurology, 6th ed, pp411-2) |
| Delphi | An iterative questionnaire designed to measure consensus among individual responses. In the classic Delphi approach, there is no interaction between responder and interviewer. |
| Dementia | An acquired organic mental disorder with loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning. The dysfunction is multifaceted and involves memory, behaviour, personality, judgment, attention, spatial relations, language, abstract thought, and other executive functions. The intellectual decline is usually progressive, and initially spares the level of consciousness. |
| De-prescribing | The process of tapering, withdrawing, discontinuing or stopping medications to reduce polypharmacy, adverse drug effects and ineffective medication use. |
| Diuretics | Agents that promote the excretion of urine through their effects on kidney function. |
| Dopamine receptor blocker | A drug which blocks dopamine receptors by receptor antagonism. |
| Dying person | This term has been used to describe the person who is dying. It is recognised that there may be uncertainty of whether they are entering the last days of life or are in fact recovering. |
| Dyspnoea | Sudden shortness of breath or breathing difficulty. |
| Eastern Cooperative Oncology Group | A cooperative group in oncology constituting of a large network of private and public medical institutions that designs and conducts cancer research. |
| Emotional state | The state of a person's emotions (especially with regard to pleasure or dejection). |
| End of life | A time frame when people are considered likely to die within the next 12 |

| Term | Definition |
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| | months. This includes people whose death is imminent (expected within a few hours or days) and those with:<br>a) Advanced, progressive, incurable conditions<br>b) General frailty and co-existing conditions that mean they are expected to die within 12 months<br>c) Existing conditions if they are at risk of dying from a sudden acute crisis in their condition<br>Life-threatening acute conditions caused by sudden catastrophic events. |
| Enteral administration | Nutritional support given via the alimentary canal or any route connected to the gastrointestinal system (that is, the enteral route). This includes oral feeding, sip feeding, and tube feeding using nasogastric, gastrostomy, and jejunostomy tubes. |
| Gastrostomy | Creation of an artificial external opening into the stomach for nutritional support or gastrointestinal compression. |
| Glycopyrronium bromide | A type of antimuscarinic. |
| Haemoglobin | The oxygen-carrying proteins of ERYTHROCYTES. They are found in all vertebrates and some invertebrates. The number of globin subunits in the haemoglobin quaternary structure differs between species. Structures range from monomeric to a variety of multimeric arrangements. |
| Haematocrit | The volume percentage of red cells in blood. It is normally 45% for men and 40% for women. |
| Haemorrhage | Blood escaping from the circulatory system. Bleeding can occur internally, where blood leaks from blood vessels inside the body, or externally through a natural opening (mouth, nose, ear, urethra, vagina, anus) or a break in the skin. |
| Hospice | Facilities or services which are especially devoted to providing palliative and supportive care to the patient with a terminal illness and to the patient's family. |
| Hyaluronidase | An enzyme that catalyses the random hydrolysis of 1,4-linkages between N-acetyl-beta-D-glucosamine and D-glucuronate residues in hyaluronate. (From Enzyme Nomenclature, 1992) There has been use as antineoplastic agents to limit neoplasm metastasis. |
| Hyoscine hydrobromide | A type of antimuscarinic. |
| Hypoalbuminemia | A condition in which albumin level in blood (serum albumin) is below the normal range. Hypoalbuminemia may be due to decreased hepatic albumin synthesis, increased albumin catabolism, altered albumin distribution, or albumin loss through the urine (albuminuria). |
| Hyponatremia | Deficiency of sodium in the blood; salt depletion. |
| Hypopharynx | The bottom portion of the pharynx situated below the oropharynx and posterior to the larynx. The hypopharynx communicates with the larynx through the laryngeal inlet, and is also called laryngopharynx. |
| Hypotension | Abnormally low blood pressure that can result in inadequate blood flow to the brain and other vital organs. Common symptom is dizziness but greater negative impacts on the body occur when there is prolonged depravation of oxygen and nutrients. |
| Hyoscine butylbromide | A type of antispasmodic. |
| Hypoxia | A state of reduced oxygen concentration or saturation |
| Individualised care plan | A record of any discussions and decision made for clinical care in the last days of life (not an advance care plan). |
| Intravenously | A method of administration of fluids into a vein |

| Term | Definition |
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| Jejunostomy | Surgical formation of an opening through the abdominal wall into the jejunum, usually for enteral hyperalimentation. |
| Lasting Power of Attorney | A lasting power of attorney (LPA) is a legal document that lets an individual (the 'donor') appoint one or more people (known as 'attorneys') to help them make decisions or to make decisions on their behalf. |
| Liverpool Care Pathway | A care pathway covering palliative care options for people in the final days or hours of life used in the UK (excluding Wales) until July 2014. The pathway has now been withdrawn from use. |
| Mandibular movement | Movements of the lower jaw. |
| Mental Capacity Act | An act designed to protect and empower individuals who may lack the **mental capacity** to make their own decisions about their care and treatment. Under this act, it is possible for adults over 16 years old who may lack mental capacity to be protected by a lasting power of attorney. Only someone with a Lasting Power of Attorney for health and welfare may act as a Decision Maker in England and Wales. The act can be found online at the following link: http://www.legislation.gov.uk/ukpga/2005/9/contents |
| Modified Borg scale | Measures perceived exertion. |
| Multiple organ failure | A progressive condition usually characterized by combined failure of several organs such as the lungs, liver, kidney, along with some clotting mechanisms, usually post injury or postoperative. |
| Multiprofessional care team | All members of the healthcare and social care team that provide care for the dying person, including clinical staff and social care staff in hospital, community and nursing home or residential settings. |
| Myoclonus | Involuntary shock-like contractions, irregular in rhythm and amplitude, followed by relaxation, of a muscle or a group of muscles. This condition may be a feature of some Central nervous system diseases; (for example, epilepsy, and myoclonic). Nocturnal myoclonus is the principal feature of the nocturnal myoclonus syndrome. (From Adams et al., Principles of Neurology, 6th ed, pp102-3). |
| Nausea | An unpleasant sensation in the stomach usually accompanied by the urge to vomit. |
| Nasogastric tube | The insertion of a tube into the stomach, intestines, or other portion of the gastrointestinal tract to allow for the passage of food products. |
| NK1 antagonists | Class of medication that possess unique antidepressant, anxiolytic and antiemetic properties. The discovery was a turning point in the prevention of nausea and vomiting associated with cancer chemotherapy. |
| Noisy respiratory secretions | Secretions within the respiratory tract causing noisy, gurgling respirations in the last hours of life. Sometimes known as the 'death rattle'. |
| NSAIDs | Anti-inflammatory agents that are non-steroidal in nature. In addition to anti-inflammatory actions, they have analgesic, antipyretic, and platelet-inhibitory actions. They act by blocking the synthesis of prostaglandins by inhibiting cyclooxygenase, which converts arachidonic acid to cyclic endoperoxides, precursors of prostaglandins. Inhibition of prostaglandin synthesis accounts for their analgesic, antipyretic, and platelet-inhibitory actions; other mechanisms may contribute to their anti-inflammatory effects. |
| Ocreotide | A potent, long-acting synthetic somatostatin octapeptide analogue that inhibits secretion of growth hormone and is used to treat hormone-secreting tumours; diabetes mellitus; hypotension, orthostatic; hyperinsulinism; hypergastrinemia; and small bowel fistula. |

| Term | Definition |
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| Opioids | Compounds with activity like opiate alkaloids, acting at opioid receptors. Properties include induction of analgesia or narcosis. |
| Oropharyngeal | Relating to the mouth and pharynx. |
| Pain | Highly unpleasant physical sensation caused by illness or injury. |
| Palliative care | Care alleviating symptoms without curing the underlying disease. |
| Pharyngeal and tracheal secretions | Respiratory secretions in the pharynx and trachea |
| Polypharmacy | The use of 4 or more medications. |
| Pulmonary oedema | Excessive accumulation of extravascular fluid in the lung, an indication of a serious underlying disease or disorder. Pulmonary oedema prevents efficient pulmonary gas exchange in the pulmonary alveoli, and can be life-threatening. |
| Pyrexia | An abnormal elevation of body temperature, usually as a result of a pathologic process. |
| Radiotherapy | The use of ionizing radiation to treat malignant neoplasms and some benign conditions. |
| Recognising dying | To understand the key features of the dying phase. |
| Recovery | Recuperation. A return to a normal state of health, mind, or strength. |
| Respiratory cycle | The cycle of inspiration and expiration. |
| Restlessness | A feeling of restlessness associated with increased motor activity. This may occur as a manifestation of nervous system drug toxicity or other conditions. |
| Sedation | A drug-induced depression of consciousness during which people respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway. (From: American Society of Anesthesiologists Practice Guidelines) |
| Shared decision making | A process in which patients, when they reach a decision crossroads in their health care, can review all the treatment options available to them and participate actively with their healthcare professional in making that decision. |
| Somatostatin analogues | Drug which slows down the production of hormones, particularly growth hormone and serotonin. |
| Somnolence | A state of strong desire for sleep, or sleeping for unusually long periods. |
| Stridor | A harsh vibrating noise when breathing, caused by obstruction of the windpipe or larynx |
| Subcutaneously | A method of administering fluid beneath the layers of the skin |
| Sublingually | Below or beneath the tongue. |
| Suction | The removal of secretions, gas or fluid from hollow or tubular organs or cavities by means of a tube and a device that acts on negative pressure. |
| Surrogate decision maker | Healthcare proxies for people who lack capacity. Almost always family members. |
| Syringe pump | Apparatus which is designed to deliver measured amounts of a drug or IV solution through IV injection over time. |
| Tachycardia | Abnormally rapid heartbeat, usually with a heart rate above 100 beats per minute for adults. Tachycardia accompanied by disturbance in the cardiac depolarization (cardiac arrhythmia) is called tachyarrhythmia. |
| Terminal restlessness | Agitated delirium with cognitive impairment occurring at the end of life. |
| Those important to them | The people important to the dying person including family members and anyone else significant as decided by them, such as a partner or close |

| Term | Definition |
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| | friends. |
| Trachea | The cartilaginous and membranous tube descending from the larynx and branching into the right and left main bronchi. |
| Transmucosal | Delivery of a drug or other substance into the body through the epithelium lining of mucous membrane involved with absorption and secretion. |
| Urea | A compound formed in the liver from ammonia produced by the deamination of amino acids. It is the principal end product of protein catabolism and constitutes about one half of the total urinary solids. |
| Vomiting | Ejecting matter from the stomach through the mouth. |
| White blood cell count | The number of white blood cells per unit volume in venous blood. A differential leukocyte count measures the relative numbers of the different types of white cells. |
| ECOG Score | Score and criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.<br>http://ecog-acrin.org/resources/ecog-performance-status |
| WHO Scale | Scale and criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.<br>https://www.nice.org.uk/guidance/ta121/chapter/appendix-c-who-performance-status-classification |

**Methodological**

| Term | Definition |
|---|---|
| Abstract | Summary of a study, which may be published alone or as an introduction to a full scientific paper. |
| Algorithm (in guidelines) | A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows. |
| Allocation concealment | The process used to prevent advance knowledge of group assignment in an RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants. |
| Applicability | How well the results of a study or NICE evidence review can answer a clinical question or be applied to the population being considered. |
| Arm (of a clinical study) | Subsection of individuals within a study who receive 1 particular intervention, for example placebo arm. |
| Association | Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal. |
| Baseline | The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared. |
| Bayesian analysis | A method of statistics, where a statistic is estimated by combining established information or belief (the 'prior') with new evidence (the 'likelihood') to give a revised estimate (the 'posterior'). |
| Before-and-after study | A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs. |
| Bias | Influences on a study that can make the results look better or worse than |

| Term | Definition |
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| | they really are. (Bias can even make it look as if a treatment works when it does not.) Bias can occur by chance, deliberately or as a result of systematic errors in the design and execution of a study. It can also occur at different stages in the research process, for example, during the collection, analysis, interpretation, publication or review of research data. For examples see selection bias, performance bias, information bias, confounding factor, and publication bias. |
| Blinding | A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting people into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias.<br>A single-blinded study is one in which people do not know which study group they are in (for example whether they are taking the experimental drug or a placebo). A double-blinded study is one in which neither patients nor the researchers and doctors know which study group the patients are in. A triple blind study is one in which neither the patients, clinicians or the people carrying out the statistical analysis know which treatment people received. |
| Carer (caregiver) | Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability. |
| Case–control study | A study to find out the cause(s) of a disease or condition. This is done by comparing a group of people who have the disease or condition (cases) with a group of people who do not have it (controls) but who are otherwise as similar as possible (in characteristics thought to be unrelated to the causes of the disease or condition). This means the researcher can look for aspects of their lives that differ to see if they may cause the condition.<br>For example, a group of people with lung cancer might be compared with a group of people the same age that do not have lung cancer. The researcher could compare how long both groups had been exposed to tobacco smoke. Such studies are retrospective because they look back in time from the outcome to the possible causes of a disease or condition. |
| Case series | Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of people. |
| Clinical efficacy | The extent to which an intervention is active when studied under controlled research conditions. |
| Clinical effectiveness | How well a specific test or treatment works when used in the 'real world' (for example, when used by a doctor with a person at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are sometimes called management trials.<br>Clinical effectiveness is not the same as efficacy. |
| Clinician | A healthcare professional who provides patient care. For example, a doctor, nurse or physiotherapist. |
| Cochrane Review | The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration). |
| Cohort study | A study with 2 or more groups of people – cohorts – with similar characteristics. One group receives a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens. See also observational study. |
| Comorbidity | A disease or condition that someone has in addition to the health problem |

| Term | Definition |
|---|---|
| | being studied or treated. |
| Comparability | Similarity of the groups in characteristics likely to affect the study results (such as health status or age). |
| Concordance | This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence. |
| Confidence interval (CI) | There is always some uncertainty in research. This is because a small group of people are studied to predict the effects of a treatment on the wider population. The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population.<br>The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150.<br>A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment – often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied). |
| Confounding factor | Something that influences a study and can result in misleading findings if it is not understood or appropriately dealt with.<br>For example, a study of heart disease may look at a group of people that exercises regularly and a group that does not exercise. If the ages of the people in the 2 groups are different, then any difference in heart disease rates between the 2 groups could be because of age rather than exercise. Therefore age is a confounding factor. |
| Consensus methods | Techniques used to reach agreement on a particular issue. Consensus methods may be used to develop NICE guidance if there is not enough good quality research evidence to give a clear answer to a question. Formal consensus methods include Delphi and nominal group techniques. |
| Control group | A group of people in a study who do not receive the treatment or test being studied. Instead, they may receive the standard treatment (sometimes called 'usual care') or a dummy treatment (placebo). The results for the control group are compared with those for a group receiving the treatment being tested. The aim is to check for any differences.<br>Ideally, the people in the control group should be as similar as possible to those in the treatment group, to make it as easy as possible to detect any effects due to the treatment. |
| Cost-effectiveness analysis (CEA) | Cost-effectiveness analysis is one of the tools used to carry out an economic evaluation. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which life is extended as a result of the intervention). |
| Cost–utility analysis (CUA) | Cost–utility analysis is one of the tools used to carry out an economic evaluation. The benefits are assessed in terms of both quality and duration of life, and expressed as quality-adjusted life years (QALYs). See also utility. |
| Credible interval (CrI) | The Bayesian equivalent of a confidence interval. |
| Deterministic analysis | In economic evaluation, this is an analysis that uses a point estimate for each input. In contrast, see Probabilistic analysis |

| Term | Definition |
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| Diagnostic odds ratio | The diagnostic odds ratio is a measure of the effectiveness of a diagnostic test. It is defined as the ratio of the odds of the test being positive if the subject has a disease relative to the odds of the test being positive if the subject does not have the disease. |
| Disutility | The loss of quality of life associated with having a disease or condition. See Utility |
| Dominance | A health economics term. When comparing tests or treatments, an option that is both less effective and costs more is said to be 'dominated' by the alternative. |
| Drop-out | A participant who withdraws from a trial before the end. |
| Economic evaluation | An economic evaluation is used to assess the cost effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits – health effects – relative to the resources available. It should be used to inform and support the decision-making process; it is not supposed to replace the judgement of healthcare professionals.<br>There are several types of economic evaluation: cost–benefit analysis, cost–consequences analysis, cost-effectiveness analysis, cost–minimisation analysis and cost–utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention. |
| Effect<br>(as in effect measure, treatment effect, estimate of effect, effect size) | A measure that shows the magnitude of the outcome in 1 group compared with that in a control group.<br>For example, if the absolute risk reduction is shown to be 5% and it is the outcome of interest, the effect size is 5%.<br>The effect size is usually tested, using statistics, to find out how likely it is that the effect is a result of the treatment and has not just happened by chance (that is, to see if it is statistically significant). |
| Effectiveness | How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care. |
| Efficacy | How beneficial a test, treatment or public health intervention is under ideal conditions (for example, in a laboratory), compared with doing nothing or opting for another type of care. |
| EQ-5D (EuroQol 5 dimensions) | A standardised instrument used to measure health-related quality of life. It provides a single index value for health status. |
| Evidence | Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals or patients). |
| Exclusion criteria (literature review) | Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence. |
| Exclusion criteria (clinical study) | Criteria that define who is not eligible to participate in a clinical study. |
| Extrapolation | An assumption that the results of studies of a specific population will also hold true for another population with similar characteristics. |
| Follow-up | Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables. |
| Generalisability | The extent to which the results of a study hold true for groups that did not participate in the research. See also external validity. |
| Gold standard | A method, procedure or measurement that is widely accepted as being the |

| Term | Definition |
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| | best available to test for or treat a disease. |
| GRADE, GRADE profile | A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile. |
| Harms | Adverse effects of an intervention. |
| Health economics | Study or analysis of the cost of using and distributing healthcare resources. |
| Health-related quality of life (HRQoL) | A measure of the effects of an illness to see how it affects someone's day-to-day life. |
| Heterogeneity<br>or Lack of homogeneity | The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity. |
| Imprecision | Results are imprecise when studies include relatively few people and few events and thus have wide confidence intervals around the estimate of effect. |
| Inclusion criteria (literature review) | Explicit criteria used to decide which studies should be considered as potential sources of evidence. |
| Incremental analysis | The analysis of additional costs and additional clinical outcomes with different interventions. |
| Incremental cost | The extra cost linked to using 1 test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently. |
| Incremental cost-effectiveness ratio (ICER) | The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for 1 treatment compared with another. |
| Indirectness | The available evidence is different from the review question being addressed, in terms of PICO (population, intervention, comparison and outcome). |
| Intention-to-treat analysis (ITT) | An assessment of the people taking part in a clinical trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully complied with the treatment or switched to an alternative treatment. Intention-to-treat analyses are often used to assess clinical effectiveness because they mirror actual practice: that is, not everyone complies with treatment and the treatment people receive may be changed according to how they respond to it. |
| Intervention | In medical terms this could be a drug treatment, surgical procedure, diagnostic or psychological therapy. Examples of public health interventions could include action to help someone to be physically active or to eat a more healthy diet. |
| Kappa statistic | A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance. |
| Lasting power of attorney | A lasting power of attorney (LPA) is a legal document that lets individuals (the 'donor') appoint one or more people (known as 'attorneys') to help them make decisions or to make decisions on their behalf. This gives more control over what happens to them if, for example, they have an accident or an illness and can't make decisions at the time they need to be made (they 'lack mental capacity'). There are 2 types: 'health and welfare' and 'property and financial affairs'. 'Health and welfare' is of relevance in the |

| Term | Definition |
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| | context of this guideline document. |
| Length of stay | The total number of days a participant stays in hospital. |
| Licence | See 'Product licence'. |
| Life years gained | Mean average years of life gained per person as a result of the intervention compared with an alternative intervention. |
| Likelihood ratio | The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a person would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by (1 minus specificity). |
| Long-term care | Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes. |
| Logistic regression or Logit model | In statistics, logistic regression is a type of analysis used for predicting the outcome of a binary dependent variable based on 1 or more predictor variables. It can be used to estimate the log of the odds (known as the 'logit'). |
| Loss to follow-up | A person, or the proportion of people, actively participating in a clinical trial at the beginning, but whom the researchers were unable to trace or contact by the point of follow-up in the trial |
| Meta-analysis | A method often used in systematic reviews. Results from several studies of the same test or treatment are combined to estimate the overall effect of the treatment. |
| Multivariate model | A statistical model for analysis of the relationship between 2 or more predictor (independent) variables and the outcome (dependent) variable. |
| Number needed to treat (NNT) | The average number of people who need to be treated to get a positive outcome. For example, if the NNT is 4, then 4 people would have to be treated to ensure 1 of them gets better. The closer the NNT is to 1, the better the treatment.<br>For example, if you give a stroke prevention drug to 20 people before 1 stroke is prevented, the number needed to treat is 20. See also number needed to harm, absolute risk reduction. |
| Observational study | Individuals or groups are observed or certain factors are measured. No attempt is made to affect the outcome. For example, an observational study of a disease or treatment would allow 'nature' or usual medical care to take its course. Changes or differences in 1 characteristic (for example, whether or not people received a specific treatment or intervention) are studied without intervening.<br>There is a greater risk of selection bias than in experimental studies. |
| Odds ratio | Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in 1 group with the probability of the same thing in another.<br>An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease, or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group.<br>Sometimes probability can be compared across more than 2 groups – in this case, 1 of the groups is chosen as the 'reference category', and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked out for |

| Term | Definition |
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| | occasional smokers compared with non-smokers and for regular smokers compared with non-smokers. See also confidence interval, relative risk, risk ratio. |
| Opportunity cost | The loss of other healthcare programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention. |
| Outcome | The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public's health could include changes in knowledge and behaviour related to health, societal changes (for example, a reduction in crime rates) and a change in people's health and wellbeing or health status. In clinical terms, outcomes could include the number of people who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins. |
| P value | The p value is a statistical measure that indicates whether or not an effect is statistically significant.<br>For example, if a study comparing 2 treatments found that 1 seems more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant.<br>If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be. |
| Placebo | A fake (or dummy) treatment given to participants in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to participants in the experimental group). The aim is to determine what effect the experimental treatment has had – over and above any placebo effect caused because someone has received (or thinks they have received) care or attention. |
| Polypharmacy | The use or prescription of multiple medications. |
| Posterior distribution | In Bayesian statistics this is the probability distribution for a statistic based after combining established information or belief (the prior) with new evidence (the likelihood). |
| Power (statistical) | The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed. |
| Pre-test probability | In diagnostic tests: The proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may depend on how a disorder is diagnosed. |
| Prevalence | See Pre-test probability. |
| Prior distribution | In Bayesian statistics this is the probability distribution for a statistic based on previous evidence or belief. |
| Primary care | Healthcare delivered outside hospitals. It includes a range of services provided by GPs, nurses, health visitors, midwives and other healthcare professionals and allied health professionals such as dentists, pharmacists and opticians. |

| Term | Definition |
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| Primary outcome | The outcome of greatest importance, usually the 1 in a study that the power calculation is based on. |
| Product licence | An authorisation from the MHRA to market a medicinal product. |
| Prognosis | A probable course or outcome of a disease. Prognostic factors are person or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes. |
| Prospective study | A research study in which the health or other characteristic of participants is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies. |
| Publication bias | Publication bias occurs when researchers publish the results of studies showing that a treatment works well and don't publish those showing it did not have any effect. If this happens, analysis of the published results will not give an accurate idea of how well the treatment works. This type of bias can be assessed by a funnel plot. |
| Quality of life | See 'Health-related quality of life'. |
| Quality-adjusted life year (QALY) | A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health.<br>QALYS are calculated by estimating the years of life remaining for a person following a particular treatment or intervention and weighting each year with a quality of life score (on a scale of 0 to 1). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance. |
| Randomisation | Assigning participants in a research study to different groups without taking any similarities or differences between them into account. For example, it could involve using a random numbers table or a computer-generated random sequence. It means that each individual (or each group in the case of cluster randomisation) has the same chance of receiving each intervention. |
| Randomised controlled trial (RCT) | A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug or treatment. One group (the experimental group) receives the treatment being tested; the other (the comparison or control group) receives an alternative treatment, a dummy treatment (placebo) or no treatment at all. The groups are followed up to see how effective the experimental treatment was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias. |
| RCT | See 'Randomised controlled trial'. |
| Receiver operated characteristic (ROC) curve | A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 minus specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal. |
| Reference standard | The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the 1 that is routinely used in practice. |
| Relative risk (RR) | The ratio of the risk of disease or death among those exposed to certain conditions compared with the risk for those who are not exposed to the same conditions (for example, the risk of people who smoke getting lung cancer compared with the risk for people who do not smoke).<br>If both groups face the same level of risk, the relative risk is 1. If the first group had a relative risk of 2, subjects in that group would be twice as |

| Term | Definition |
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| | likely to have the event happen. A relative risk of less than 1 means the outcome is less likely in the first group. Relative risk is sometimes referred to as risk ratio. |
| Reporting bias | See 'Publication bias'. |
| Resource implication | The likely impact in terms of finance, workforce or other NHS resources. |
| Retrospective study | A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected. |
| Review question | In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations. |
| Secondary outcome | An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes. |
| Selection bias | Selection bias occurs if:<br>a) The characteristics of the people selected for a study differ from the wider population from which they have been drawn, or<br>b) There are differences between groups of participants in a study in terms of how likely they are to get better. |
| Sensitivity | How well a test detects the thing it is testing for.<br>If a diagnostic test for a disease has high sensitivity, it is likely to pick up all cases of the disease in people who have it (that is, give a 'true positive' result). But if a test is too sensitive it will sometimes also give a positive result in people who don't have the disease (that is, give a 'false positive').<br>For example, if a test were developed to detect if a woman is 6 months pregnant, a very sensitive test would detect everyone who was 6 months pregnant, but would probably also include those who are 5 and 7 months pregnant.<br>If the same test were more specific (sometimes referred to as having higher specificity), it would detect only those who are 6 months pregnant, and someone who was 5 months pregnant would get a negative result (a 'true negative'). But it would probably also miss some people who were 6 months pregnant (that is, give a 'false negative').<br>Breast screening is a 'real-life' example. The number of women who are recalled for a second breast screening test is relatively high because the test is very sensitive. If it were made more specific, people who don't have the disease would be less likely to be called back for a second test but more women who have the disease would be missed. |
| Significance (statistical) | A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$). |
| Specificity | The proportion of true negatives that are correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases correctly diagnosed as non-cases.<br>See related term 'Sensitivity'.<br>In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers. |
| Stakeholder | An organisation with an interest in a topic that NICE is developing a clinical guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scope and the draft guidance. Stakeholders may be:<br>• manufacturers of drugs or equipment |

| Term | Definition |
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| | • national patient and carer organisations<br>• NHS organisations<br>• organisations representing healthcare professionals. |
| Systematic review | A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. It may include a meta-analysis. |
| Treatment allocation | Assigning a participant to a particular arm of a trial. |
| Univariate | Analysis which separately explores each variable in a data set. |
| Utility | In health economics, a 'utility' is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost–utility analysis is the quality-adjusted life year, but other measures include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs). |

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