The Clinical Management of Cancer-Related Hypercalcaemia

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Summary of Main Recommendations

Clinical assessment of hypercalcaemia

- Hypercalcaemia is the most common life-threatening metabolic disorder associated with malignancy, occurring primarily in patients with more advanced disease, and is generally indicative of a poor prognosis.[1]
- Clinical assessment of the patient is crucial in determining whether treatment of hypercalcaemia is appropriate. In general a decision to treat should be motivated by the patient's symptomatology rather than the absolute calcium level. The main goal of treatment is to improve clinical symptoms.[2, 3]
- Symptoms of hypercalcaemia include: fatigue, weakness, constipation, nausea, vomiting, polyuria, polydipsia, cardiac arrhythmias, delirium, drowsiness and coma.[1] The severity of symptoms correlates more closely with the **rate** of increase in calcium rather than the actual calcium level.[7]
- It may not be appropriate to treat cancer-related hypercalcaemia in a patient who is thought to be in the last hours or days of life.[13]

Rehydration and discontinuation of other drugs

- The patient should be rehydrated with 1-3 litres of parenteral sodium chloride 0.9% over 24 to 48 hours prior to the administration of bisphosphonates.[4, 5, 16, 18, 20]
- The volume and rate of fluid replacement should be adjusted in each patient depending on: age, severity of hypercalcaemia, degree of dehydration and the ability of the cardiovascular system to tolerate rehydration.[4, 5, 16, 18, 20]
- Rehydration may reduce serum calcium levels (and in some cases normalise serum calcium), but this response may be of short duration and hypercalcaemia often recurs.[18, 20]
- Medications which reduce renal blood flow or renal calcium excretion should be discontinued/avoided where appropriate e.g. non-steroidal anti-inflammatory agents and thiazide diuretics.[3, 9, 13]

Bisphosphonates and side effects

- Bisphosphonates are synthetic analogues of pyrophosphate and those most commonly used to treat cancer-related hypercalcamia in clinical practice are zoledronic acid, pamidronate and ibandronate.[5]
- Side effects of bisphosphonates include: hypocalcaemia[2, 34, 35], deterioration in renal function,[36] transient pyrexia,[4, 21, 22] osteonecrosis of the jaw,[15, 35-38] atypical femoral fracture and osteonecrosis of the external auditory canal.[39,41]

Monitoring of hypercalcaemia

- Corrected calcium levels should be rechecked 7-10 days after the bisphosphonate infusion.[3, 35, 38, 42]
- Calcium levels should be rechecked every 3-4 weeks or when symptoms of hypercalcaemia occur.[43]

Role of other agents available in the treatment of hypercalcaemia

- Calcitonin should only be used in exceptional circumstances when the corrected calcium level is extremely high and there is a clinical indication for the rapid reduction of the serum calcium level e.g. symptomatic cardiac arrhythmias.[2, 4, 44, 45]
- The role of corticosteroids in severe hypercalcaemia is confined to haematological tumours that respond to the cytostatic effects of steroids.[4, 46-48]
- Denosumab should be considered for the management of resistant or recurrent hypercalcaemia of malignancy where repeated treatment with bisphosphonates fails to normalise the serum calcium. It may potentially be useful in patients with renal impairment who may not be able to be treated with bisphosphonates.[4, 49, 50]

Section 1: Introduction

- The normal range for serum corrected calcium or albumin-adjusted calcium is 2.2-2.6mmol/l.[1]

- Most laboratories now give corrected calcium results. An uncorrected calcium level may be adjusted for the serum albumin using the following formula:

  Adjusted calcium (mmol/l) = Total calcium + 0.02(40-serum albumin).[1, 2]

- Correction of calcium is particularly important in patients with cancer who often have low albumin levels. In such patients the corrected calcium is a better indicator of free physiologically active (ionised) calcium than the total calcium level.[4, 5]

- Hypercalcaemia is the most common life-threatening metabolic disorder associated with malignancy, occurring in approximately 10-30% of patients with cancer. It occurs primarily in those with more advanced disease and is generally indicative of a poor prognosis.[1-3, 6-12]

- In the past it was thought that tumour-associated hypercalcaemia only occurred in patients with bone metastases and resulted from either the osteolytic process at the site of a bone metastasis or was due to release of parathyroid hormone related protein (PTHrP) and possibly tumour growth factors from the tumour cells [4, 7] It is now known that most cases of cancer-associated hypercalcaemia are due to the release of PTHrP from the underlying malignancy, including patients without bone metastases. The diagnosis of hypercalcaemia should be considered in all patients with cancer, including those who do not have bone metastases[5] [2, 8]

- Symptoms of hypercalcaemia include: fatigue, weakness, constipation, nausea, vomiting, polyuria, polydipsia, cardiac arrhythmias, delirium, drowsiness and coma.[1, 5, 8, 12-15] The severity of symptoms correlates more closely with the rate of increase in calcium rather than the actual level.[7, 14, 16, 17]

- Treatment of hypercalcaemia includes rehydration [8, 18, 19] and the use of bisphosphonates.[6, 9, 21-33]

- Hypercalcaemic patients are dehydrated and sodium depleted. Rehydration with parenteral sodium chloride 0.9% should always be the first line management. This may improve some symptoms and may reduce calcium levels by 0.4-0.6mmol/l.[14] It has three main effects:
  - Replaces lost sodium
  - Increases the glomerular filtration rate and circulating volume
  - Promotes urinary calcium excretion[10, 18. 2-6, 8,10 11]

- Sodium chloride 0.9% should be used in preference to dextrose as the reabsorption of calcium in the proximal convoluted tubule is linked with that of sodium, hence sodium chloride produces a more effective calcium diuresis.[2]

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- Bisphosphonates are synthetic analogues of pyrophosphate and may be highly effective in the treatment of hypercalcaemia of malignancy. [6, 11, 21-33] They inhibit bone resorption but have no effect on renal tubular calcium reabsorption.[14]

- Disodium pamidronate was the initial drug of choice for cancer-related hypercalcaemia when bisphosphonates first became available.[21, 23, 38, 40] Zoledronic acid is a newer aminobisphosphonate which is also licensed for the treatment of cancer-related hypercalcaemia.[22, 26, 35] Studies have shown it to be superior to pamidronate with a more rapid onset and a longer duration of action.[17, 34] Ibandronic acid is a third generation bisphosphonate which appears to have a better renal profile.[29-31, 37] Other bisphosphonates include Clodronate,[12, 32, 33] Etidronate[25] and Alendronate.[28] Local policies may govern which bisphosphonate is available for clinical use.

- Side effects of bisphosphonates include: a transient rise in body temperature, renal toxicity, osteonecrosis of the jaw, asymptomatic hypocalcaemia, rarely ocular toxicity (uveitis and scleritis), atypical femoral fracture and osteonecrosis of the external auditory canal.[4, 10, 35-39, 41]

- Denosumab is a human monoclonal antibody that binds to the receptor activator of nuclear factor-κB ligand (RANKL) which is essential for differentiation, function and survival of osteoclasts. Denusomab has high affinity and specificity for RANKL and by preventing it from binding to the RANK receptor on osteoclasts it reduces osteoclast-mediated bone resorption. Randomised controlled trials have shown it to be more effective than zoledronic acid in preventing skeletal-related events in patients with bone metastases from breast and prostate cancer and other solid tumours. Recent small trials have shown that Denosumab is effective in lowering corrected calcium levels in patients with hypercalcaemia that has recurred after, or is resistant to,bisphosphonate treatment.[4, 49, 50]

- Denusomab is administered as a subcutaneous injection. Side-effects include osteonecrosis of the jaw, dyspnoea and diarrhoea.[4, 51] It does not cause renal toxicity. The medication is more expensive than bisphosphonate therapy.[7, 52, 53] Further economic review is warranted. Please see Applications and Implications section.

Section 2: Scope and Purpose

- The following guideline is an update of the *Guidelines for the Treatment of Cancer Associated Hypercalcaemia* developed in 1995 and reviewed in 2009.[54]
- This guideline aims to support healthcare professionals to develop a plan of care for the clinical management of cancer-related hypercalcaemia in adults.
- This guideline may be used by practitioners who care for patients with cancer in different care settings including doctors, nurses and pharmacists. It is also a source of information for people with cancer-related hypercalcaemia and those important to them.

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Table 1 summarises the scope and purpose of this guideline.

Table 1: Scope of guideline	
Population	• Adults with incurable cancer-related hypercalcaemia.
Populations not covered	• Under 18 years of age and not likely to die from an incurable, advanced illness
Healthcare setting	• People in their usual place of residence • Primary and community care • Secondary and tertiary care including acute hospital and mental health trusts • Hospice care
Topics	• Use of bisphosphonates to manage cancer-related hypercalcaemia and associated symptoms • Use of clinically assisted hydration to manage cancer-related hypercalcaemia and symptoms • Monitoring of hypercalcaemia following treatment • Management of treatment resistant hypercalcaemia • Management of recurrent hypercalcaemia • Role of other medications in the management of hypercalcaemia
Topics not covered	• Management of non cancer-related hpercalcaemia.

Section 3: Methods

The guideline is based on the AGREE II criteria, which may be found in the Cheshire and Merseyside Palliative and End of Life Care Network Audit Group (CMPCNAG) Guideline Development Manual.[55]

3.1 Clinical Questions & Interventions

Clinical questions were derived from the previous guideline published in 1995 and reviewed in 2009. The questions were initially framed by delegates attending the CMPCNAG Review meeting on 3rd March 2015 and refined at a meeting of the Guideline Development Group on 15th September 2015. The clinical question used to guide the literature review in PICO (Patient, Intervention, Control, and Outcome) format is:

- What evidence exists in the literature for the appropriate clinical management strategy for cancer-related hypercalcaemia in adults?

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3.1.1 Outcomes

To provide safe, timely and effective medication to improve the management of cancer-related hypercalcaemia and to review:

- Effective management of *symptoms* attributable to cancer-related hypercalcaemia.
- Differences in survival between those with appropriately treated cancer-related hypercalcaemia compared to those who are not treated.
- Success in normalising hypercalcaemia.
- Time to recurrent and re-retreatment of hypercalcaemia.

3.2 Literature Search

Systematic electronic database searches were done to find potentially relevant articles. PubMED, EMBASE (Scopus), CINAHL and Cochrane databases were searched in September 2015. A full outline of the search strategy, results and appraisal of evidence can be found in Appendix 1. Grading of the levels of evidence and recommendations follows the Cheshire and Merseyside Palliative and End of Life Care Network Audit Group Guideline Development Manual and uses SIGN criteria.[55]

Section 4: Guideline Recommendations

4.1 Clinical assessment of hypercalcaemia

- Clinical assessment of the patient is crucial in determining whether treatment of hypercalcaemia is appropriate. Generally a decision to treat should be motivated by the patient's symptomatology rather than absolute calcium level. The most important goal of treatment is to improve clinical symptoms.[2, 3, 7, 53] [Level 4]
- It may not be appropriate to treat cancer-related hypercalcaemia in a patient who is judged to be in the last days or hours of life.[12, 13] If a decision not to treat cancer-related hypercalcaemia is made this should be clearly recorded in the case notes and communicated to the patient and/or those close to them where this is possible. [Level 4]

4.2 Rehydration and discontinuation of other drugs

- The patient should be rehydrated with 1-3 litres of parenteral sodium chloride 0.9% over 24 to 48 hours before the administration of bisphosphonates. The volume and rate of fluid replacement should be adjusted in each patient according to age, severity of hypercalcaemia, degree of dehydration and the ability of the cardiovascular system to tolerate rehydration.[4, 5, 16, 18, 20] [Level 4]

- Medications which reduce renal blood flow or renal calcium excretion should be discontinued or avoided where appropriate e.g. non-steroidal anti-inflammatory agents and thiazide diuretics.[3, 9, 13] If a diuretic is needed, a loop diuretic such as furosemide, which inhibits the reabsorption of calcium and sodium in the ascending limb of the loop of Henle, is the drug of choice.[3, 14, 16, 56] However there

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is little evidence of benefit and diuretic use may exacerbate hypovolaemia, hypokalaemia and hypomagnesaemia.[56] [Level 4]

- Some local clinical guidelines advocate initial parenteral rehydration and rechecking of the serum calcium prior to further treatment. It is important to note that although rehydration may achieve a reduction in the serum calcium level (and in some cases normalise serum calcium), this response may be of short duration and studies demonstrate that hypercalcaemia often recurs.[15, 18, 20] [Level 3]

4.3 Bisphosphonates

- Please see Table 2 and Table 3 for details of the bisphosphonates available. Local policies will govern which bisphosphonate is used.

4.3.1 Side effects of bisphosphonates

- Renal toxicity has been associated with bisphosphonate treatment and may be manifested as deterioration in renal function or renal failure.[36] Monitoring of renal function is recommended.[3, 14, 34-38, 42] Ibandronate has a better renal profile and may be the bisphosphonate of choice for patients with moderate renal failure or if nephrotoxic medications are being used concomitantly.[30, 37, 57] [Level 4] If renal impairment is secondary to hypercalcaemia, renal function may improve as the calcium level reduces.[3, 14] [Level 4]
- If symptomatic or severe hypocalcaemia occurs post bisphosphonate therapy, then short-term supplemental calcium therapy may be required. Patients who have undergone thyroid or parathyroid surgery may be particularly susceptible to developing hypocalcaemia due to relative hypoparathyroidism.[35] When bisphosphonates are administered with aminoglycosides and/or loop diuretics, caution is advised as both drugs can lower the calcium and magnesium levels for long periods.[2, 14, 34, 35] [Level 4]
- In aspirin-sensitive patients, treatment with bisphosphonates has been associated with bronchospasm so caution is recommended in this group of patients.[16, 34] [Level 4]
- Transient pyrexia has been reported in up to 30% of patients receiving bisphosphonates.[4, 21, 22] [Level 3]
- Atypical femoral fractures have been reported rarely with bisphosphonate treatment, mainly in patients receiving long-term treatment for osteoporosis. Patients should be advised to report any thigh, hip, or groin pain during treatment with a bisphosphonate. Discontinuation of bisphosphonate treatment in patients suspected to have an atypical femoral fracture should be considered after an assessment of the benefits and risks of continued treatment.[39] (see Guideline on the Management of Pathological Fractures [70]) [Level 4]

- Osteonecrosis of the jaw has been reported in patients receiving bisphosphonates.[15, 17, 35-38] (See Guidelines on the use of Bisphosphonates in Bone Pain[71]). [Level 4]
- Osteonecrosis of the external auditory canal has been very rarely reported (fewer than 1 in 10 000 patients) with bisphosphonates, mainly in association with long-term therapy i.e. two years or longer.[41] [Level 4]

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4.4 Monitoring of hypercalcaemia

- Corrected calcium levels should be rechecked 7-10 days after the bisphosphonate infusion. Checking calcium levels prior to this is not appropriate, as the bisphosphonate will not have achieved its maximal effect.[3, 35, 38, 42] [Level 4]
- Corrected calcium levels should also be rechecked 7-10 days following treatment of hypercalcaemia with parenteral rehydration alone, if further treatment of recurrent hypercalcaemia would be appropriate. If the serum calcium level transiently normalised following rehydration alone, it is possible for the hypercalcaemia to have reoccurred in this time.[17, 18, 26, 58, 59] [Level 4]
- Calcium levels should subsequently be rechecked every 3-4 weeks or when symptoms of hypercalcaemia occur.[43] [Level 4]

4.5 Management of treatment-resistant and/or recurrent hypercalcaemia

- If at 7-10 days post bisphosphonate infusion, the corrected calcium level is greater than 3.0mmol/l or symptoms of hypercalcaemia persist, it may be appropriate to consider a further bisphosphonate infusion. At least seven days should elapse before a further treatment is given, to allow maximal response to the initial dose. Options for treatment include: repeat the same dose of bisphosphonate; increased dose of same bisphosphonate or changing to an alternative bisphosphonate.[3, 34, 35, 37, 38, 42] [Level 4]

- If the patient experiences subsequent episodes of symptomatic hypercalcaemia, a further infusion of bisphosphonate may be given. Depending on how close the recurrence is to the original episode, it may be appropriate to give the same dose of bisphosphonate, an increased dose of the same bisphosphonate or change to an alternative bisphosphonate.[34, 35, 42] [Level 4]

- Relapsing hypercalcaemia usually does not respond as well to bisphosphonates as in the initial episode.[7, 10, 35, 37, 38] [Level 4]

- If recurrent or resistant hypercalcaemia fails to respond to re-treatment with bisphosphonates, Denosumab should be considered as an alternative if it is locally available.[49, 50] [Level 4]

- In patients with hypercalcaemia which is unresponsive to treatment, the focus of management should be on relieving symptoms. [Level 4] (See Guidelines for Symptom Control Medication in the Dying Person).[60]

4.6 Role of other agents available in the treatment of cancer-related hypercalcaemia

4.6.1 Calcitonin (Salcatonin)

- Calcitonin should only be used in exceptional circumstances when the corrected calcium level is extremely high and there is a clinical indication for the rapid reduction of the serum calcium level e.g. symptomatic cardiac arrhythmias.[2, 4, 44, 45] [Level 3]

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- Calcitonin should be given in addition to the bisphosphonate. It reduces the calcium level rapidly whilst the slower acting bisphosphonate will take longer to work but achieve a more long lasting effect.[2, 7, 15, 45] [Level 3]
- The dose range of calcitonin is 100 international units every 6- 8 hours to a maximum of 400 international units QDS. It can be administered via subcutaneous or intramuscular injection.[2, 14, 15] [Level 3]
- Calcitonin is highly emetogenic. Nausea with or without vomiting occurs in approximately 10% of patients. [2, 7] A antiemetic should be co-prescribed. (See Guidelines for Nausea and Vomiting).[61] [Level 4]
- Other common side effects of calcitonin include rash and flushing.[2, 7, 15, 16] [Level 4]

4.6.2 Corticosteroids

- The role of corticosteroids in severe hypercalcaemia is confined to haematological tumours that respond to the cytostatic effects of steroids including myeloma, leukaemia and lymphoma.[4, 46-48] [Level 4]

4.6.3 Gallium Nitrate

- Gallium Nitrate has been shown to have comparable efficacy to bisphosphonates in treating cancer-related hypercalcaemia in several non-UK based studies. However it requires administration via a continuous intravenous infusion over several days and is not used in clinical practice in the UK.[62-65] [Level 4]

4.6.4 Denosumab

- Denosumab should be considered for the management of resistant or recurrent cancer-related hypercalcaemia where repeated treatment with bisphosphonates has failed to normalise the serum calcium.[4, 49, 50] [Level 3]
- Denosumab may potentially be useful in patients with renal impairment who may not be able to receive bisphosphonates.[4, 49, 50] [Level 4]

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Table 2 Bisphosphonates available for clinical use

Name of drug	Initial Dose		Route / Diluent / Rate	Contraindications/ Cautions	Notes
Disodium Pamidronate	**Adj $Ca2^+$** (mmol/l)	**Dose (mg)**	Intravenous. Dilute in 250ml-500ml of sodium chloride 0.9% Maximum rate:1mg/min. Concentration of solution should not be greater than 60mg/250ml.[38] [Level 4]	Patients with mild (creatinine clearance 61-90 mL/min) to moderate renal impairment (creatinine clearance 30-60 mL/min). In such patients, the infusion rate should not exceed 90 mg/4h (approximately 20-22 mg/h).[66] [Level 4] Do not use if creatinine clearance is less than 30ml/min **except** if there is life threatening tumour induced hypercalcaemia and the benefits outweigh the potential risk.[38] [Level 4]	No dose recommendations for patients with severe renal impairment as only limited pharmacokinetic data.[38] [Level 4]
	Up to 3.0	15 - 30			
	3.0 – 3.5	30 - 60			
	3.5 – 4.0	60 - 90			
	>4.0	90			
	From Medicines & Healthcare Products Regulatory Agency.[66]				
Zoledronic acid	Recommended dose is 4mg.[2, 34, 35] [Level 1-]		Intravenous. Dilute in 100ml of sodium chloride 0.9% or 100ml of 5% dextrose. Rate: administer over a minimum of 15 minutes.	Monitor renal function. Do not use in patients with severe renal impairment i.e. creatinine clearance less than 30ml/min as there is no safety data.[34, 35] [Level 4]. Use with caution in conjunction with other potentially nephrotoxic drugs plus aminoglycosides or loop diuretics as these may increase risk of hypocalcaemia.[35, 43]	Has been associated with renal dysfunction and osteonecrosis of the jaw.[34, 35] May be a risk of bronchospasm in asthmatic patients.[34][Level 4] Pancytopenia is a rare side effect. ≥ 1 in 10000,<1 in1000.

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Table 2: Bisphosphonates available for clinical use (contd)				
Name of drug	**Initial Dose**	**Route / Diluent / Rate**	**Contraindications/ Cautions**	**Notes**
Ibandronic acid	Dose varies according to the serum calcium level. [7, 30, 37] If the corrected Ca^{2++} level is greater than 3mmol/l the dose is 4mg. If the corrected calcium level is less than 3 mmol/l the dose is 2mg.	Intravenous. Dilute in 500ml sodium chloride 0.9%. Rate: administer over at least 2 hours. [30, 37]	Favourable renal safety profile. Deterioration in renal function not associated with use but monitoring of renal function is recommended.[30, 37] [Level 4]	More effective than pamidronate in the treatment of severe hypercalcaemia.[10] [Level 1-]
Clodronate	1500mg [57] [Level 3]	Intravenous or subcutaneous(see notes). Dilute in 500-1000ml sodium chloride 0.9% Rate: administer over 24 hours[15] [Level 3]	Site reactions can be managed with 150-300IU hyaluronidase.[67] [Level 4]	Useful if venous access difficult. Unlicensed for intravenous use.[39]
Calcitonin	Give **in addition** to the bisphosphonate as calcitonin will give a rapid effect and the bisphosphonate will have a long lasting effect.[45, 68] Dose:100 international units tds/qds-400 international units qds (max)	Subcutaneous or intramuscular injection. Use either human or salmon form (more potent)	Highly emetogenic. Nausea+/- vomiting in 10% of patients. Co prescribe an antiemetic e.g. haloperidol.[68] Other common side effects include rash and flushing.[2, 3, 16, 44] [Level 4]	Only use in exceptional situations when there is the need for rapid reduction of the serum calcium level and the level is very high e.g. symptomatic cardiac arrhythmias.[3, 10, 42, 45] [Level 3]

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Section 5: Standards

1. All patients with cancer who have symptoms of hypercalcaemia should have their serum calcium measured if treatment is likely to be appropriate. [Grade D]

2. In patients with proven hypercalcaemia, treatment should be started within 24 hours, if this is considered to be clinically appropriate. [Grade D]

3. If treatment is considered inappropriate, the reasons for this should be documented. [Grade D]

4. When hydrating patients with cancer-related hypercalcaemia, intravenous 0.9% sodium chloride should be used. [Grade D]

5. All patients with an adjusted serum calcium of greater or equal to 3.0mml/l should be treated with 0.9% sodium chloride and intravenous bisphosphonate. [Grade D]

6. All patients treated with bisphosphonates for cancer-related hypercalcaemia should receive intravenous fluids prior to treatment. [Grade D]

7. Following treatment of hypercalcaemia (including when intravenous fluids used alone) the serum calcium should be rechecked after 7-10 days. [Grade C]

8. Calcium levels should be rechecked every 3-4 weeks (if clinically appropriate), following the completion of hypercalcaemia treatment, or when symptoms of hypercalcaemia occur. [Grade C]

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Section 6: Applications and Implications

This guideline is intended to support multi-professional decision-making and to help facilitate an individualised approach to the management of cancer-related hypercalcaemia. Decision making should include discussions with the patient and those important to them. These discussions should cover the benefits and burdens of treatment, and clearly explain the focus to manage symptoms (as opposed to prolonging survival). It is important that the prognostic significance of hypercalcaemia is explained, so there is understanding that it is potentially life limiting.

There is little data about the economic impact of treatment of cancer-related hypercalcaemia. A Cochrane Review in 2004 of the use of bisphosphonates in metastatic disease reported that medications with the longest cumulative duration of normocalcaemia were most cost-effective.[69] Zoledronate 4 mg was the most costly but most cost-effective treatment (approximately £22,900 per life year gained). The estimates of cost-effectiveness were sensitive to the amount of time spent in hospital. As this data is from 2004 a further economic analysis of the effect of treatment of cancer-related hypercalcaemia is warranted.

Section 7: Acknowledgments and Declaration of Interest

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The authors contributed as follows:

Literature review: RMc, CM, AN, AW, JS, AF, MK, MB
Audit tools: RMc, CM, AN, AW, JS, AF, MK, MB
Updating guideline and guideline recommendations: RMc, CM, AN, AW, JS, AF, MK, MB
Developing standards: RMc, CM, AN, AW, JS, AF, MK, MB
Final writing of guideline manuscript: AN, RMc, MB, JS

Section 8: Review Date

The guidelines will be reviewed three years after publication as outlined in the Cheshire and Merseyside Palliative and End of Life Care Network Audit Group Guideline Development Manual.

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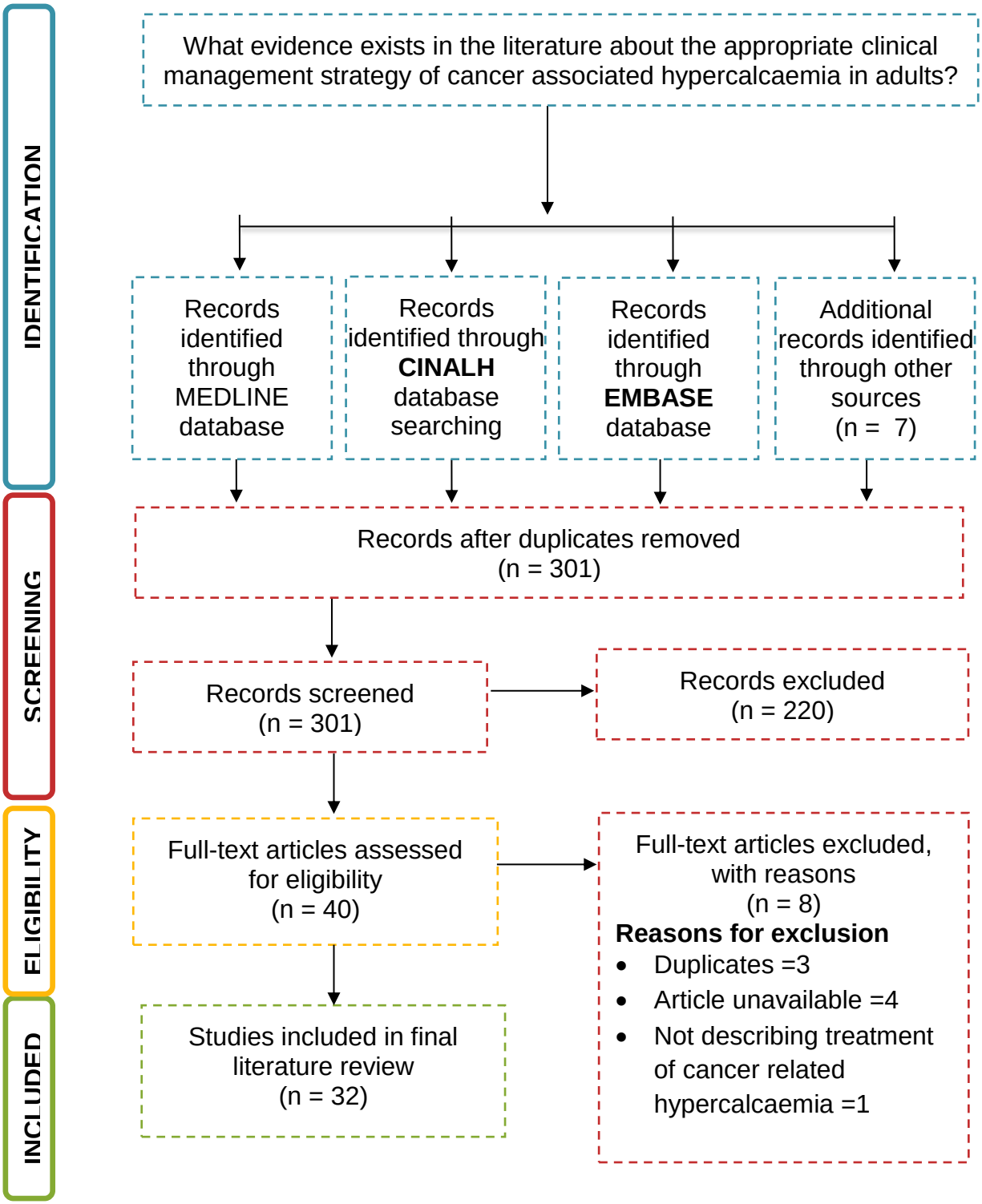
APPENDIX 1 : SYSTEMATIC REVIEW SUMMARY FORM



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