National Institute for Health and Care Excellence

FINAL

Prostate cancer: diagnosis and management

[A] Evidence review for bisphosphonates

NICE guideline NG131

Evidence review

May 2019

These evidence reviews were developed by the NICE Guideline Updates Team

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Bisphosphonates for metastatic prostate cancer

Review question

RQ7: What is the clinical and cost-effectiveness of the use of bisphosphonates in people with metastatic prostate cancer?

Introduction

The aim of the review was to determine the effectiveness of the use of bisphosphonates in people with metastatic prostate cancer. This is an expansion of the review question in previous versions of this guideline, which focused only on hormone-relapsed metastatic prostate cancer (referred to in future as hormone-refractory metastatic prostate cancer).

Bisphosphonates are hypothesised to decrease the level of pain experienced and reduce the risk of skeletal events (e.g. pathologic fractures, hypercalcemia, and the need for radiotherapy or surgery) in patients with bone metastases. They are believed to act predominantly by inhibiting bone-resorbing osteoclasts that are associated with the formation of osteolytic bone lesions (softened areas of bone). Prostate cancer is associated with osteoblastic (not osteoclastic) bone lesions, which result in the deposition of calcium in new bone rather than the breaking down of bone. The rationale for the use of bisphosphonates in the treatment of prostate cancer is that biochemical studies have indicated that osteolysis may also be present in prostate cancer bone metastases.

This review aims to investigate and determine the efficacy of bisphosphonates in people with metastatic prostate cancer, focusing on the outcomes listed in Table 1. Please see full protocol in Appendix A.

Table 1: PICO table

Population	People with metastatic prostate cancer
Interventions	Bisphosphonates: • zoledronic acid • Ibandronic acid • Pamidronate sodium • Sodium clodronate
Comparator	Placebo
Outcomes	• Pain scales • Analgesia use • All-cause mortality • Health-related quality of life • Number of severe adverse events • Number of dropouts because of adverse events • Skeletal-related events ○ Atypical fractures, spinal compression, tumour associated hypercalcemia, osteonecrosis of the jaw

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A, and the methods section in appendix B.

Declarations of interest were recorded according to both NICE's 2014 and 2018 conflicts of interest policy.

Clinical evidence

Included studies

This review was conducted as part of a larger update of the NICE Prostate Cancer guideline (CG175).

A systematic literature search for randomised controlled trials (RCTs) and systematic reviews with no date limit yielded 2,048 references. These were screened on title and abstract, with 130 full-text papers ordered as potentially relevant systematic reviews or RCTs. RCTs were excluded if they did not meet the criteria of enrolling patients with metastatic prostate cancer in a bisphosphonate trial.

Eighteen papers were included after full text screening because all studies were RCTs. Eight systematic reviews were identified, however; none were included because all the randomised control studies included in these systematic reviews were already identified at full text screening. References were checked from the old guideline to cover the period before 2008 (1 systematic review containing 10 RCTs of which 6 were relevant RCTs) to ensure they had been identified during the process.

In order to include the most recent studies in this review the committee agreed that it was necessary to deviate from the protocol and include studies where the comparator was another active agent, rather than placebo.

Multiple papers reporting results of the same study were identified and collated, so that each study rather than individual reports was the unit of interest in the review; therefore there were 12 unique studies.

For the study selection process, please see PRISMA flow diagram in appendix D.

For the full evidence tables and full GRADE profiles for included studies, please see appendix E and appendix G.

Excluded studies

Details of the studies excluded at full-text review are given in appendix H along with a reason for their exclusion.

Summary of clinical studies included in the evidence review

Twelve randomised controlled trials were included in this review. The protocol defined the comparator of interest as a placebo, however there was deviation from this as the most recent evidence identified investigated bisphosphonates against other agents. These studies were included within the review but were then downgraded for indirectness (see GRADE profiles in appendix G. The studies (where possible) were stratified by the type of metastatic

prostate cancer – hormone-sensitive, hormone-refractory or unspecified. The overall evidence was as follows-:

- Bisphosphonates compared to placebo – 7 RCTs (Elomaa et al. 1992, Kylmala et al. 1997), Saad et al. 2002, Dearnaley et al 2003, Small et al 2003, Ernst et al 2003 and Smith et al 2014).
    - Hormone-refractory metastatic prostate cancer - 2 RCTs (Saad et al. 2002 and Ernst et al 2003)
    - Hormone-sensitive metastatic prostate cancer - 2 RCTs (Dearnaley et al. 2003 and Smith et al. 2014)
    - Unspecified metastatic prostate cancer – 3 RCTs (Elomaa et al. 1992, Kylmala et al. 1997 and Small et al. 2003)
- Bisphosphonates compared to radiotherapy – 1 RCT (Hoskin et al. 2015), localized metastatic prostate cancer
- Bisphosphonates combined with docetaxel compared to docetaxel alone - 1 RCT (James et al. 2016b), hormone-refractory metastatic prostate cancer
- Bisphosphonates combined with androgen blockade compared to androgen blockade alone – 2 RCTs (Ueno et al. 2013), Kamba (2017)), unspecified prostate cancer and hormone-naïve prostate cancer respectively
- Bisphosphonates combined with standard care compared to standard are alone – 1 RCT (James (2016a)), hormone-sensitive metastatic prostate cancer

Study locations

Five randomised control studies were from the United Kingdom (Saad et al. 2002 (multicentre including UK participants), Dearnaley et al. 2003, James et al. 2016a, James et al. 2016b, Hoskin et al. 2015), 2 from Japan (Kamba et al. 2017 and Ueno et al. 2013), 2 from Finland (Kymala et al. 1997 and Elomaa et al. 1992), 2 from the United States of America (Small et al. 2003 and Smith et al. 2014) and 1 from Canada (Ernst et al. 2003).

Outcomes and sample sizes

The reported outcomes where data was extractable were:-

- overall survival
- symptomatic bone progression free survival
- time to first skeletal event
- pain score
- analgesic use
- adverse event.

The sample sizes ranged from 60 participants to 1,288 across studies.

See full evidence tables in appendix E.

Quality assessment of clinical studies included in the evidence review

See appendix G for full GRADE tables.

Economic evidence

Standard health economic filters were applied to the clinical search strategy for this question. Details are provided in appendix C. In total, 872 records were returned, of which 855 could be confidently excluded on sifting of titles and abstracts. The remaining 17 studies were

reviewed in full text, and 11 were found not to be relevant. This left 5 unique cost–utility analyses (CUAs) in 6 publications, from which 1 study was selectively excluded, as it adopted a Chinese perspective, when more applicable evidence was available. Therefore, 4 unique CUAs in 5 publications were included.

Two older CUAs came from outside the UK and explored the cost effectiveness of zoledronic acid at a proprietary price (it has since become available more cheaply in generic formulations). Reed et al. (2004) developed an analysis from a US payer's perspective based on the Saad et al. (2002) RCT of zoledronic acid. The authors found that zoledronic acid was associated with benefits amounting to around 0.03 QALYs compared with placebo, but at an additional net cost of over $5,000, leading to high ICERs in excess of $150,000/QALY. Carter et al. (2011) replicated the benefits from this analysis, and calculated costs from the perspective of 4 European (non-UK) countries. Because the authors estimated greater savings might be achieved by prevention of skeletal-related events, they found that the incremental costs associated with zoledronic acid were lower (ranging from €100 to €1,300, depending on country), leading to ICERs in the range €2,500–€36,000. Neither study performed probabilistic sensitivity analysis. They were both judged to be partially applicable with very serious limitations.

The primary focus of the CUA reported by Ford et al. (2013) was the cost effectiveness denosumab for people with hormone-refractory prostate cancer with painful bone metastases. Denosumab is beyond the scope of this question; however, because it was compared with both zoledronic acid and no bone therapy, incremental results between those 2 comparators may be inferred. This suggests that, over a lifetime horizon, zoledronic acid is associated with around 0.025 extra QALYs, at an additional cost (assuming proprietary acquisition costs) of a little under £3,000, leading to an ICER of over £100,000/QALY. Probabilistic results for the comparison of interest cannot be inferred; similarly, it is not possible to calculate the results of a deterministic sensitivity analysis that varied the cost of zoledronic acid (in anticipation of generic products becoming available). The study was judged to be directly applicable with very serious limitations.

James et al. (2016) and Andronis et al. (2017) report the results of an economic evaluation conducted alongside the TRAPEZE RCT (James et al., 2016b). The authors found that zoledronic acid, compared with no treatment, generated around 0.03 additional QALYs, at a net cost of around £250 (when a generic price was used). This represents an ICER of approximately £8,000/QALY. The finding that the ICER is likely to be less than £20,000/QALY was robust to most deterministic sensitivity analyses, and probabilistic analysis suggested that there is a 64% chance that zoledronic acid is associated with an ICER of £20,000/QALY or better. However, a sensitivity analysis in which adjustment was made for baseline imbalances in EQ-5D found that zoledronic acid was no longer associated with a QALY gain. Subsequent threshold analysis showed that, despite this, zoledronic acid would still be considered cost effective if QALYs are valued at £20,000 each, as long as it is associated with an acquisition cost lower than £28 per vial. This is because it is observed to generate net cost savings (mostly due to reduced future radiotherapy and surgery costs), even though there is no evidence of improved quality of life. The study was judged to be directly applicable with potentially serious limitations.

For more details of these studies, please see the economic evidence profiles in appendix K.

Evidence statements

Bisphosphonate versus placebo

Very low- to moderate-quality evidence from up to 3 RCTs reporting data on up to 1,165 people with hormone-refractory or hormone sensitive metastatic prostate cancer found there were more people reporting that they had no bone pain at 3 months, and there was a reduction in symptomatic bone progression and a reduction in risk in worsening performance status, in people offered a bisphosphonate compared to a placebo.

High-quality evidence from 2 RCTs reporting data on 994 people with hormone-refractory or hormone sensitive metastatic prostate cancer found there were no differences in mean pain scores between people offered a bisphosphonate compared to a placebo.

Very low- to low-quality evidence from up to 3 RCTs reporting data on up to 1,288 people with hormone-refractory or hormone sensitive metastatic prostate cancer could not differentiate analgesic use or overall survival between people offered a bisphosphonate compared to those offered a placebo. However, in those with hormone refractory metastatic cancer, there was a reduction in time to first skeletal event in those receiving a bisphosphonate (specifically zoledronic acid) compared to those receiving a placebo. This means zoledronic acid led to people getting skeletal events sooner than if they received placebo.

Bisphosphonate with standard care versus standard care alone

Low-quality evidence from 1 RCT reporting data from 1,090 people with hormone sensitive metastatic prostate cancer, could not differentiate overall survival and time to first skeletal event between people who were offered a bisphosphonate (zoledronic acid) and standard care compared to those offered standard care alone.

Bisphosphonate versus radiotherapy

Low-quality evidence from 1 RCT reporting data from 470 people with unspecified localised metastatic prostate cancer, could not differentiate survival between people who were offered a bisphosphonate (ibandronate) compared to those offered radiotherapy.

Bisphosphonate with docetaxel versus docetaxel alone

Low quality evidence from 1 RCT reporting data from 137 people with metastatic hormone-refractory prostate cancer, found there was no meaningful difference in overall and clinical progression free survival and pain progression free interval between people who were offered a bisphosphonate (combination of docetaxel and zoledronic acid) compared to those offered docetaxel alone.

Moderate quality evidence from 1 RCT reporting data from 137 people with hormone-refractory metastatic prostate cancer, found that the skeletal related event-free interval was prolonged in those who were offered a bisphosphonate (combination of docetaxel and zoledronic acid) compared to those offered docetaxel alone.

Bisphosphonate with combined androgen blockade (CAB) versus CAB alone

Low quality evidence from 1 RCT reporting data from 224 people with treatment-naïve metastatic prostate cancer, found time to first skeletal related event was prolonged in those

participants offered a bisphosphonate (zoledronic acid combined with CAB) compared to those offered CAB alone.

Very low-quality to low quality evidence from 2 RCTs reporting data from 224 people with hormone-refractory or treatment naive metastatic prostate cancer, could not differentiate overall survival, prostate specific-antigen (PSA) progression free survival and occurrence of adverse events between those who were offered zoledronic acid combined with CAB compared to those offered CAB alone.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that the critical outcomes were symptomatic skeletal-related events, pain and analgesic use, as these have the most impact on the patient. The committee noted that the definition of skeletal-related events differed across studies, as some studies detected skeletal-related events via radiology assessments and others through the presence of relevant symptoms. The committee also noted that, though pain and analgesia use were critical outcomes, there was limited extractable evidence that could be used as part of this review.

The quality of the evidence

When considering all 12 included studies, 3 were at moderate or higher risk of bias owing to lack of random sequence generation, blinding of participants and/or investigators. The committee agreed that the evidence on bisphosphonate versus placebo was outdated, with only 1 study providing evidence that was not considered in CG175 (Smith et al. 2014). As a result, it also reviewed evidence that looked at bisphosphonates in combination with other agents (notably docetaxel) versus these agents alone. The committee agreed that this evidence was likely to be more representative of current practice, and acknowledged that it is possible that the newer technologies influence the effectiveness of bisphosphonates. This was shown by the evidence that showed zoledronic acid (a newer technology) had better efficacy compared to older bisphosphonates such as clodronate acid.

The committee was interested in whether or not the study populations had hormone-refractory or hormone-sensitive metastatic prostate cancer. Across the evidence there were 3 RCTs (Saad et al. 2002; Ernst et al. 2003 and James et al. 2016b) whose study population had hormone-refractory metastatic prostate cancer, 3 RCTs (Dearnaley et al. 2003; Smith et al 2014 and James et al. 2016a) whose study population had hormone-sensitive metastatic prostate cancer and 6 RCTs that either included both or did not specify their population.

The committee acknowledged that there were variations in definitions of outcomes, for example the earlier studies detected skeletal-related events using radiology assessments (Saad et al. 2002), whilst more recent studies referred to symptomatic skeletal-related events (James et al. 2016b), which were clinically detected and with impact to the patient affected.

Overall, when the evidence was assessed using GRADE, the majority of the evidence was of very low to moderate quality, and most evidence was drawn from 3 randomised control trials. The committee also noted that some of the trials had large sample sizes, for example Saad et al. (2002) and Smith et al. (2014) had a total of at least 1,600 participants each.

Benefits and harms

Based on the evidence, the committee agreed that bisphosphonates (specifically zoledronic acid) can prolong the time to first symptomatic skeletal-related event in people with hormone-refractory metastatic prostate cancer (Saad et al. 2002; James et al. 2016b and Kamba et al. 2017). The evidence showed that this effect was observed in studies where the comparison was between zoledronic acid alone compared with placebo (Saad et al. 2002) as well as where zoledronic acid was added to standard care or chemotherapy (docetaxel) compared with standard care or chemotherapy alone (James et al. 2016b and Kamba et al. 2017). As a result, the committee concluded that zoledronic acid should be considered for people with hormone-refractory metastatic prostate cancer to prevent or reduce skeletal-related events.

In addition, the evidence could not detect whether bisphosphonates affect mortality in people with hormone-refractory metastatic prostate cancer when compared with radiotherapy (Hoskin et al. 2015); placebo (Ernst et al. 2003) and chemotherapy (docetaxel) alone (James 2016b). There were also concerns that zoledronic acid may increase occurrence of adverse events such as osteonecrosis; however, the committee concluded that the risk was small (as evidenced by Kamba et al. 2017) compared with the benefit of preventing skeletal-related events.

Bisphosphonates were found to reduce mortality in people with hormone-sensitive prostate cancer when compared with placebo in older studies (Dearnaley et al. 2003) though that effect was not detected in more recent studies (Smith et al. 2014 and James et al. 2016a). The committee concluded that it was predictable that any benefit that was historically present in this area would have been eliminated by the introduction of more modern treatments – for example docetaxel as used in the study by James et al. (2016a). Moreover, the studies by Smith et al. (2014) and James et al. (2016a) could not differentiate between bisphosphonates and placebo in prolonging time to skeletal-related events in people with hormone-sensitive metastatic prostate cancer. For these reasons, the committee agreed not to extend the recommendation to include this population.

The committee agreed that bisphosphonates may be considered for pain relief in people with hormone-refractory metastatic prostate cancer; this was based on evidence from earlier studies by Kylmala et al. (1997) and Elomaa et al. (1992).

Cost effectiveness and resource use

The committee reviewed the included economic evidence. It noted that there was reasonable agreement about the magnitude of benefits, with all 4 studies estimating gains of around 0.03 QALYs in their base-case analyses. The committee agreed that cost and cost-effectiveness evidence from the 3 older studies was of limited relevance, as it was based on the historical, proprietary price of zoledronic acid. The committee noted that this was very much higher – for example, the list price of proprietary zoledronic acid was reported by James et al. (2016b) at £174 per vial, whereas an equivalent product is now available generically in the NHS at around £11 (eMIT 2018).

The committee agreed that the economic evaluation conducted alongside the TRAPEZE RCT (James et al., 2016b) provided more directly applicable evidence. However, it questioned the authors' decision to report results that had been adjusted for imbalances in baseline EQ-5D only as a sensitivity analysis, when this would normally be expected as the base-case method for an analysis of this type. The committee agreed that it was plausible that (assuming generic prices) zoledronic acid might be cost saving, though it noted that the areas in which significantly lower resource use had been observed in the zoledronic acid arms of the trial (radiotherapy and surgery) were not necessarily those that were directly

associated with the skeletal-related events that zoledronic acid had been observed to reduce.

However, the committee was confident in drawing the conclusion that, if zoledronic acid is associated with benefits in reducing skeletal-related events in people with hormone-refractory disease, it is likely that this would lead to small QALY gains (and implausible that it could lead to QALY losses). Additionally, it is plausible that the net costs of providing generic zoledronic acid – including its nontrivial administration costs – would be close to zero and could well represent cost savings.

This was agreed to be sufficient evidence to underpin a relatively weak ('consider') recommendation in favour of zoledronic acid for people with hormone-refractory disease.

Other factors the committee took into account

The committee discussed whether it should recommend bisphosphonates as a class or zoledronic acid in particular. It noted that all the evidence it had seen of benefit in reducing skeletal-related events was for zoledronic acid. Additionally, no economic evidence had been identified for other bisphosphonates. Therefore, the committee agreed that it should confine its recommendation to the only agent for which positive evidence had been shown.

Appendix A – Review protocol

Review protocol for bisphosphonates for metastatic prostate cancer

ID	Field (based on PRISMA-P)	Content
I	Review question	What is the clinical and cost- effectiveness of the use of bisphosphonates in people with metastatic prostate cancer?
II	Type of review question	Intervention
III	Objective of the review	To determine the effectiveness of the use of bisphosphonates in people with hormone- relapsed metastatic prostate cancer
IV	Eligibility criteria – population/disease/condition/issue/domain	People with metastatic prostate cancer
V	Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Bisphosphonates – • zoledronic acid (also known as zoledronate) • Ibandronic acid (also known as ibandronate) • Pamidronate sodium (also known as pamidronic acid)

		• sodium clodronate (also known as clodronic acid)
VI	Eligibility criteria – comparator(s)/control or reference (gold) standard	Placebo

VII	Outcomes and prioritisation	• Pain scales
		• Analgesia use
		• All-cause mortality
		• Health-related quality of life - for example:
		  ○ European Organisation for Research and Treatment of Cancer quality of life
		  ○ EPIC instrument
		
		If reported – psychological aspects of quality of life to be reported separately
		
		• Number of severe adverse events
		  ○ Osteonecrosis of the jaw
		  ○ atypical fractures
		• Number of dropouts because of adverse events
		• Skeletal related events including the following
		  ○ Fractures,
		  ○ spinal compression,
		  ○ tumour associated hypercalcemia

VIII	Eligibility criteria – study design	Randomised control studies Systematic reviews of randomised control studies

IX	Other exclusion criteria	• Non English-language papers • Non-UK licensed drugs • Studies for alendronate and risedronate • Abstract/conference proceeding • Expert opinion/narrative review
X	Proposed sensitivity/sub-group analysis, or meta-regression	Subgroup analysis was carried out by disease state: • Hormone-refractory metastatic prostate cancer • Hormone – sensitive metastatic prostate cancer
XI	Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer
XII	Data management (software)	See appendix B
XIII	Information sources – databases and dates	See appendix C
XIV	Identify if an update	This question is to update the following recommendations in the 2008 NICE prostate cancer guideline (CG175): 1.5.17 Do not offer bisphosphonates to prevent or reduce the complications of bone metastases in men with hormone-relapsed prostate cancer. [2008]

		1.5.18 Bisphosphonates for pain relief may be considered for men with hormone-relapsed prostate cancer when other treatments (including analgesics and palliative radiotherapy) have failed. Choose the oral or intravenous route of administration according to convenience, tolerability and cost. [2008]
XV	Author contacts	Guideline update
XVI	Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
XVII	Search strategy – for one database	For details please see appendix C
XVIII	Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or H (economic evidence tables).
XIX	Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or H (economic evidence tables).
XX	Methods for assessing bias at outcome/study level	See Appendix B
XXI	Criteria for quantitative synthesis	See Appendix B

XXII	Methods for quantitative analysis – combining studies and exploring (in)consistency	See Appendix B
XXIII	Meta-bias assessment – publication bias, selective reporting bias	See Appendix B
XXIV	Confidence in cumulative evidence	See Appendix B
XXV	Rationale/context – what is known	For details please see the introduction to the evidence review in the main file.
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the NICE Guideline Updates Team and chaired by Waqaar Shah in line with section 3 of Developing NICE guidelines: the manual. Staff from NICE undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
XXVII	Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
XXVIII	Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.

XXIX	Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
XXX	PROSPERO registration number	N/A

Appendix B – Methods

Incorporating published systematic reviews

For all review questions where a literature search was undertaken looking for a particular study design, systematic reviews containing studies of that design were also included. All included studies from those systematic reviews were screened to identify any additional relevant primary studies not found as part of the initial search.

Quality assessment

Individual systematic reviews were quality assessed using the ROBIS tool, with each classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.
- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.
- Low quality – It is possible that relevant and important studies have been missed by the review.

Each individual systematic review was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.
- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline (for example, some of the factors in the protocol only).
- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

Using systematic reviews as a source of data

If systematic reviews were identified as being sufficiently applicable and high quality, and were identified sufficiently early in the review process (for example, from the surveillance review or early in the database search), they were used as the primary source of data, rather than extracting information from primary studies. The extent to which this was done depended on the quality and applicability of the review, as defined in Table 2. When systematic reviews were used as a source of primary data, and unpublished or additional data included in the review which is not in the primary studies was also included. Data from these systematic reviews was then quality assessed and presented in GRADE/CERQual tables as described below, in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were cross-referenced to ensure none of the data had been double counted through this process.

Table 2: Criteria for using systematic reviews as a source of data

Quality	Applicability	Use of systematic review
High	Fully applicable	Data from the published systematic review were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review.
High	Partially applicable	Data from the published systematic review were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.

Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of studies for each outcome. For mean differences, where change from baseline data were reported in the studies and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. All studies were assessed to ensure that baseline values were balanced across the treatment/comparison groups; if there were significant differences in important confounding variables at baseline these studies were not included in any meta-analysis and were reported separately.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Cohort studies were quality assessed using the CASP cohort study checklist. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method). Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis.

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Meta-analyses were performed in Cochrane Review Manager v5.3.

Minimal clinically important differences (MIDs)

The Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another)

required an MID to be defined to act as a non-inferiority margin. The committee did not identify any specific minimal important difference thresholds relevant to this guideline.

For standardised mean differences where no other MID was available, an MID of 0.2 was used, corresponding to the threshold for a small effect size initially suggested by Cohen et al. (1988). For relative risks where no other MID was available, a default MID interval for dichotomous outcomes of 0.8 to 1.25 was used. The line of no effect was specified by the committee as an MID for hazard ratios.

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review should make explicit the committee's view of the expected clinical importance and relevance of the findings. In particular, this includes consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from RCTs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point. If non-RCT evidence was included for intervention-type systematic reviews then these were initially rated as either moderate quality (quasi-randomised studies) or low quality (cohort studies) and the quality of the evidence for each outcome was further downgraded or not from this point, based on the criteria given in Table 3.

Table 3: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic.

GRADE criteria	Reasons for downgrading quality
	N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if any of the following three conditions were met:

- Data from non-randomised studies showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data showing a dose-response gradient.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Evidence was downgraded once for indirectness if studies' comparator was another active agent, rather than placebo.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts, trial protocols or trial records without accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Evidence statements

Evidence statements for pairwise intervention data are classified in to one of four categories:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect.
- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is

most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence could not demonstrate a meaningful difference.

- Situations where the data are consistent, at a 95% confidence level, with an effect in either direction (i.e. one that is not 'statistically significant') but the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no difference.
- In all other cases, we state that the evidence could not differentiate between the comparators.

For outcomes without a defined MID or where the MID is set as the line of no effect (for example, in the case of mortality), evidence statements are divided into 2 groups as follows:

- We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
- We state the evidence could not differentiate between comparators if the 95% CI crosses the line of no effect.

The number of trials and participants per outcome are detailed in the evidence statements, but in cases where there are several outcomes being summarised in a single evidence statement and the numbers of participants and trials differ between outcomes, then the number of trials and participants stated are taken from the outcome with the largest number of trials. This is denoted using the terminology ‘up to’ in front of the numbers of trials and participants.

The evidence statements also cover the quality of the outcome based on the GRADE table entry. These can be included as single ratings of quality or go from one quality level to another if multiple outcomes with different quality ratings are summarised by a single evidence statement

Appendix C – Literature search strategies

Search summary

The search strategies were based on the review protocol provided. Bisphosphonates terms were taken from the British National Formulary (BNF), Martindale: The Complete Drug Reference and the electronic Medicines Compendium (eMC).

Clinical searches

Source searched for this review question:

- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley)
- Health Technology Assessment Database – HTA (Wiley)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)
- PubMed (NLM)

The clinical searches were conducted in October 2017.

The MEDLINE search strategy is presented below. It was translated for use in all other databases.

Database: Ovid MEDLINE(R) 1946 to September Week 4 2017
1 exp Prostatic Neoplasms/
2 Prostatic Intraepithelial Neoplasia/
3 (prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump*)).tw.
4 PIN.tw.
5 or/1-4
6 Diphosphonates/
7 (Bisphosphon* or diphosphon*).tw.
8 (Zoledron* or zerlinda or zometa or aclasta).tw.
9 (Ibandron* or bonviva or bondron* or iasibon or quodixor).tw.
10 Pamidron*.tw.
11 Clodronic Acid/
12 (Clodron* or loron or bonefos or clasteon or aredia).tw.
13 Alendronate/
14 (Alendron* or binosto or fosamax or fosavance).tw.
15 Risedronate Sodium/
16 (Risedron* or actonel).tw.
17 or/6-16
18 5 and 17

Study design filters and limits

The MEDLINE systematic review (SR) and Randomized Controlled Trial (RCT) filters were appended to the review question above and are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

The MEDLINE SR and RCT filters are presented below.

Systematic Review

1 Meta-Analysis.pt.
2 Network Meta-Analysis/
3 Meta-Analysis as Topic/
4 Review.pt.
5 exp Review Literature as Topic/
6 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.
7 (review$ or overview$).ti.
8 (systematic$ adj5 (review$ or overview$)).tw.
9 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw.
10 ((studies or trial$) adj2 (review$ or overview$)).tw.
11 (integrat$ adj3 (research or review$ or literature)).tw.
12 (pool$ adj2 (analy$ or data)).tw.
13 (handsearch$ or (hand adj3 search$)).tw.
14 (manual$ adj3 search$).tw.
15 or/1-14

RCT

1 Randomized Controlled Trial.pt.
2 Controlled Clinical Trial.pt.
3 Clinical Trial.pt.
4 exp Clinical Trials as Topic/
5 Placebos/
6 Random Allocation/
7 Double-Blind Method/
8 Single-Blind Method/
9 Cross-Over Studies/
10 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.
11 (random$ adj3 allocat$).tw.
12 placebo$.tw.
13 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
14 (crossover$ or (cross adj over$)).tw.
15 or/1-14

An English language limit has been applied. Animal studies and certain publication types (letters, historical articles, comments, editorials, news and case reports) have been excluded.

Health Economics search strategy

Economic evaluations and quality of life data.

Sources searched:

- NHS Economic Evaluation Database – NHS EED (Wiley) (legacy database)

- Health Technology Assessment (HTA Database)
- EconLit (Ovid)
- Embase (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Search filters to retrieve economic evaluations and quality of life papers were appended to population search terms in MEDLINE, MEDLINE In-Process and Embase to identify relevant evidence and can be seen below.

An English language limit has been applied. Animal studies and certain publication types (letters, historical articles, comments, editorials, news and case reports) have been excluded.

The economic searches were conducted in October 2017.

Health Economics filters

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

Economic evaluations

1 Economics/
2 exp "Costs and Cost Analysis"/
3 Economics, Dental/
4 exp Economics, Hospital/
5 exp Economics, Medical/
6 Economics, Nursing/
7 Economics, Pharmaceutical/
8 Budgets/
9 exp Models, Economic/
10 Markov Chains/
11 Monte Carlo Method/
12 Decision Trees/
13 econom$.tw.
14 cba.tw.
15 cea.tw.
16 cua.tw.
17 markov$.tw.
18 (monte adj carlo).tw.
19 (decision adj3 (tree$ or analys$)).tw.
20 (cost or costs or costing$ or costly or costed).tw.
21 (price$ or pricing$).tw.
22 budget$.tw.
23 expenditure$.tw.
24 (value adj3 (money or monetary)).tw.
25 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26 or/1-25

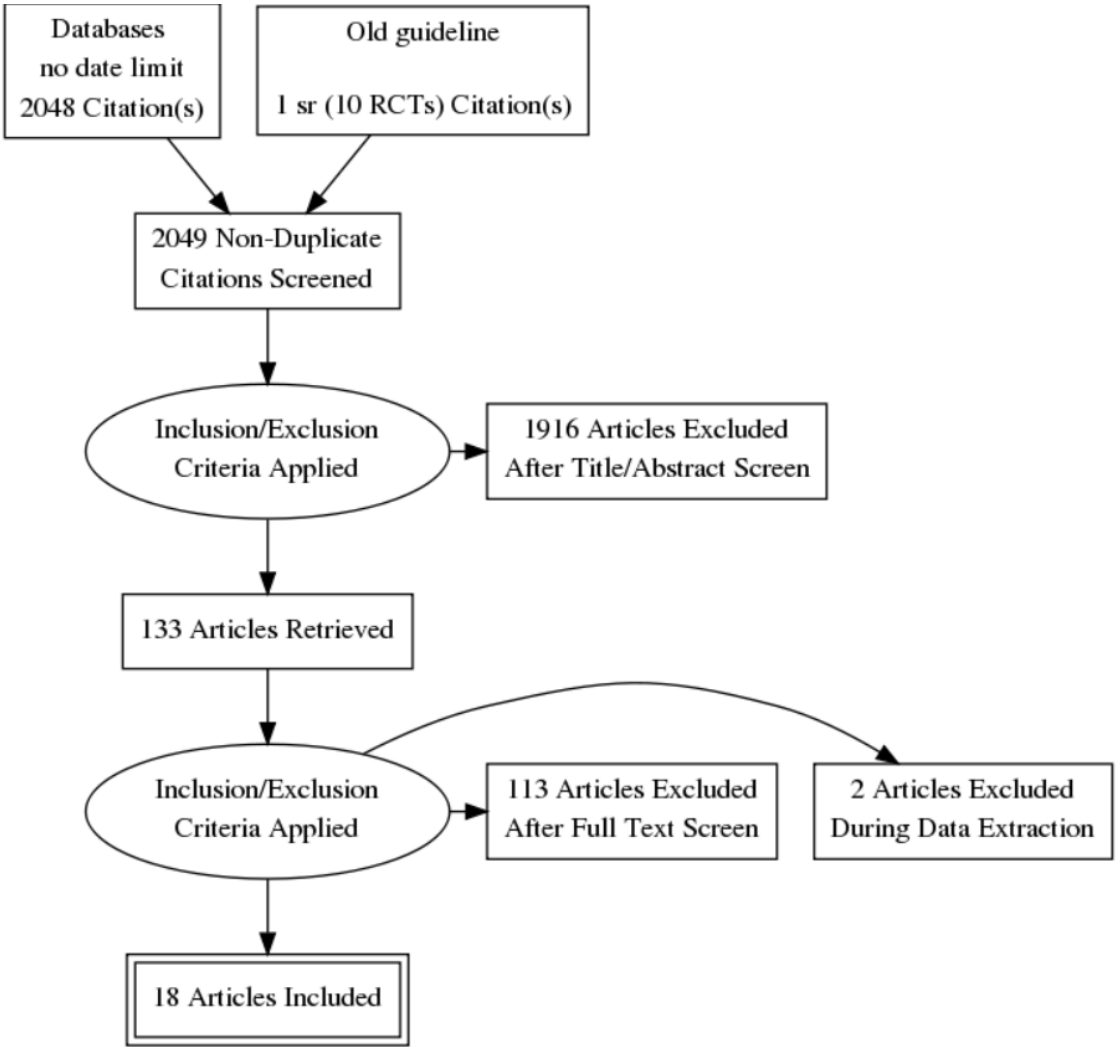
Quality of life

1 "Quality of Life"/
2 quality of life.tw.
3 "Value of Life"/

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

4 Quality-Adjusted Life Years/
5 quality adjusted life.tw.
6 (qaly$ or qald$ or qale$ or qtime$).tw.
7 disability adjusted life.tw.
8 daly$.tw.
9 Health Status Indicators/
10 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15 (euroqol or euro qol or eq5d or eq 5d).tw.
16 (qol or hql or hqol or hrqol).tw.
17 (hye or hyes).tw.
18 health$ year$ equivalent$.tw.
19 utilit$.tw.
20 (hui or hui1 or hui2 or hui3).tw.
21 disutili$.tw.
22 rosser.tw.
23 quality of wellbeing.tw.
24 quality of well-being.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble$.tw.
28 time trade off.tw.
29 time tradeoff.tw.
30 tto.tw.
31 or/1-30

Appendix D – Clinical evidence study selection



Appendix E – Clinical evidence tables

Short Title	Title	Study Characteristics	Risk of Bias
Dearnaley (2003)	A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial) Hormone-sensitive metastatic prostate cancer	**Study type** Bisphosphonate vs Placebo Randomised controlled trial Associated studies *Dearnaley Dp, Mason Md, Parmar Mk, Sanders K, and Sydes Mr (2009) Adjuvant therapy with oral sodium clodronate in locally advanced and metastatic prostate cancer: long-term overall survival results from the MRC PR04 and PR05 randomised controlled trials. Lancet oncology 10(9), 872-876* **Study details** Study location - United Kingdom and New Zealand Study setting - 34 centres Study dates - June 1994 and July 1998 Duration of follow-up - 2 years then every 6 months, results available at 5 months Sources of funding - UK Medical research council Boehringer Mannheim (later taken over by Roche products LTD) **Inclusion criteria** Performance status WHO ranged from 0 to 2 Commencing or showing a positive response to initial hormone therapy with orchiectomy, luteinizing hormone-releasing hormone analogs, cypoterone acetate, flutamide, or maximal androgen blockade, normocalcemia Serum creatinine level less than twice the upper limit of the local normal range, No other active malignancy within the past 5 years	**Random sequence generation** Low risk of bias "*Randomisation was performed centrally at the MRC CTU. Treatment was allocated in a 1:1 ratio using the method of minimisation over four stratification factors* **Allocation concealment** Low risk of bias *As above, the randomisation was performed centrally* **Blinding of participants and personnel** Low risk of bias *Study described as double blinded* **Blinding of outcome assessment** Unclear risk of bias *No details provided* **Incomplete outcome data** Low risk of bias *None identified* **Selective reporting** Low risk of bias *None identified* **Other sources of bias** High risk of bias *Products were provided by the Pharma company free of charge as well as £250 per patient to cover*

Short Title	Title	Study Characteristics	Risk of Bias
		No acute, severe inflammatory conditions of the GI tract No serious concomitant physical or psychiatric disease, no use of any investigational drug within 12 months of the 1st dose of study tablets No previous long-term hormone therapy **Exclusion criteria** Prior treatment with a bisphosphonate **Sample characteristics** Sample size - 311 patients Split between study groups Mean age (SD) not provided, median age - 71years (47-88) **Intervention** Clodronate *Oral sodium clodronate 4 Loron 520 tablets taken each evening at least one hour before or after food with little fluid, not milk.* **Control** Placebo *similar regimen as the intervention group* **Outcome measure(s)** Skeletal related events Adverse events Time to disease progression Quality of life Use of Analgesic drugs Progression free survival WHO performance status	*administration cost* **Overall risk of bias** Moderate *due to uncertainties surrounding outcome assessments.* **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
Elomaa (1992)	Effect of oral clodronate on bone pain. A controlled study in patients with metastatic prostatic cancer Hormone-refractory metastatic prostate cancer	**Study type** Bisphosphonate vs Placebo Randomised controlled trial **Study details** Study location - Finland Study dates - not stated Duration of follow-up - 6 months Sources of funding - Finnish Cancer Foundation and to Leiras Pharmaceutical Company **Inclusion criteria** No radiation therapy in the 2 weeks preceding the trial Predicted life expectancy of more than 3 months Estramustine therapy, but the patients had to enter the study at a time when the disease was progressive despite continuous treatment Bone pain as a result of bone metastasis **Exclusion criteria** None reported **Sample characteristics** Sample size 75 patients Split between study groups Mean age (SD) 72 years Site of metastases at baseline All bone **Intervention** Clodronate	**Random sequence generation** Unclear risk of bias *the authors stated that study participants were randomly allocated to clodronate and placebo, no mention of random sequence generation* **Allocation concealment** Unclear risk of bias *no details provided* **Blinding of participants and personnel** Unclear risk of bias *no details provided* **Blinding of outcome assessment** Unclear risk of bias *no details provided* **Incomplete outcome data** Low risk of bias none identified **Selective reporting** Low risk of bias *none identified* **Overall risk of bias** High *There were no details provided regarding sequence generation, allocation concealment or blinding.*

Short Title	Title	Study Characteristics	Risk of Bias
		3.2g for the first month and 1.6g for a further 5 months, orally **Control** Placebo **Outcome measure(s)** Use of Analgesic drugs	**Directness** Directly applicable
Ernst (2003)	Randomized, double-blind, controlled trial of mitoxantrone/prednisone and clodronate versus mitoxantrone/prednisone and placebo in patients with hormone-refractory prostate cancer and pain Hormone-refractory metastatic prostate cancer	**Study type** Bisphosphonate vs placebo Randomised controlled trial **Study details** Study location - Canada Study setting- 17 Canadian Centres affiliated with the National Cancer institute of Canada Clinical Trials group Study dates - October 1997 to May 2001 **Inclusion criteria** ECOG performance status 0 to 2 Ability to comply with pain chart Ability to participate in quality of life assessments Ability to provide written consent Hormone-refractory prostate cancer A mean PPI score of 1 was required Stable analgesic use as measured in a diary Radiologically confirmed progressive bone disease, which was defined as the presence of new lesions on bone scan Increased isotope uptake at previous sites of disease, or increasing bone pain Castrate level of testosterone (<3 nmol/L) achieved by bilateral orchiectomy or administration of a luteinizing-hormone releasing	**Random sequence generation** Unclear risk of bias *The authors did not provide any details on sequence generations* **Allocation concealment** Unclear risk of bias *No details provided* **Blinding of participants and personnel** Low risk of bias *the study was a "double blind controlled trial*" **Blinding of outcome assessment** Unclear risk of bias *no details provided* **Incomplete outcome data** Low risk of bias *none identified* **Selective reporting** Low risk of bias

Short Title	Title	Study Characteristics	Risk of Bias
		agonist. Baseline measurement of left ventricular ejection fraction greater than 50% **Exclusion criteria** Had chemotherapy before Patient receive radiation therapy within 3 months Prior treatment with a bisphosphonate Prior malignancy excluding non-melanoma skin cancer **Sample characteristics** Sample size 227 patients Split between study groups Mean age (SD) Not reported - median 70.6 years **Interventions** Clodronate 1500mg administered intravenously over 3 hours **Control** Placebo Saline given over 3 hours **Outcome measure(s)** Quality of life measured by the Prostate Cancer -Specific Quality of Life Instrument Performance scale Palliative response Present Pain Intensity	*none identified* **Overall risk of bias** High *though the study was randomised and double blinded, the authors did not provide any information on random sequence generation or allocation concealment*. **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
Hoskin (2015)	A Multicentre Randomized Trial of Ibandronate Compared With Single-Dose Radiotherapy for Localized Metastatic Bone Pain in Prostate Cancer Unspecified localised prostate cancer	**Study type** Bisphosphonate vs Radiotherapy Randomised controlled trial **Study details** Study location - United Kingdom Study setting - 58 centres across the National Cancer Research Network Study dates - April 2003 and November 2009 Duration of follow-up - 12 weeks to 52 weeks Sources of funding - Sponsored by University College London, funding from Cancer Research UK. Roche products limited provided Ibandronate free of charge **Inclusion criteria** Histologically confirmed prostate cancer Radiological bone metastasis confirmation using x-ray isotope, CT or MR scan Predicted life expectancy of more than 3 months Ability to comply with pain chart Ability to participate in quality of life assessments Ability to provide written consent **Exclusion criteria** Significant renal, hepatic or non-malignant-related diseases External-beam radiation therapy within 4 weeks Prior treatment with a bisphosphonate within the previous 6 months Prior treatment with radio-pharmaceuticals Hypocalcaemia, hypercalcaemia known hypersensitivity to ibandronate or other bisphosphonates Allergy to aspirin	**Random sequence generation** Low risk of bias "...*Randomisation within this non inferiority trial was computer generated and stratified by centre with a 1:1 allocation using block sizes of 4...*" **Allocation concealment** Low risk of bias *"…Patients were randomly assigned to treatment groups by Cancer Research UK and UCL Trials Centre..."* **Blinding of participants and personnel** High risk of bias *This was a "...non blind two arm trial..."* **Blinding of outcome assessment** High risk of bias *blinding was not used in the assessments* **Incomplete outcome data** Low risk of bias *none identified* **Selective reporting** Low risk of bias *none identified* **Other sources of bias** High risk of bias *Ibandronate was provided by the pharma company for free*

Short Title	Title	Study Characteristics	Risk of Bias
		Pregnancy or lactation (when breast and lung patients were recruited) Aminoglycoside antibiotics within 4 weeks of the study drug Change in systemic chemotherapy or hormone therapy within 4 weeks of trial entry Any investigational drug within 30 days of study trial **Sample characteristics** Sample size 470 patients Split between study groups Loss to follow-up 8 patients did not receive a bisphosphonate 11 patients did not receive the control treatment Mean age (SD) not provided median age (range) - 72 years (50-97) **Interventions** Ibandronate *Single 6mg intravenous infusion over 15 minutes, recommended volume was 100ml but infusions of up to 250mL were allowed* **Control** Radiotherapy *Megavoltage external beam therapy delivering a single dose of 8Gy* **Outcome measure(s)** Use of Analgesic drugs Brief Pain Inventory Pain - verbal ordinal scale Pain - visual analogue scale (patient) Pain response at 4 weeks (and 12 weeks)	**Overall risk of bias** High *The study was none blinded and the authors mentioned that assessment was not blinded either* **Directness** Partially applicable *comparator not placebo as stated in the protocol*

Short Title	Title	Study Characteristics	Risk of Bias
James (2016a)	Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multi-arm, multistage, platform randomised controlled trial Hormone-sensitive metastatic prostate cancer	**Study type** Bisphosphonate with SOC vs SOC alone Randomised controlled trial **Study details** Study location - Multicentre study - 100UK and Swiss sites Study setting - Hospitals Study dates - October 2005 and March 2013 Duration of follow-up followed up 6 weekly to 6 months, 12 weekly to 12 months, 6 monthly to 5 years, then annually Sources of funding Cancer research UK, Medical Research Council, Norvatis, Sanofi-Aventis, Pfizer, Jansen, Astellas, NIHR Clinical Research Network, Swiss Group for clinical research group **Inclusion criteria** Men with metastatic high risk localised or node positive prostate cancer, new diagnosis All commencing first-line long term hormone therapy patient had to be fit for chemotherapy with no clinically significant cardiovascular history **Sample characteristics** Sample size 3983 (total enrolled and randomly assigned) Split between study groups 4 arms reported in this paper but will only report on the relevant 2 Mean age (SD) median reported 65years (61-71years)	**Random sequence generation** Low risk of bias *"Patients were randomised centrally using a computerised algorithm, developed and maintained by the trials unit..."* **Allocation concealment** *Low risk of bias* *the authors provide justification for not masking treatment allocation as was considered impractical and of limited value to their primary out come* **Blinding of participants and personnel** Unclear risk of bias Unclear **Blinding of outcome assessment** Low risk of bias *some assessments were blinded e.g. "cause of death was determined by masked central review..."* **Incomplete outcome data** Low risk of bias *None identified* **Selective reporting** Low risk of bias *none identified* **Overall risk of bias** Low

Short Title	Title	Study Characteristics	Risk of Bias
		Interventions Standard of care and zoledronic acid zoledronic acid was given for six 3 weekly cycles, then 4 weekly cycles with prednisolone (10mg) daily and standard premedication before each injection **Control** Standard care Hormone therapy for at least 2 years with gonadotropin-releasing hormone agonists or antagonists or only between 2006 and 2011 for patients with non-metastatic disease Radiotherapy at 6-9 months after randomisation for patients with N0M0 disease **Outcome measure(s)** Adverse events Overall survival defined as time from randomisation to death from any cause Failure free survival defined as time from randomisation to first evidence of at least one biochemical failure, progression either locally, lymph nodes or in distant metastases or death from prostate cancer	**Directness** Partially directly applicable Not a placebo controlled trial - deviated from protocol
James (2016b)	Clinical Outcomes and Survival Following Treatment of Metastatic Castrate-Refractory Prostate Cancer With Docetaxel Alone or With Strontium-89, zoledronic Acid, or Both: The	**Study type** Bisphosphonate with Docetaxel or docetaxel alone Randomised controlled trial **Study details** Study location - United Kingdom Study setting - Hospitals Study dates - February 2005 and February 2012 Duration of follow-up - 12 months Sources of funding - Sanofi Aventis and Novartis Pharmaceuticals UK	**Random sequence generation** Low risk of bias *Patients were stratified by investigation centre and ECOG performance status at trial entry in a 1:1:1:1 allocation ratio using a computerized minimization algorithm accessed by telephone to the trials unit.* **Allocation concealment** Low risk of bias *Patients were stratified by investigation centre*

Short Title	Title	Study Characteristics	Risk of Bias
	TRAPEZE Randomized Clinical Trial Hormone-refractory metastatic prostate cancer	National Institute for Health Research Health Technology Assessment Programme **Inclusion criteria** Patients were confirmed of mCRPC by three sequential rises in serum PSA level with castrate levels of serum testosterone (50ng/dl) and/or an increase in cancer related pain and/or new metastatic lesions while on hormone therapy At least 2 radiographic methods being evidences of bone metastases Performance status ECOG ranged from 0 to 2 **Exclusion criteria** Prior treatment with a bisphosphonate within 2 months of trial entry Prior chemotherapy or radionuclide therapy for CRPC prior radiotherapy to more than 25% of bone marrow Bisphosphonate therapy within 2 months of trial entry Other malignant disease within the previous 5 years Known brain metastases Symptomatic peripheral neuropathy **Sample characteristics** Sample size 757 patients Split between study groups Loss to follow-up no loss to follow up in the intervention group and 3 patients loss to follow in the control group I**nterventions** Docetaxel with zoledronic acid *Intravenous doses of 4mg docetaxel plus zoledronic acid (DZA) per week during chemotherapy then 4 doses per week until disease*	**Blinding of participants and personnel** High risk of bias *this was an open label study* **Blinding of outcome assessment** High risk of bias open label study **Incomplete outcome data** Low risk of bias none identified **Selective reporting** Low risk of bias none identified **Overall risk of bias** Low **Directness** Indirectly applicable the comparator is not a placebo as stated in the protocol

Short Title	Title	Study Characteristics	Risk of Bias
		progression; **Control** Docetaxel alone *3 intravenous doses of75mg/m2 docetaxel per week up to 10 cycles* **Outcome measure(s)** Skeletal related events Adverse events Progression free survival	
Kamba (2017)	A phase III multicentre, randomized, controlled study of combined androgen blockade with versus without zoledronic acid in prostate cancer patients with metastatic bone disease: results of the ZAPCA trial Not specified metastatic prostate cancer	**Study type** Bisphosphonate with CAB versus CAB alone Randomised controlled trial **Study details** Study location - Japan Study dates - May 2008 and December 2010 Duration of follow-up - median follow-up 41.5 months Sources of funding - Grant for Urologic Research from Kyoto University Hospital. **Inclusion criteria** Histologically confirmed prostate cancer Performance status ECOG ranged from 0 to 2 Treatment-naive prostate cancer At least one bone metastasis detected by bone scan Baseline PSA concentration of >/=30ng/mL **Exclusion criteria** Severe cardiovascular disease, refractory hypertension, symptomatic coronary artery disease, a serum creatine of more than	**Random sequence generation** Low risk of bias *"...computer-based randomization was conducted at the Translational Research Informatics Centre with stratification according to the treatment institution...."* **Allocation concealment** Unclear risk of bias *No details provided* **Blinding of participants and** personnel *Unclear risk of bias* *No details provided* **Blinding of outcome assessment** Unclear risk of bias *No details provided* **Incomplete outcome data** Low risk of bias *None identified*

Short Title	Title	Study Characteristics	Risk of Bias
		3.0mg/dl(265mmol/L) or a corrected serum calcium of less than 8.0mg/dL or greater than 11.6mg/dL Prior treatment with a bisphosphonate Prior local curative therapy prior ADT for >2weeks, chemotherapy, or bisphosphonate treatment **Sample characteristics** Sample size 222 participants Split between study groups Loss to follow-up CAB only group - 78% loss to follow up zoledronic Acid - 72% loss to follow up Mean age (SD) provided as a median - 72 years(50,89) Prostate specific antigen ng/mL (mean, SD) provided only as median 371.0 (30, 16,600) **Interventions** Combined Androgen blockade and zoledronic acid delivered intravenously every 4 weeks for up to 2 years. Doses of ZA were 4, 3.5 and 3.0mg for patients with creatinine clearances of >60, 50-60 and 30-49mL/min **Control** Combined androgen blockade alone **Outcome measure(s)** Time to the first skeletal-related event Adverse events Defined using the Common terminology criteria for Adverse events Time to treatment failure interval between the date of randomisation and the earliest date of	**Selective reporting** Low risk of bias *none identified* **Overall risk of bias** Moderate *Due to uncertainties surrounding randomisation concealment and blinding* **Directness** Partially applicable *comparator not placebo as stated in the protocol*

Short Title	Title	Study Characteristics	Risk of Bias
		PSA progression, clinical progression, clinical progression, first SRE, death for any reason, or cessation of protocol treatment for any reason.	
Kylmälä (1997)	Concomitant i.v. and oral clodronate in the relief of bone pain--a double-blind placebo-controlled study in patients with prostate cancer Not-specified metastatic prostate cancer	**Study type** Bisphosphonate vs Placebo Randomised controlled trial **Study details** Study location - Finland Study setting - hospital Duration of follow-up - 12 months Sources of funding - Finish Academy of Sciences Finnish Cancer Foundation Finnish Medical society duodecim Reino Lahtikari Foundation Leiras Clinical Research **Inclusion criteria** Estimated life expectancy of at least 6months No signs of clinically relevant renal or liver sufficient No peptic ulcer treated with antacids No radiation therapy in the 2 weeks preceding the trial **Sample characteristics** Sample size 57 patients Split between study groups **Interventions** Clodronate *5 days of intravenous administration (300mg/day) and was continued orally 1.6g/day for 12 months*	**Random sequence generation** Unclear risk of bias No details provided **Allocation concealment** Unclear risk of bias *No details provided* **Blinding of participants and personnel** Low risk of bias *double blind controlled study* **Blinding of outcome assessment** Unclear risk of bias *No details provided* **Selective reporting** Unclear risk of bias *none identified* **Overall risk of bias** High *Small sample size and uncertainties surrounding sequence generation and allocation concealment* **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		Control Placebo **Outcome measure(s)** Use of Analgesic drugs Pain - verbal ordinal scale Pain - visual analogue scale (patient) Performance scale five step grading scale(0, asymptomatic; 1,minor symptoms; 2, <50% of the time in bed; 4, totally bedridden)	
Saad (2002)	A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma Hormone refractory metastatic prostate cancer	**Study type** Bisphosphonate vs Placebo Randomised controlled trial Associated studies *Saad Fred (2005) Clinical benefit of zoledronic acid for the prevention of skeletal complications in advanced prostate cancer. Clinical prostate cancer 4(1),* *31-7 Saad F, Gleason Dm, Murray R, Tchekmedyian S, Venner P, Lacombe L, Chin Jl, Vinholes Jj, Goas Ja, and Zheng M (2004) Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. Journal of the national cancer institute 96(11), 879-882* *Saad F, Chen Ym, Gleason Dm, and Chin J (2007) Continuing benefit of zoledronic acid in preventing skeletal complications in patients with bone metastases. Clinical genitourinary cancer 5(6), 390-396* *Weinfurt K P, Li Y, Castel L D, Saad F, Timbie J W, Glendenning G A, and Schulman K A (2005) The significance of skeletal-related events for the health-related quality of life of patients with metastatic prostate cancer. Annals of oncology: official journal of the European Society for Medical Oncology 16(4), 579-84*	**Random sequence generation** Low risk of bias *"....randomly assigned to treatment according to a computer-generated list of randomization numbers provided to each centre..."* **Allocation concealment** Low risk of bias *"....double blind study. The pharmacist at each participating centre was responsible for maintaining the blinding of the study"* **Blinding of participants and personnel** Low risk of bias *"at each study drug treatment visit, patients received a 100mL-infusion of normal saline with or without study drug to maintain the blinding of the*

Short Title	Title	Study Characteristics	Risk of Bias
		Weinfurt Kp, Anstrom Kj, Castel Ld, Schulman Ka, and Saad F (2006) Effect of zoledronic acid on pain associated with bone metastasis in patients with prostate cancer. Annals of oncology : official journal of the European society for medical oncology 17(6), 986-989 **Study details** Study location Multi centres - USA, Argentina, Australia, Canada, France, Brazil, Germany and United Kingdom Study setting hospitals Study dates June 1998 to January 2001 Duration of follow-up 3 years Sources of funding Norvatis Pharmaceuticals **Inclusion criteria** Documented history of bone metastases and had 3 consecutive increasing serum PSA while on hormonal therapy Serum testosterone levels within the castrate range (50ng/dl) Past or current objective evidence of bone metastasis (defined as more than three foci increased activity on a bone scan) ECOG performance status 0 to 2 **Exclusion criteria** Previous usage of bisphosphonates within 1 year Bone pain requiring strong narcotic therapy Patients receiving cytotoxic chemotherapy (with the exception of Estramustine) Patient receive radiation therapy within 3 months Severe cardiovascular disease, refractory hypertension, symptomatic coronary artery disease, a serum creatine of more than	*study..."* **Blinding of outcome assessment** Low risk of bias *"all radiologic assessments were reviewed by a central radiologist, who was blinded to treatment assignment."* **Incomplete outcome data** Low risk of bias *None identified* **Selective reporting** Low risk of bias *none identified* **Overall risk of bias** Low **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		3.0mg/dl(265mmol/L) or a corrected serum calcium of less than 8.0mg/dL or greater than 11.6mg/dL **Sample characteristics** Sample size 643 patients Split between study groups Loss to follow-up zoledronic Acid 4mg- 55% zoledronic Acid 8/4mg - 65% Placebo - 63% loss of follow up as a result of consent withdrawal, adverse events, death and unsatisfactory therapeutic effect Mean age (SD) 71.8 years (7.9) Mean number of bone metastases (SD) ZA 4mg-4.2(2.5) ZA 8/4mg - 4.1(2.5) Placebo - 4.2(2.6) Site of metastases at baseline ZA 4mg ZA 8/4mg placebo Bone 100% 100% 100% distant lymph nodes 13.6% 8.6% 7.2% Lung 2.8% 1.8% 2.5% Liver 0.5% 2.3% 0.5% Prostate specific antigen ng/mL (mean, SD) ZA 4mg group - 276.5(737.1) ZA 8/4mg group -350.9(1148.9) Placebo group - 211.1(464.9) **Interventions** zoledronic Acid at 4mg every 3 weeks for 20 cycles (15 months) zoledronic Acid 8/4mg every 3 weeks for 20 cycles (15 months) **Control** Placebo every 3 weeks for 20 cycles (15 months)	

Short Title	Title	Study Characteristics	Risk of Bias
		Outcome measure(s) Skeletal related events Pathologic bone fractures (vertebrae, non-vertebrae), spinal cord compression, surgery to bone, radiation therapy to bone, or a change of antineoplastic therapy to treat bone pain. (only one skeletal event was included in the count of the total number of skeletal related events) Time to the first skeletal-related event Proportion of patients with individual skeletal related events Skeletal morbidity rate Time to disease progression Quality of life Functional Assessment of Cancer therapy -general Euro Quality of life EQ-5D (EURO QOL)	
Small (2003)	Combined analysis of two multicentre, randomized, placebo-controlled studies of Pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer Unspecified metastatic prostate cancer	**Study type** Bisphosphonate vs placebo Randomised controlled trial **Study details** Study location 2 studies - International Study and USA study Study setting hospitals Study dates February 1998 and November 1999 Duration of follow-up 27 weeks Sources of funding Norvatis Pharmaceuticals **Inclusion criteria** Histologically confirmed prostate cancer hormone- refractory	**Random sequence generation** Unclear risk of bias *the authors did not state any details regarding random sequence generation* **Allocation concealment** Unclear risk of bias *no details provided though study is described as double blinded study* **Blinding of participants and personnel** Low risk of bias *Study described as double -blind trial but no farther information provided* **Blinding of outcome assessment** Unclear risk of bias *no information provided*

Short Title	Title	Study Characteristics	Risk of Bias
		estimated life expectancy of at least 6months Radiological bone metastasis confirmation using x ray isotope, CT or MR scan developed progressive systemic disease despite androgen deprivation as evidenced by progression of metastatic disease in bone or extra skeletal sites **Exclusion criteria** Prior treatment with a bisphosphonate more than 3 doses or treatment within 90 days of randomisation Clinically significant abnormal ECG, ascites, impending spinal cord compression or spinal orthosis or a skeletal event within 1 month before randomisation Change in chemotherapy or hormone therapy regimen Drugs or therapies that affected osteoclast therapy **Sample characteristics** Sample size 180 patients Split between study groups Loss to follow-up 8% loss to follow up in both groups Mean age (SD) not provided, median age 71years (42-88) Prostate specific antigen ng/mL (mean, SD) Intervention group 453 ng/ml (1,630) Placebo group 539 ng/ml (1,347) I**nterventions** Pamidronate *90mg admixed in 250mL 5% Dextrose via 2 hour IV infusion every 3 weeks for 27 weeks (9 visits)*	**Incomplete outcome data** Low risk of bias *none identified* **Selective reporting** Low risk of bias none identified **Overall risk of bias** Moderate *uncertainties regarding allocation concealment and sequence generation*. **Directness** Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		Control Placebo *250mL 5% Dextrose via 2 hour IV infusion every 3 weeks for 27 weeks (9 visits) consenting patients were provided open label treatment after week 27* **Outcome measure(s)** Skeletal related events weeks 9 and 27, defined as hypercalcemia, a pathologic fracture, requirement of radiation therapy to bone for pain relief, spinal cord compression, Adverse events Use of Analgesic drugs Brief Pain Inventory	
Smith (2014)	Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: results of CALGB 90202 (alliance) Hormone-sensitive metastatic prostate cancer	**Study type** Bisphosphonate vs placebo Randomised controlled trial **Study details** Study location USA Study dates January 2004 and May 2012 Duration of follow-up approx. 12 months (11.8 months an 13.6 months median follow up time in the bisphosphonate and placebo respectively) Sources of funding National Cancer Institute to the Alliance for Clinical Trials in Oncology and to the Alliance Statistics and Data Centre as well as Novartis Oncology and research awards from the Prostate Cancer Foundation	**Random sequence generation** Low risk of bias "...randomised block design was used..." **Allocation concealment** Unclear risk of bias No details provided **Blinding of participants and personnel** Unclear risk of bias No details provided **Blinding of outcome assessmen**t Unclear risk of bias *No details provided* **Incomplete outcome** data Low risk of bias

Short Title	Title	Study Characteristics	Risk of Bias
		Inclusion criteria Histologically confirmed prostate cancer At least 2 radiographic methods being evidences of bone metastases Performance status ECOG ranged from 0 to 2 **Exclusion criteria** External-beam radiation therapy within 4 weeks Prior treatment with a bisphosphonate Prior treatment with radio-pharmaceuticals Patients who received ADT at any time more than 6 months before enrolment **Sample characteristics** Sample size 645 patients Split between study groups Mean age (SD) not provided - Median age bisphosphonate group - 66.1 years placebo group - 66.7 years **Interventions** zoledronic Acid at 4mg 4mg was provided to patients with creatinine clearance higher than 60mL/min, then those with levels of 50-60mL/min, 40 to 49mL/min, 30-39mL/min received doses of 3.5, 3.3 and 3.0mg respectively **Control** Placebo **Outcome measure(s)** Skeletal related events clinical fracture, spinal cord compression, surgery to bone, death as a result of prostate cancer	*None identified* **Selective reporting** Low risk of bias None identified **Overall risk of bias** Moderate *Due to uncertainties regarding allocation concealment and blinding* **Directness** Directly applicable

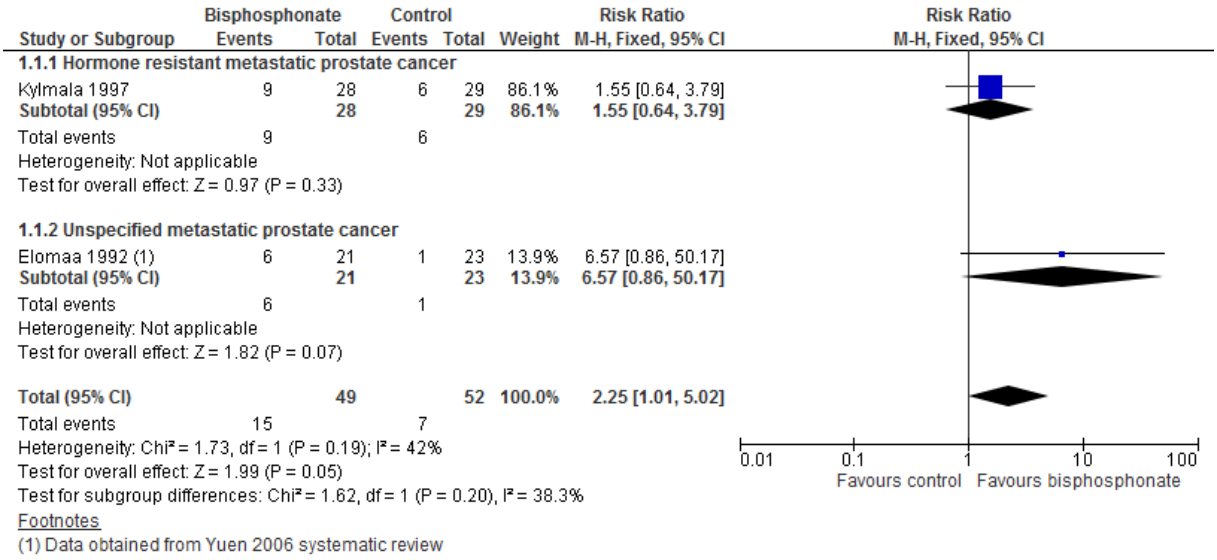
Short Title	Title	Study Characteristics	Risk of Bias
		Time to the first skeletal-related event Adverse events Progression free survival	
Ueno (2013)	Efficacy of combined androgen blockade with zoledronic acid treatment in prostate cancer with bone metastasis: the ZABTON-PC (zoledronic acid/androgen blockade trial on prostate cancer) study Unspecified metastatic cancer	**Study type** Bisphosphonate with CAB versus CAB alone Randomised controlled trial **Study details** Study location Japan Study setting 12 domestic medical institutions including University hospitals Study dates July 2006 to June 2011 **Inclusion criteria** Histologically confirmed prostate cancer but untreated prostate cancer At least one bone metastasis detected by bone scan developed progressive systemic disease despite androgen deprivation as evidenced by progression of metastatic disease in bone or extra skeletal sites **Exclusion criteria** receiving an invasive dental treatment such as tooth extraction or implant within 6 months before participating in the study **Sample characteristics** Sample size 60 patients Split between study groups Mean age (SD)	**Random sequence generation** Unclear risk of bias "patients were screened at each institution after verification of eligibility criteria and were randomly assigned..." no details provided regarding sequence generation **Allocation concealment** Unclear risk of bias no details provided **Blinding of participants and personnel** High risk of bias open label study **Blinding of outcome assessment** High risk of bias open label study **Incomplete outcome data** Low risk of bias no issues identified **Selective reporting** Low risk of bias no issues identified **Overall risk of bias** High

Short Title	Title	Study Characteristics	Risk of Bias
		71.8 years (no SD) **Interventions** Combined Androgen blockade and zoledronic acid 4 mg of ZA were administered by intravenous infusion within one month after starting the CAB therapy and thereafter the intravenous infusion was repeated every 4 weeks **Control** Combined androgen blockade alone **Outcome measure(s)** Skeletal related events Adverse events ECOG performance status Pain - verbal ordinal scale Progression free survival	Study was not blinded and details on sequence generation or allocation concealment are not provided **Directness** Indirectly applicable study comparator not placebo as detailed in the protocol

Appendix F – Forest plots

Bisphosphonate versus Placebo

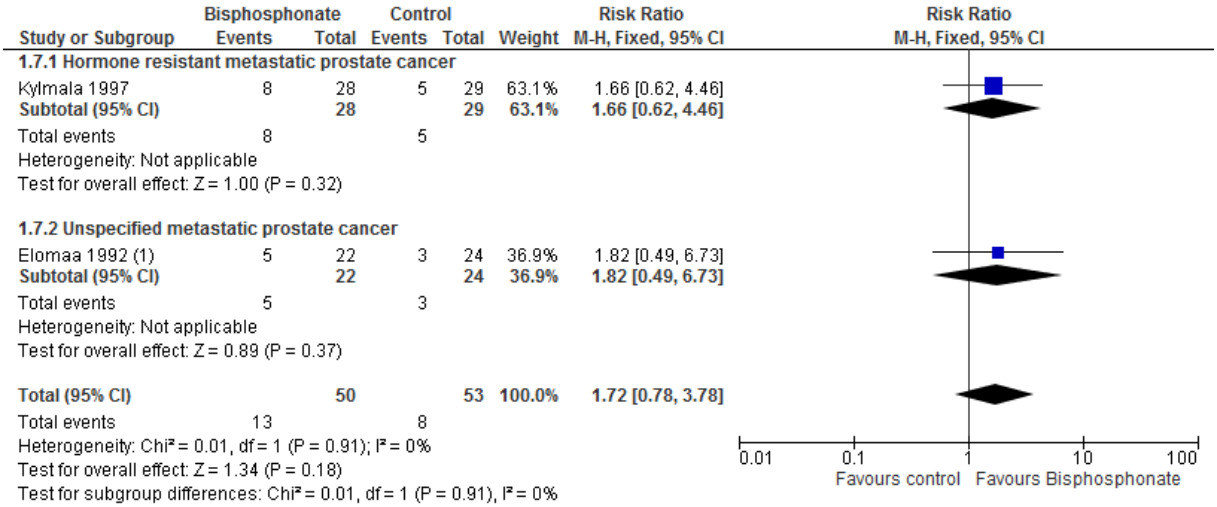
Patients reporting no pain



Footnotes

(1) Data obtained from Yuen 2006 systematic review

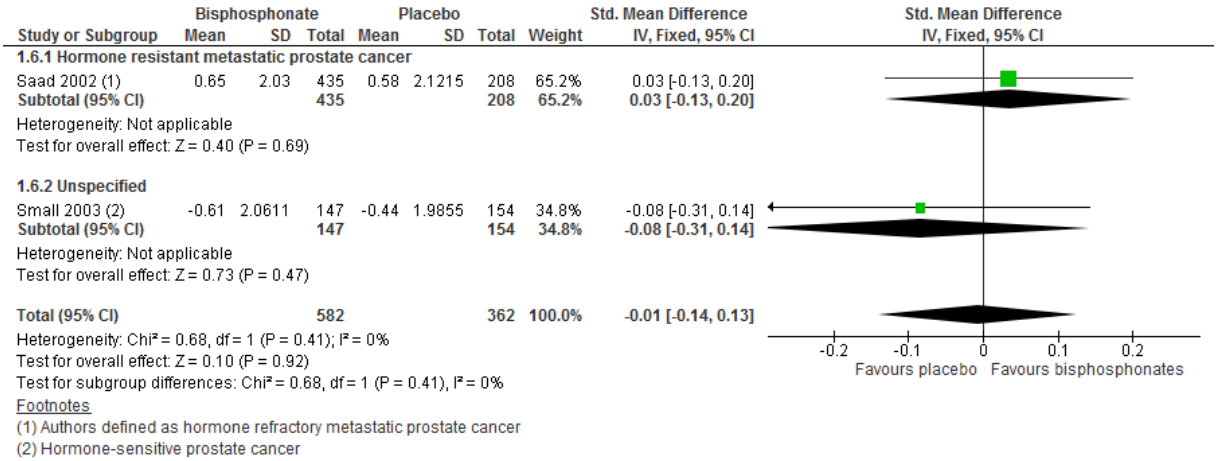
Patients with decreased analgesic use



Footnotes

(1) Data obtained from Yuen 2006 systematic review

Change in mean scores

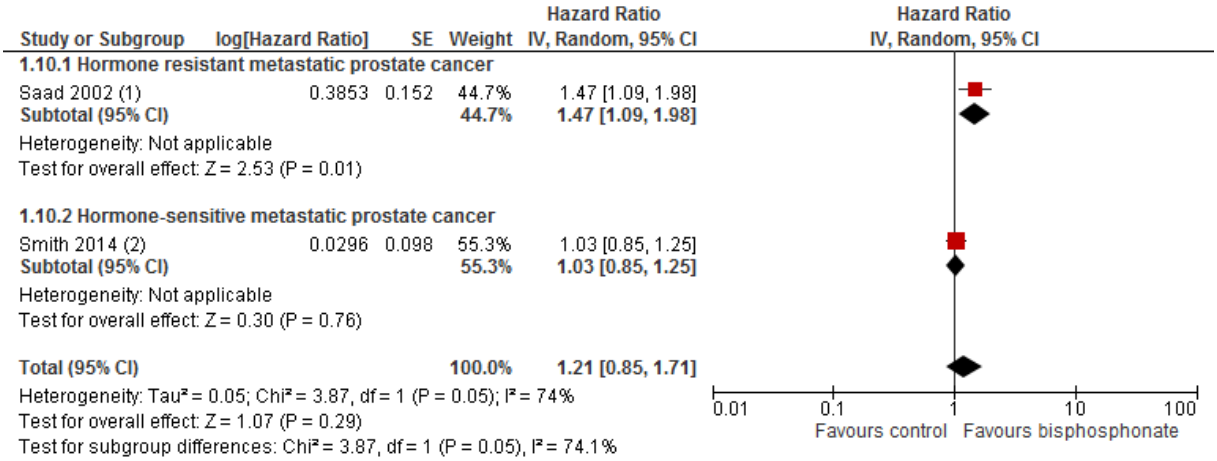


Footnotes

(1) Authors defined as hormone refractory metastatic prostate cancer

(2) Hormone-sensitive prostate cancer

Time to first skeletal event

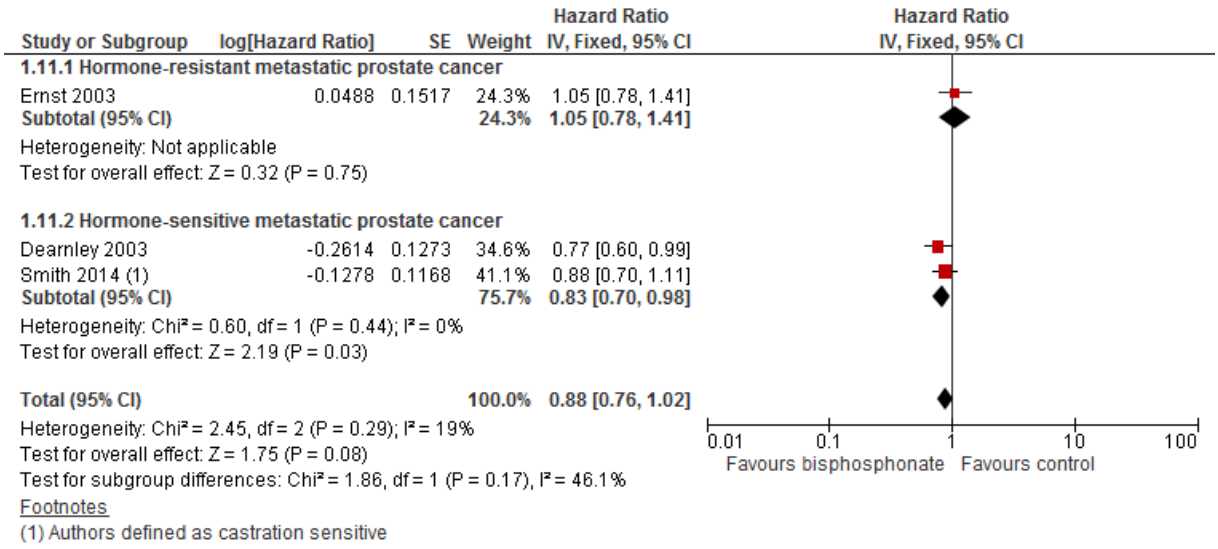


Footnotes

(1) Authors defined as hormone refractory

(2) Authors defined a castration sensitive

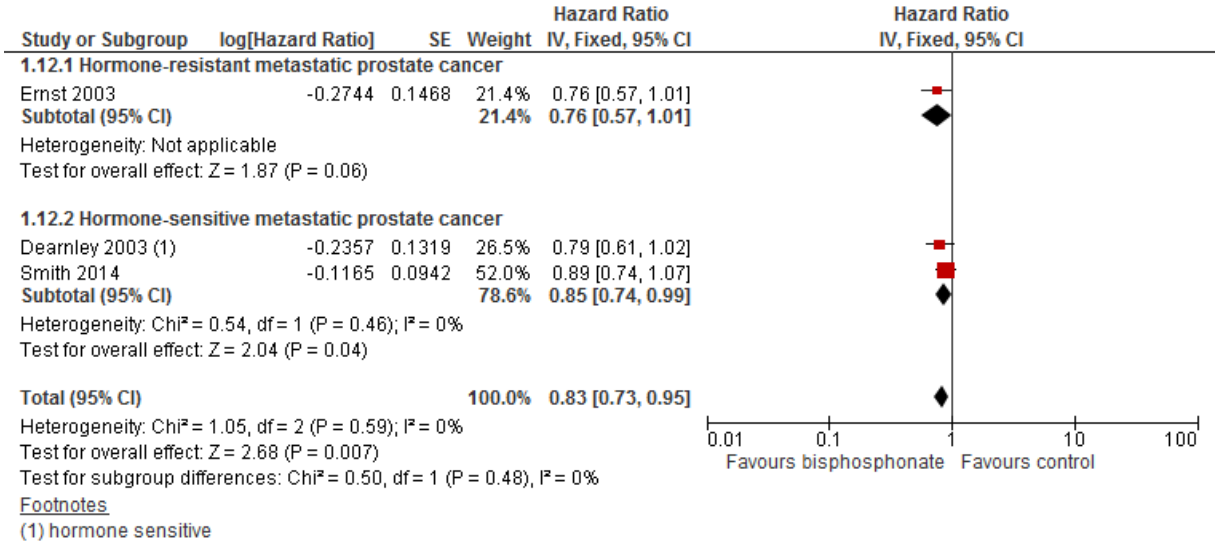
Overall survival



Footnotes

(1) Authors defined as castration sensitive

Symptomatic bone progression-free survival

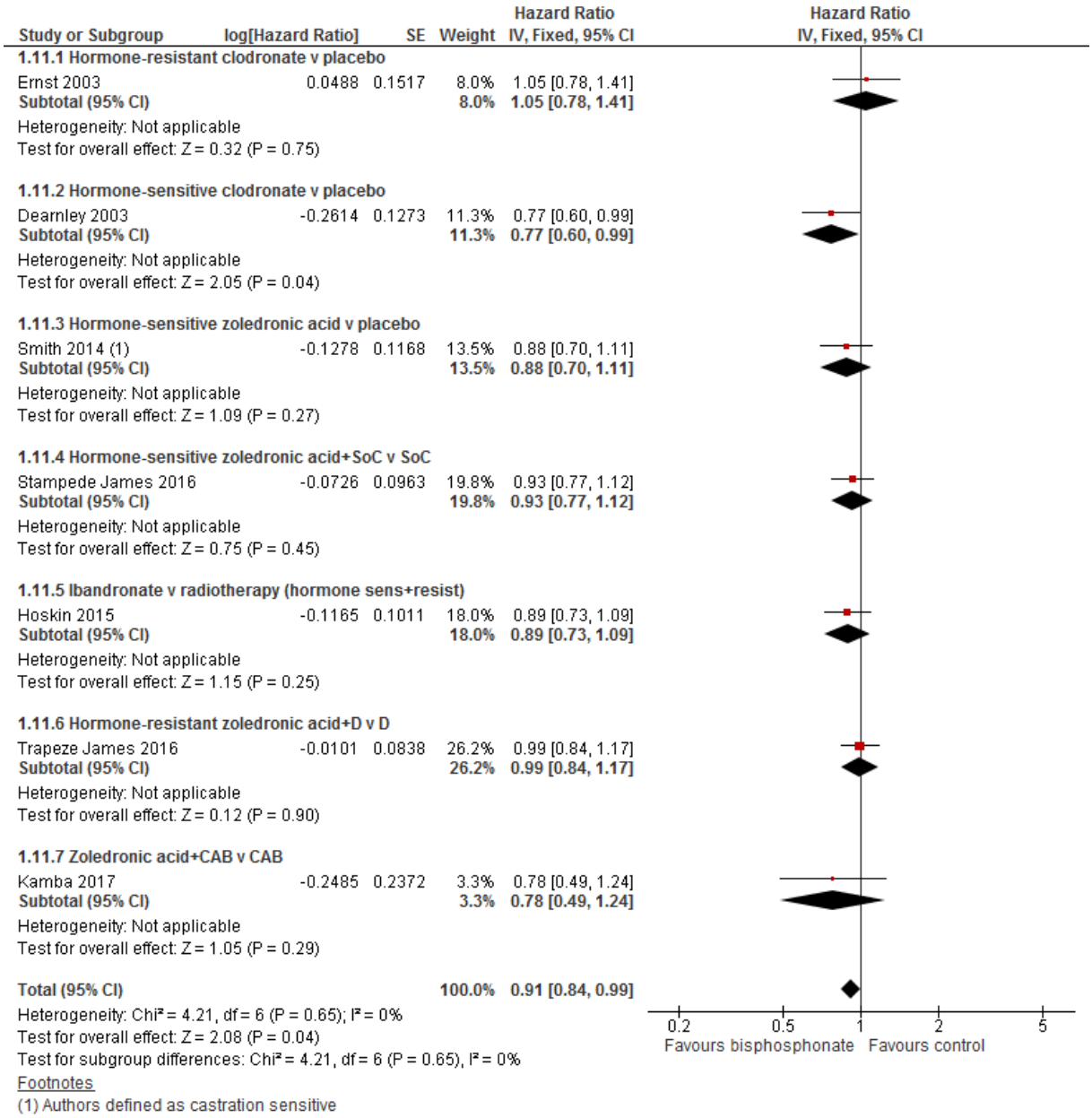


Footnotes

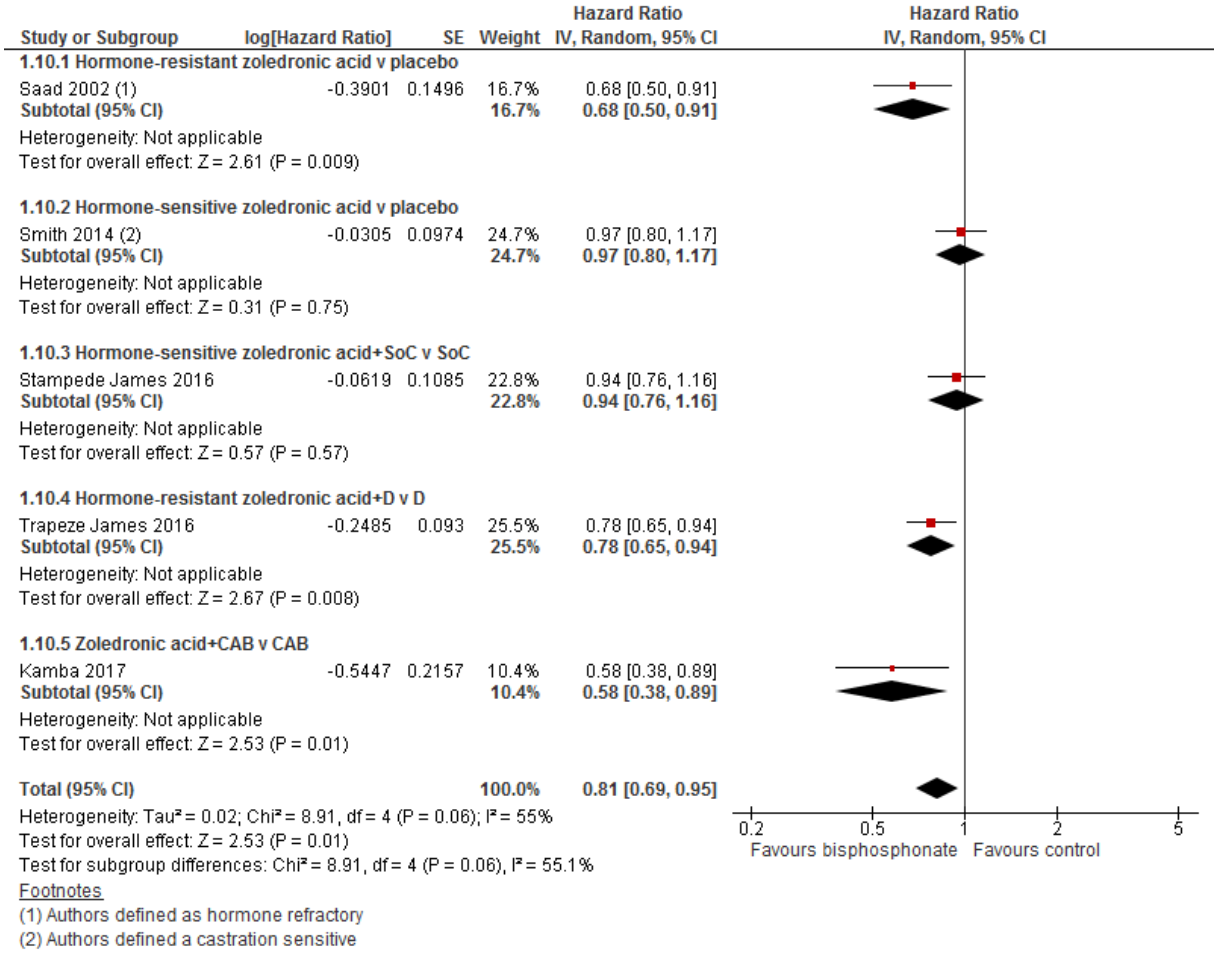
(1) hormone sensitive

All studies stratified by population and comparator

Overall survival



Time to first Skeletal-related events



Footnotes

(1) Authors defined as hormone refractory

(2) Authors defined a castration sensitive

Appendix G – GRADE tables

Bisphosphonate versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control*	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Patients reporting no pain (RR >1 favours bisphosphonate)										
2 studies (Elomaa[a] 1992, Kylmala[b] 1997)	RCTs	101	RR 2.25 (1.01, 5.02)	6.93 per 100 people	15.6 per 100 people (from 7 fewer to 35 more)	Very serious[1]	Not serious	N/A	Serious[2]	Very Low
Hormone-refractory metastatic prostate cancer (clodronate versus placebo)										
(Elomaa[a] 1992,	RCTs	44	RR 6.57 (0.87, 50.17)	2.2 per 100 people	15 per 100 people (from 2 fewer to 110 more)	Very serious[1]	N/A	N/A	Serious[2]	Very Low
Unspecified-metastatic prostate cancer (clodronate versus placebo)										
Kylmala[b] 1997)	RCTs	57	RR 1.55 (0.64, 3.79)	11 per 100 people	16 per 100 people (from 7 fewer to 42 more)	Very serious[1]	N/A	N/A	Very Serious[4]	Very Low
Patients reporting no analgesic use (RR >1 favours bisphosphonate)										
2 studies (Elomaa[a] 1992, Kylmala[b] 1997)	RCTs	103	RR 1.72 (0.78, 3.78)	8 per 100 people	13.6 per 100 people (from 6 fewer to 30 more)	Very serious[1]	Serious[3]	N/A	Very Serious[4]	Very low
Hormone-refractory metastatic prostate cancer (clodronate versus placebo)										
(Elomaa[a] 1992,	RCTs	46	RR 1.82 (0.46, 6.73)	6.5 per 100 people	11.8 per 100 people (from 3 fewer to 44 more)	Very serious[1]	N/A	N/A	Very Serious[4]	Very Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control*	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Unspecified- metastatic prostate cancer (clodronate versus placebo)										
Kylmala[b] 1997)	RCTs	57	RR 1.66 (0.78, 3.78)	5.3 per 100 people	8.73 per 100 people (4 fewer to 20 more)	Very serious[1]	N/A	N/A	Very Serious[4]	Very Low
Change in mean pain scores (SMD >0 favours bisphosphonate)										
2 studies (Saad[A] (2002), Small[b] (2003)	RCTs	944	SMD -0.01 (-0.14, 0.13)	-	-	Not serious	Not serious	Not serious	Not serious	High
Hormone-refractory metastatic cancer (zoledronic acid versus prostate cancer)										
Saad (2002)	RCTs	643	SMD -0.01 (-0.13, 0.20)	-	-	Not serious	Not serious	Not serious	Not serious	High
Unspecified metastatic prostate cancer (Clodronate versus placebo)										
Small (2003)	RCTs	301	SMD -0.08 (-0.31, 0.14)	-	-	Not serious	Not serious	Not serious	Serious[6]	Moderate
Time to first skeletal event (HR <1 favours bisphosphonate) **Hormone sensitive/refractory prostate cancer**										
2 studies (Saad[a] (2002), Smith[A] (2014))	RCTs	1288	HR 0.82 (0.58, 1.17)	-	-	Not serious	Very serious[5]	Not serious	Serious[6]	Very low
Hormone-refractory metastatic prostate cancer (zoledronic acid versus placebo)										
1 study (Saad[a] (2002),	RCTs	645	HR 0.68 (0.50, 0.91)	-	-	Not serious	N/A	Not serious	Serious[6]	Moderate
Hormone-sensitive metastatic prostate cancer (zoledronic acid versus placebo)										
1 study Smith (2014))	RCTs	643	HR 0.97 (0.80, 1.17)	-	-	Not serious	N/A	Not serious	Serious[6]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control*	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Overall survival (HR <1 favours bisphosphonate) **Hormone sensitive/refractory prostate cancer**										
3 studies (Dearnaley[c] (2003), Ernst[a] (2003), Smith[a] (2014))	RCTs	1,165	HR 0.88 (0.75, 1.02)	-	-	Not serious	Not serious	Not serious	Serious[6]	Moderate
Hormone-refractory metastatic prostate cancer (clodronate versus placebo)										
1 study (Ernst (2003),	RCTs		HR 1.05 (0.78, 1.41)	-	-	Not serious	N/A	Not serious	Serious[6]	Moderate
Hormone-sensitive metastatic prostate cancer										
2 studies (Dearnaley (2003), Smith (2014)	RCTs		HR 0.83 (0.70, 0.98)	-	-	Not serious	Not serious	Not serious	Not serious	High
Analysis excluding studies with an overall high risk of bias										
1 study Smith (2014)	RCTs		HR 0.88 (0.70, 1.11)	-	-	Not serious	N/A	Not serious	Serious[6]	Moderate
Symptomatic bone progression-free survival (HR <1 favours bisphosphonate) **Hormone sensitive/refractory prostate cancer**										
3 studies (Dearnaley (2003), Ernst (2003), Smith (2014))	RCTs	1,165	HR 0.83 (0.73, 0.95)	-	-	Serious[7]	Not serious	Not serious	Not serious	Moderate
Hormone-refractory metastatic prostate cancer (clodronate versus placebo)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control*	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 study (Ernst (2003),	RCTs		HR 0.76 (0.57, 1.01)	-	-	Very serious[1]	N/A	Not serious	Serious[6]	Very low
Hormone-sensitive metastatic prostate cancer										
2 studies (Dearnaley (2003), Smith (2014))	RCTs		HR 0.85 (0.74, 0.99)	-	-	Serious[7]	Not serious	Not serious	Not serious	Moderate
Analysis excluding studies with an overall high risk of bias										
1 study (Smith (2014))	RCTs		HR 0.89 (0.74, 1.07)	-	-	Serious[7]	N/A	Not serious	Serious[6]	Low
Worsened performance status (HR <1 favours bisphosphonate) **Hormone-sensitive metastatic prostate cancer**										
1 studies (Dearnaley (2003),	RCT	311	HR 0.71 (0.56, 0.90)	-	-	Very serious[1]	N/A	Not serious	Serious[6]	Very Low
Time to performance status greater than 2 (HR <1 favours bisphosphonate) **Hormone-sensitive metastatic prostate cancer**										
1 studies (Dearnaley (2003),	RCT	311	HR 0.75 (0.57, 0.99)	-	-	Very serious[1]	N/A	Not serious	Not serious	Low
Time to first regular analgesic use (HR <1 favours bisphosphonate) **Hormone-sensitive metastatic prostate cancer**										
1 studies (Dearnaley (2003),	RCT	311	HR 1.12 (0.86, 1.46)	-	-	Very serious[1]	N/A	Not serious	Serious[6]	Very low

1. Outcome based high risk of bias due to studies not blinded and open label – downgraded twice
2. 95% confidence intervals for the effect size crossed one line of the MID – downgraded once
3. I^2 was between 33.3% and 66.7% - downgraded once
4. 95% confidence intervals for the effect size crossed both lines of the MID – downgraded twice

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control*	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality

5. I^2 was greater than 66.7%, outcome - downgraded twice
6. Confidence intervals crossed line of no effect - downgraded once
7. Outcome based moderate risk of bias due to unclear allocation concealment and outcome assessment – downgrade once

* Derived by taking the overall number of events/total number of participants and multiply by 100

Bisphosphonate with standard of care versus standard care alone

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Overall survival* (HR <1 favours bisphosphonate) **Hormone-sensitive metastatic prostate cancer (zoledronic acid with standard of care versus standard of care alone)**										
1 study (James (2016a)	RCT	1,090	HR 0.93 (0.77, 1.12)	-	-	Not serious	N/A	Serious[1]	Serious[2]	Low
Time to first skeletal event (HR <1 favours bisphosphonate) **Hormone-sensitive metastatic prostate cancer (zoledronic acid with standard of care versus standard of care alone)**										
1 study (James (2016a),	RCT	1,090	HR 0.94 (0.76, 1.16)	-	-	Not serious	N/A	Serious[1]	Serious[2]	Low

1. Partial indirectness – comparator not placebo as stated in the protocol - downgraded once
2. Confidence intervals crossed line of no effect - downgraded once

Bisphosphonate versus radiotherapy

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Overall survival (I HR <1 favours bisphosphonate) **Localised prostate cancer (unspecified, ibandronate versus radiotherapy)**										
1 study (Hoskin (2015)	RCT	470	HR 0.89 (0.73, 1.09)	-	-	Not serious	N/A	Serious[1]	Serious[2]	Low

1. Partially applicable, comparator was not placebo as stated in the protocol – downgraded once
2. Confidence intervals crossed line of no effect – downgraded once

Bisphosphonate with docetaxel versus docetaxel alone

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Overall Survival (HR <1 lower favours bisphosphonate) **Hormone-refractory metastatic prostate cancer (zoledronic acid with docetaxel versus docetaxel alone)**										
1 study (James 2016b)	RCT	137	HR 0.99 (0.84, 1.17)	-	-	Not serious	N/A	Serious[1]	Serious[2]	Low
Clinical Progression free survival (HR <1 favours bisphosphonate)										
1 study (James 2016b)	RCT	137	HR 0.98 (0.85, 1.13)	-	-	Not serious	N/A	Serious[1]	Serious[2]	Low
Pain progression free interval (HR <1 favours bisphosphonate)										
1 study (James 2016b)	RCT	137	HR 0.91 (0.75, 1.10)	-	-	Not serious	N/A	Serious[1]	Serious[2]	Low
Skeletal related event – free interval (HR <1 favours bisphosphonate)										
1 study (James 2016b)	RCT	137	HR 0.78 (0.65, 0.94)	-	-	Not serious	N/A	Serious[1]	Not serious	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1. Partially applicable, comparator was not placebo as stated in the protocol, downgraded once 2. Confidence intervals crossed line of no effect, downgraded once										

Bisphosphonate with Combined androgen blockade (CAB) versus CAB alone

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control*	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Overall survival (HR <1 favours bisphosphonate) **Not specified metastatic prostate cancer (zoledronic acid with CAB versus CAB)**										
1 study (Kamba 2017)	RCT	224	HR 0.78 (0.49, 1.24)	-	-	Not serious	N/A	Serious[1]	Serious[2]	Low
Prostate specific-antigen Progression-free survival (I HR <1 favours bisphosphonate)										
1 study (Ueno 2013)	RCT	60	HR 1.91 (0.94, 3.86)	-	-	Not serious	N/A	Serious[1]	Very Serious[3]	Very Low
Time to first skeletal event (HR <1 favours bisphosphonate) **Not specified metastatic prostate cancer (zoledronic acid with CAB versus CAB)**										
1 study (Kamba 2017)	RCT	224	HR 0.58 (0.38, 0.89)	-	-	Not serious	N/A	Serious[1]	Not serious	Moderate
Patients with adverse events within 6 months of trial (RR <1 favours bisphosphonate) **Not specified metastatic prostate cancer (zoledronic acid with CAB versus CAB)** **1. Total**										
1 Study (Kamba 2017)	RCT	224	RR 1.28 (0.85, 1.92)	25.9 per 100 people	33.2 per 100 people (from 22 fewer to 49.7 more)	Not serious	N/A	Serious[1]	Serious[4]	Low
2. Urinary retention (RR <1 favours bisphosphonate)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control*	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 Study (Kamba 2017)	RCT	224	RR 0.67 (0.19, 2.30)	5.4 per 100 people	3.6 per 100 people (from 1 fewer to 12 more)	Not serious	N/A	Serious[1]	Very Serious[5]	Very Low
3. Urinary incontinence (RR <1 favours bisphosphonate)										
1 Study (Kamba 2017)	RCT	224	RR 1.00 (0.14, 6.98)	1.8 per 100 people	1.8 per 100 people (from 0.25 fewer to 12.5 more)	Not serious	N/A	Serious[1]	Very Serious[5]	Very Low
4. Erectile dysfunction (RR <1 favours bisphosphonate)										
1 Study (Kamba 2017)	RCT	224	RR 1.09 (0.66, 1.80)	20.5 per 100 people	22.3 per 100 people (from 22 fewer to	Not serious	N/A	Serious[1]	Very Serious[5]	Very Low
5. Osteonecrosis of the jaw (RR <1 favours bisphosphonate)										
1 Study (Kamba 2017)	RCT	224	RR 5.00 (0.24, 102.99)	No events in control group	-	Not serious	N/A	Serious[1]	Very Serious[5]	Very low

1. Partially applicable, comparator was not placebo as stated in the protocol - downgraded once
2. Confidence intervals crossed line of no effect - downgraded once
3. Confidence intervals crosses line of no effect and study had a small sample size – downgraded twice
4. 95% confidence intervals for the effect size crossed one line of the MID – downgraded once
5. 95% confidence intervals for the effect size crossed both lines of the MID – downgraded twice

* Derived by taking the overall number of event/total number of participants and multiply by 100

Appendix H – Excluded Studies

Short Title	Title	Reason for exclusion
Abetz (2006)	Impact of zoledronic acid (Z) on pain in prostate cancer patients with bone metastases in a randomised placebo-control trial	Conference abstract
Adami (1989)	Clodronate therapy of metastatic bone disease in patients with prostatic carcinoma	Linked to the Yuen 2006 SR study Data not reported in an extractable format
Adamo (2008)	Current knowledge and future directions on bisphosphonate-related osteonecrosis of the jaw in cancer patients	Review article but not a systematic review
Adler (2007)	Cancer treatment-induced bone loss	Review article but not a systematic review
Alibhai (2017)	Bone Health and Bone-Targeted Therapies for Nonmetastatic Prostate Cancer: A Systematic Review and Meta-analysis	Does not include population with metastatic prostate cancer
Andronis (2016)	Cost-effectiveness of zoledronic acid and strontium-89 as bone protecting treatments in addition to chemotherapy in patients with metastatic castrate-refractory prostate cancer: results from the TRAPEZE trial (ISRCTN 12808747)	Cost-effectiveness article
Anonymous (2001)	New drugs slow progression of prostate cancer	Review article but not a systematic review
Anonymous (2001)	Pamidronate prevents cancer treatment related bone loss in men	Review article but not a systematic review
Anonymous (2003)	Studies support bisphosphonate use in cancer patients with bone metastases	Not a peer-reviewed publication
Anonymous (2006)	Management of High Risk Metastatic Prostate Cancer	Discussion paper
Anonymous (2016)	Ongoing clinical trials in prostate cancer: The STAMPEDE Trial	Not a peer-reviewed publication
Anonymous (2016)	Correction to Lancet Oncol 2016; 17: 248, 252. Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data	Expert summary and comments
Aragon-Ching (2009)	Further analysis of the survival benefit of clodronate	Review article but not a systematic review
Athanassiou (1994)	Response of patients with bone metastasis of breast, lung and prostate cancer to radiation therapy (RT) alone, versus radiation therapy and diphosphonate (Pamidronate)	Conference abstract

Short Title	Title	Reason for exclusion
Atkins (2003)	Re: a randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma	Duplicate reference
Bankhead (2003)	Clinical trials test bisphosphonates in hormone-sensitive prostate cancer	Review article but not a systematic review
Barghout (2006)	Effect of zoledronic acid (Z) on pain in prostate cancer patients with bone metastases based on performance status	Conference abstract
Berenson (2001)	zoledronic acid in cancer patients with bone metastases: Results of phase I and II trials	Dose finding study
Berruti (2012)	Prognostic role of serum parathyroid hormone levels in advanced prostate cancer patients undergoing zoledronic acid administration	Data not reported in an extractable format
Bilen (2011)	A randomized phase II study of bone-targeted therapy in advanced androgen-dependent prostate cancer	Conference abstract
Bloomfield (1998)	Should bisphosphonates be part of the standard therapy of patients with multiple myeloma or bone metastases from other cancers? An evidence-based review	Systematic review relevant RCTs references included in the review
Brown (2004)	The role of bisphosphonates in breast and prostate cancers	Review article but not a systematic review
Brown (2008)	Survival benefits of zoledronic acid in patients with bone metastases from non-small cell lung cancer and high NTX levels: The role of BALP	Conference abstract
Carter (2011)	Cost effectiveness of zoledronic acid in the management of skeletal metastases in hormone-refractory prostate cancer patients in France, Germany, Portugal, and the Netherlands	Cost-effectiveness article
Choo (2011)	Double-blinded, placebo-controlled randomized study evaluating the efficacy of risedronate to prevent the loss of bone mineral density in non-metastatic prostate cancer patients undergoing radiotherapy plus 2-3 years of androgen ablation therapy	Does not include population with metastatic prostate cancer
Choo (2013)	Randomized, double-blinded, placebo-controlled, trial of risedronate for the prevention of bone mineral density loss in nonmetastatic prostate cancer patients receiving radiation therapy plus androgen deprivation therapy	Does not include population with metastatic prostate cancer
Clarke (1998)	The effects of Pamidronate disodium treatment in metastatic prostate cancer	Review article but not a systematic review

Short Title	Title	Reason for exclusion
Coleman (1999)	Double-blind, randomised, placebo-controlled, dose-finding study of oral ibandronate in patients with metastatic bone disease	Dose finding study
Coleman (2013)	Possible survival benefits from zoledronic acid treatment in patients with bone metastases from solid tumours and poor prognostic features - An exploratory analysis of placebo-controlled trials	Post hoc analysis of a phase 2/3 trial
Cookson (2013)	Castration-resistant prostate cancer: AUA guideline	Systematic review relevant RCTs references included in the review
Dearnaley (2001)	Preliminary evidence that oral clodronate delays symptomatic progression of bone metastases from prostate cancer: first results of the MRC Pr05 trial	Conference abstract
Dearnaley (2001)	Preliminary evidence that an oral bisphosphonate can delay symptomatic progression of bone metastases from prostate cancer: first results of the MRC PR05 trial	Conference abstract
Denham (2011)	Bone mineral density loss and fractures in the trog 03.04 (RADAR) trial	Conference abstract
Denham (2012)	Quality of life in men with locally advanced prostate cancer treated with leuprorelin and radiotherapy with or without zoledronic acid (TROG 03.04 RADAR): secondary endpoints from a randomised phase 3 factorial trial	Does not include population with metastatic prostate cancer
Denham (2014)	Impact of androgen suppression and zoledronic acid on bone mineral density and fractures in the Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomised Androgen Deprivation and Radiotherapy (RADAR) randomized controlled trial for locally advanced prostate cancer	Does not include population with metastatic prostate cancer
Denham (2014)	Short-term androgen suppression and radiotherapy versus intermediate-term androgen suppression and radiotherapy, with or without zoledronic acid, in men with locally advanced prostate cancer (TROG 03.04 RADAR): an open-label, randomised, phase 3 factorial trial	Does not include population with metastatic prostate cancer
Denham (2014)	Main oncologic endpoints of the TROG 03.04 (RADAR) Trial for men with locally advanced prostate cancer	Conference abstract
Di Lorenzo (2007)	Docetaxel, Vinorelbine, and zoledronic Acid as First-Line Treatment in	Combined therapy with non bisphosphonates agents

Short Title	Title	Reason for exclusion
	Patients with Hormone Refractory Prostate Cancer: A Phase II Study	
Diamond (2001)	The antiosteoporotic efficacy of intravenous Pamidronate in men with prostate carcinoma receiving combined androgen blockade: a double blind, randomized, placebo-controlled crossover study	Not a randomised control trial the authors state that data from men who had been treated with radiotherapy was collected for comparison.
Fulmar (1998)	The role of bisphosphonates in the treatment of painful metastatic bone disease: A review of phase III trials	Review article but not a systematic review
Greenspan (2007)	Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: a randomized trial	Does not include population with metastatic prostate cancer
Harding (2011)	A single bisphosphonate infusion does not accelerate fracture healing in high tibia osteotomies	Does not contain a population of people with prostate cancer
Himelstein (2015)	CALGB 70604 (Alliance): A randomized phase III study of standard dosing vs. Longer interval dosing of zoledronic acid in metastatic cancer	Conference abstract
Himelstein (2017)	Effect of Longer-Interval vs Standard Dosing of zoledronic Acid on Skeletal Events in Patients With Bone Metastases: a Randomized Clinical Trial	Comparator in study does not match that specified in protocol
Hong (2007)	A prospective, multicentre, open-label trial of zoledronic acid in patients with hormone refractory prostate cancer	Not a randomised control trial
Israeli (2007)	The effect of zoledronic acid on bone mineral density in patients undergoing androgen deprivation therapy	Does not include population with metastatic prostate cancer
James (2009)	Systemic therapy for advancing or metastatic prostate cancer (STAMPEDE): a multi-arm, multistage randomized controlled trial	Rationale paper
James (2015)	Docetaxel and/or zoledronic acid for hormone-naive prostate cancer: First overall survival results from STAMPEDE (NCT00268476)	Conference abstract
Kachnic (2013)	RTOG 0518: randomized phase III trial to evaluate zoledronic acid for prevention of osteoporosis and associated fractures in prostate cancer patients	Does not include population with metastatic prostate cancer
Kamba (2015)	A phase III, multicentre, randomized, controlled study of maximum androgen blockade with versus without zoledronic acid in treatment-naive prostate cancer patients with bone metastases: Results of ZAPCA study	Conference abstract

Short Title	Title	Reason for exclusion
Kamiya (2012)	Additive effect of zoledronic acid on serum prostate-specific antigen changes for hormone-sensitive prostate cancer patients with bone metastasis treated by combined androgen blockade	Not a randomised control trial
Kapoor (2011)	Effect of zoledronic Acid on bone mineral density in men with prostate cancer receiving gonadotropin-releasing hormone analog	Does not include population with metastatic prostate cancer
Kattan (2008)	Weekly docetaxel, zoledronic acid and Estramustine in hormone-refractory prostate cancer (HRPC)	Not a randomised control trial
Kattan (2008)	Phase II trial of weekly docetaxel, zoledronic acid and selenium for hormone refractory prostate cancer	Conference abstract Not a randomised control trial
Kearns (2010)	Osteoporosis prevention in prostate cancer patients receiving androgen ablation therapy: placebo-controlled double-blind study of estradiol and risedronate: n01C8	Comparator in study does not match that specified in protocol
Kimura (2016)	Re: Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: Results of CALGB 90202 (Alliance)	Expert summary and comments
Kohno (2006)	Efficacy of zoledronic acid versus placebo on biochemical markers of bone metabolism in patients with breast cancer metastatic to bone	Conference abstract
Kylmala (1993)	Evaluation of the effect of oral clodronate on skeletal metastases with type 1 collagen metabolites. A controlled trial of the Finnish Prostate Cancer Group	Data not reported in an extractable format
Lang (2013)	A randomized phase II trial evaluating different schedules of zoledronic acid on bone mineral density in patients with prostate cancer beginning androgen deprivation therapy	Does not include population with metastatic prostate cancer
Lipton (2002)	The new bisphosphonate, Zometa (zoledronic acid), decreases skeletal complications in both osteolytic and osteoblastic lesions: a comparison to Pamidronate	Study compared bisphosphonate with a bisphosphonate
Lipton (2007)	Efficacy and safety of intravenous bisphosphonates in patients with bone metastases caused by metastatic breast cancer	Does not contain a population of people with prostate cancer
Liu (2015)	Bisphosphonates in the Treatment of Patients With Metastatic Breast, Lung, and Prostate Cancer: A Meta-Analysis	Systematic review, relevant RCTs references included in the review

Short Title	Title	Reason for exclusion
Machado (2009)	Efficacy of clodronate, Pamidronate, and zoledronate in reducing morbidity and mortality in cancer patients with bone metastasis: A meta-analysis of randomized clinical trials	Systematic review, relevant RCTs references included in the review
Major (2002)	Efficacy of bisphosphonates in the management of skeletal complications of bone metastases and selection of clinical endpoints	More recent systematic review included that covers the same topic
Mason (2007)	Oral sodium clodronate for nonmetastatic prostate cancer--results of a randomized double-blind placebo-controlled trial: medical Research Council PR04 (ISRCTN61384873)	Does not include population with metastatic prostate cancer
Mason (2017)	Adding Celecoxib With or Without zoledronic Acid for Hormone-Naïve Prostate Cancer: long-Term Survival Results From an Adaptive, Multiarm, Multistage, Platform, Randomized Controlled Trial	Comparator in study does not match that specified in protocol
Mercatali (2013)	RANK/RANK-L/OPG in patients with bone metastases treated with anticancer agents and zoledronic acid: a prospective study	Not a randomised control trial
Michaelson (2006)	Annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: a randomized placebo-controlled trial	Conference abstract
Michaelson (2007)	Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer	Does not include population with metastatic prostate cancer
Morgan (2009)	Is there a role for ibandronate in the treatment of prostate cancer patients with bony metastases?	Review article but not a systematic review
Morgan (2011)	Can bisphosphonates improve outcomes in patients with newly diagnosed multiple myeloma?	Review article but not a systematic review
Okegawa (2014)	zoledronic acid improves clinical outcomes in patients with bone metastatic hormone-naive prostate cancer in a multicentre clinical trial	Not a randomised control trial histological cohort used as control
Ozyuvaci (2005)	The effects of clodronate for the pain treatment of bone metastasis due to prostate cancer	Study not reported in English
Pan (2014)	Docetaxel with or without zoledronic acid for castration-resistant prostate cancer	Data not reported in an extractable format
Piga (1998)	A double blind randomized study of oral clodronate in the treatment of	Does not contain a population of people with prostate cancer

Short Title	Title	Reason for exclusion
	bone metastases from tumours poorly responsive to chemotherapy	
Pitts (2003)	Re: randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer (multiple letters)	Does not include population with metastatic prostate cancer
Poon (2013)	Incidence of Skeletal-related Events Over Time from Solid Tumour Bone Metastases Reported in Randomised Trials Using Bone-modifying Agents	Systematic review, relevant RCTs references included in the review
Price (2004)	Benefit of extended zoledronate therapy for patients with bone metastases from hormone-refractory prostate cancer	Post hoc analysis of a phase 2/3 trial
Purohit (1995)	A randomised double-blind comparison of intravenous Pamidronate and clodronate in the hypercalcaemia of malignancy	Does not include population with metastatic prostate cancer
Rao (2008)	Prevention of bone mineral loss by zoledronic acid in men with prostate carcinoma receiving androgen deprivation therapy: a prospective randomized trial in an Indian population	Does not include population with metastatic prostate cancer
Reed (2004)	Cost-effectiveness of zoledronic acid for the prevention of skeletal complications in patients with prostate cancer	Cost-effectiveness article
Robertson (1995)	Effect of oral clodronate on metastatic bone pain: A double-blind, placebo-controlled study	Results not stratified to type of cancer
Rodrigues (2005)	Comparative study on the protective effect of different bisphosphonates in decreasing bone mineral density in patients submitted to androgen deprivation therapy. A placebo controlled study	Full text paper not available
Rosen (2003)	zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumours: a phase III, double-blind, randomized trial--the zoledronic Acid Lung Cancer and Other Solid Tumours Study Group	Results not stratified to type of cancer
Rosenthal (2003)	A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma	Duplicate reference
Ryan (2006)	zoledronic acid initiated during the first year of androgen deprivation therapy increases bone mineral density in patients with prostate cancer	Does not include population with metastatic prostate cancer

Short Title	Title	Reason for exclusion
Saad (2002)	Treatment of bone complications in advanced prostate cancer: rationale for bisphosphonate use and results of a phase III trial with zoledronic acid	Rationale paper
Saad (2002)	zoledronic acid significantly reduces pathologic fractures in patients with advanced-stage prostate cancer metastatic to bone	Could not be sourced
Saad (2007)	Bisphosphonates Can Prevent Skeletal Complications of Malignant Bone Disease from Prostate Cancer and Renal Cell Carcinoma	Review article but not a systematic review
Satoh (2009)	Single infusion of zoledronic acid to prevent androgen deprivation therapy-induced bone loss in men with hormone-naive prostate carcinoma	Does not include population with metastatic prostate cancer
Sawyer (1990)	Fast (4-h) or slow (24-h) infusions of Pamidronate disodium (aminohydroxypropylidene diphosphonate (ADP)) as single shot treatment of hypercalcaemia	Dose finding study
Serpa (2012)	Bisphosphonate therapy in patients under androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis	Systematic review, relevant RCTs references included in the review
Shamseddine (2013)	High-dose calcitriol, docetaxel and zoledronic acid in patients with castration-resistant prostate cancer: A phase II study	Combined therapy with non bisphosphonates agents
Simon (2010)	Disease progression increases the risk of skeletal-related events in patients with bone metastases from castration-resistant prostate cancer, lung cancer, or other solid tumours	Post hoc analysis of a phase 2/3 trial
Smith (1989)	Palliation of painful bone metastases from prostate cancer using sodium etidronate: results of a randomized, prospective, double-blind, placebo-controlled study	Linked to the Yuen 2006 SR study Bisphosphonate not licensed for bone mets
Smith (2003)	Bisphosphonates to prevent skeletal complications in men with metastatic prostate cancer	Review article but not a systematic review
Smith (2003)	Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer	Does not include population with metastatic prostate cancer
Smith (2006)	CALGB 90202: A randomized double-blind, placebo-controlled phase III study of early vs standard zoledronic acid to prevent skeletal-related events in men with prostate cancer metastatic to the bone	Abstract

Short Title	Title	Reason for exclusion
Smith (2007)	Predictors of skeletal complications in men with hormone-refractory metastatic prostate cancer	Secondary publication of an included study that does not provide any additional relevant information
Smith (2013)	Efficacy and safety of zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: Results of CALGB 90202 (Alliance)	Conference abstract
Sternberg (2016)	Re: Addition of Docetaxel, zoledronic Acid, or Both to First-line Long-term Hormone Therapy in Prostate Cancer (STAMPEDE): Survival Results from an Adaptive, Multiarm, Multistage, Platform Randomised Controlled Trial	Expert summary and comments
Strang (1997)	The analgesic efficacy of clodronate compared with placebo in patients with painful bony metastases from prostatic cancer	Could not be sourced
Taylor (2008)	Palliative response measurement in a phase III study of patients with prostate cancer and painful bone metastases: Secondary analysis of NCIC-CTG PR6	Post hoc analysis of a phase 2/3 trial
Thumbigere -Math (2012)	A retrospective study evaluating frequency and risk factors of osteonecrosis of the jaw in 576 cancer patients receiving intravenous bisphosphonates	Not a randomised control trial
Vale (2015)	What is the current evidence for adding docetaxel or bisphosphonates to androgen deprivation therapy (ADT) in men with hormone sensitive prostate cancer? A systematic review and meta-analyses	Conference abstract
Vale (2016)	Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: A systematic review and meta-analyses of aggregate data	Systematic review relevant RCTs references included in the review
Van den Wyngaert (2009)	Bisphosphonates in oncology: Rising stars or fallen heroes	Review article but not a systematic review
Vinholes (1997)	Relationships between biochemical and symptomatic response in a double- blind randomised trial of Pamidronate for metastatic bone disease	Results not stratified to type of cancer
Walsh (2002)	The antisteoporotic efficacy of intravenous Pamidronate in men with prostate carcinoma receiving combined androgen blockade. A double blind, randomized, placebo-controlled crossover study	Duplicate reference

Short Title	Title	Reason for exclusion
Wang (2013)	Comparison between zoledronic acid and clodronate in the treatment of prostate cancer patients with bone metastases	Study compared bisphosphonate with a bisphosphonate
Witjes (2006)	Effectiveness of zoledronic acid for the prevention of bone metastases in high risk prostate cancer patients: a randomised, open label, multicentre study of the European Association of Urology (EAU) in cooperation with the Scandinavian Prostate Cancer Group (SPCG) and the Arbeitsgemeinschaft Urologische Onkologie (AUO). An initial report of the "ZEUS" study	Conference abstract
Yee (2011)	zoledronic acid to prevent bone loss in Chinese men receiving androgen deprivation therapy for prostate cancer	Does not include population with metastatic prostate cancer
Yuen (2006)	Bisphosphonates for advanced prostate cancer.	Systematic review, relevant RCTs references included in the review
Zaghloul (2008)	A controlled prospective randomized placebo-controlled trial of zoledronic acid in bony metastatic bladder cancer patients	Conference Abstract

Appendix I – References

Clinical Studies - Included

Dearnaley DP, Sydes MR, Mason MD et al. Mk (2003) A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial). Journal of the national cancer institute 95(17), 1300-1311

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Economic Studies - Included

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Appendix J – Research recommendations

Question	**What is the effectiveness and cost-effectiveness of different scheduling** (for example dose, frequency, oral or intravenous) **of zoledronic acid in the prevention and reduction of skeletal events in people with hormone-refractory prostate cancer?**
Population	People with metastatic prostate cancer
Intervention	Zoledronic acid
Comparator	Placebo / no treatment / standard treatment
Outcomes	Skeletal-related events Pain scales Analgesia use Health-related quality of life Number of severe adverse events Number of dropouts because of adverse events Atypical fractures, spinal compression, tumour associated hypercalcemia, osteonecrosis of the jaw
Study design	Randomised control trials
Potential criterion	**Explanation**
Importance to patients, service users or the population	Evidence shows that zoledronic acid can reduce skeletal related events in people with hormone refractory prostate cancer, therefore research aiming to find the optimum dose is important to this population as this will allow future guidelines to make recommendations about how much of the drug is therapeutic for this population.
Relevance to NICE guidance	The current guidelines do not mention dose and frequency. Research on this will help NICE provide complete guidance
Current evidence base	There were multiple studies available looking at zoledronic acid against other agents. However, it is not clear what is the optimum dose as this differs across studies
Equality	No additional equality issues are envisaged relating to this study over and above those applying generally to vulnerable groups of people.
Feasibility	There is a large enough population of people with metastatic prostate cancer that dose and frequency finding studies (scheduling) in this area should be feasible

Appendix K – Economic evidence profiles

Study, population, country and quality	Data sources	Other comments	Incremental			Authors' conclusions	Uncertainty
			Cost (95%CI)	Effect (95%CI)	ICER		
Reed et al. (2004) hormone-resistant prostate cancer with a documented history of bone metastases Multinational trial; US focus to analysis	Effects: Rate of skeletal events and EQ-5D VAS from Saad et al. (2002) Costs: FDA costs of ZA; administration costs from published micro-costing (DeaHarnais Castel et al., 2001). Direct medical costs from Medicare (or 'local health economists' for non-US). $US2000 Utilities: EQ-5D VAS, with skeletal events assumed to have 60-day effects	• 15-month time horizon • zoledronic acid -v- placebo • No discounting • Funded by manufacturer of proprietary ZA	$5,353	0.0336	$159,200	• The cost-effectiveness ratios for bisphosphonates are higher than commonly cited thresholds for conferring cost-effectiveness.	• Deterministic analyses showed ZA was associated with an ICER of c$50,000/QALY when the acquisition & administration cost was $300 per dose and skeletal events were assumed to last 120 days. • No probabilistic analysis
Partially applicable[c,f]							
Potentially serious limitations[g,h,i,j]							

Study, population, country and quality	Data sources	Other comments	Incremental			Authors' conclusions	Uncertainty
			Cost (95%CI)	Effect (95%CI)	ICER		
Carter et al. (2011) hormone-refractory prostate cancer patients with bone metastases France, Germany, Portugal, Netherlands	Effects: Survival benefit and rate of skeletal events from Saad et al. (2002) Costs: costs of ZA from 'IMS pricing' or manufacturer; administration costs micro-costed for each country. Cost of treating skeletal events from cost registries (France and Germany) or published sources (Portugal and Netherlands). Utilities: Assumed same as in CUA by Reed et al. (2004)	• 15-month time horizon • zoledronic acid -v- placebo • No discounting • Funded by manufacturer of proprietary ZA	**France**			• 'the results strongly suggest that ZOL is cost effective versus placebo in French, German, Portuguese, and Dutch patients' • Comparatively poorer cost effectiveness in France and Germany due to lower cost of skeletal events, which were based on all pathologic fractures, whereas Portuguese and Dutch costs were from prostate-cancer-specific costing studies	• Results sensitive to assumed QALY gain, cost of skeletal events, skeletal event rate, cost of ZA or number of infusions • No probabilistic analysis
			€1,284	0.0357	€36,007		
			Germany				
			€841	0.0357	€23,584		
			Portugal				
			€309	0.0357	€8,665		
			Netherlands				
			€87	0.0357	€2,440		
Partially applicable[c,f]							
Potentially serious limitations[g,h,i]							

Study, population, country and quality	Data sources	Other comments	Incremental			Authors' conclusions	Uncertainty
			Cost (95%CI)	Effect (95%CI)	ICER		
Ford et al. (2013) Men with hormone-refractory prostate cancer with painful bone metastases for whom other treatments (including analgesics and palliative radiotherapy) have failed UK	Effects: HR for time to first skeletal event from NMA of RCTs (ZA -v- placebo from Saad 2002) Prob of discontinuation and AEs (inc. osteonecrosis) from denosumab manufacturer's submission (AiC) Costs: unit costs from BNF (ZA at proprietary price), NHS RefCosts. Cost of vertebral fracture treatment assumed £0. Utilities: EQ-5D for skeletal events and AEs from denosumab manufacturer's submission (AiC)	• Markov model with 10-year time horizon • zoledronic acid -v- best supportive care • Primary focus of model is denosumab, but ZA -v- BSC can be inferred as both are comparators • Discounted at 3.5%pa • Funded by NIHR	**All patients**			• Do not comment on ZA -v- BSC	• Not possible to infer from presented results; however, in all CEAFs, the frontier is always formed by BSC or denosumab
			£2,892.00	0.025	£115,680		
			No previous skeletal events				
			£2,908.00	0.028	£103,857		
			Previous skeletal events				
			£2,844.00	0.019	£149,684		
Partially[b,c] applicable							
Potentially serious limitations[d,e]							

Study, population, country and quality	Data sources	Other comments	Incremental			Authors' conclusions	Uncertainty
			Cost (95%CI)	Effect (95%CI)	ICER		
James et al. (2016); Andronis et al. (2017) – TRAPEZE Metastatic castration-refractory prostate cancer UK **Directly applicable** **Potentially serious limitations[a]**	Effects: within-RCT measurement of EQ-5D with area-under-the-curve calculation of QALYs, with various assumptions tested in sensitivity analysis Costs: within-RCT NHS resource-use (missing values multiply imputed); unit costs from BNF, NHS RefCosts. Scenarios with zoledronic acid at proprietary and generic costs.	• zoledronic acid -v- no zoledronic acid • Owing to factorial design, some patients in each arm received Sr-89 and some did not • Discounted at 3.5%pa • Funded by NIHR	**Proprietary zoledronic acid**			• 'ZA had a positive, albeit minimal, effect on QoL' • 'A predictable outpatient therapy with modest net acquisition costs may well be attractive to trusts if it prevents emergency, unpredictable visits.'	• Probabilistic results: ○ Proprietary ZA had a 26% chance of having an ICER of £20,000/QALY or better ○ Generic ZA had a 64% chance of having an ICER of £20,000/QALY or better • One-way sensitivity analysis showed ZA was dominated when baseline EQ-5D imbalance was adjusted for
			£1,319 (−£34 to £2,671)	0.031 (−0.07 to 0.133)	£42,047		
			Generic zoledronic acid				
			£251 (−£1,099 to £1,602)	0.031 (−0.07 to 0.133)	£8,005		

[a] Base case and PSA do not adjust for baseline imbalance in EQ-5D
[b] Evaluation is not designed to compare bisphosphonate with no bisphosphonate
[c] Only proprietary price of zoledronic acid considered
[d] Many inputs are redacted because academic confidentiality is asserted by manufacturer of denosumab
[e] Impossible to infer relevant results of any sensitivity analyses
[f] Non-UK setting
[g] Utility based on EQ-5D VAS only
[h] No adverse events or discontinuations
[i] No probabilistic sensitivity analysis
[j] Potential conflict of interest