Table 1. Summary of methods employed in the reviewed studies.

Study (year)	Country (perspective)	Type of economic evaluation (analytic method employed)	Time horizon (discounting and rate)	Main cost categories and year of valuation	Measure of benefit (instrument)
Andronis *et al.* [18], James *et al.* [29] (2016)	UK (health care system)	CUA (trial-based economic evaluation)	24 months (discounting performed at 3.5% per year)	-Treatment-related costs -Hospital care cost -Primary/community care costs Valuation year: 2011/12	QALY (EQ-5D-3L)
Botteman *et al.* [19] (2006)	UK (health care system)	CUA (model-based economic evaluation)	10 years (discounting performed at 3.5% per year)	-Treatment-related costs -Hospital care costs -Primary/community care costs Valuation year: 2005	QALY (QoL weights taken from the literature)
Botteman *et al.* [20] (2011)	France, Germany, UK (health care system)	CUA (model-based economic evaluation)	21 months (discounting performed at 5% per year for France and Germany, 3.5% per year for the UK)	- Treatment-related costs - Hospital care costs Valuation year: 2008	QALY (QoL weights taken from the literature)
Carter *et al.* [21] (2011)	France, Germany, Portugal, the Netherlands (third-party payer)	CUA (model-based economic evaluation)	15 months (discounting not performed)	-Treatment-related costs -Hospital care cost Valuation year: 2011	- SRE avoided -QALY (QoL weights taken from the literature)
Collinson *et al.* [22] (2016)	New Zealand (health care system)	CUA (model-based economic evaluation)	Lifetime (discounting performed at 3% per year)	-Treatment-related costs -Hospital care cost -Primary/community care costs -Patient out-of-pocket expenditures (travel costs) Valuation year: 2011	QALY (calculated using disability weights from the Global Burden of Disease study [67])
De Cock *et al.* [23] (2005)	UK (health care system)	CUA (model-based economic evaluation)	14.3 months (discounting not performed)	-Treatment-related costs -Hospital care costs Valuation year: 2003	QALY (QoL weights taken from the literature)

De Cock *et al.* [24] (2005)	UK (health care system)	CUA (model-based economic evaluation)	14.3 months (discounting not performed)	- Treatment-related costs - Hospital care costs Valuation year not reported	QALY (QoL weights taken from the literature)
Dranitsaris and Hsu [25] (1999)	Canada (health care system)	CUA (model-based economic evaluation)	12 months (discounting not applicable)	- Treatment-related costs - Hospital and specialist care costs Valuation year: 1999	QALY (derived through a TTO exercise)
Ford *et al.* [26] (2013)	UK (health care system)	CUA (model-based economic evaluation)	10 years (discounting performed at 3.5% per year)	- Treatment-related costs - Hospital care costs Valuation year: 2010	- QALY (QoL weights taken from drug manufacturer's evidence submission to NICE) - SRE avoided
Gessner *et al.* [27] (2000)	Switzerland (third-party payer)	CCA (trial-based economic evaluation)	10.5 months (discounting not applicable)	- Treatment-related costs - Hospital and specialist care costs Valuation year: 1995	Linear analogue scale measuring pain levels
Hillner *et al.* [28] (2000)	US (societal)	CEA, CUA (model-based economic evaluation)	24 months (discounting not performed)	- Treatment-related costs - Hospital care costs - Primary/community care costs - Productivity cost of patients' companion Valuation year not reported	- SRE avoided - QALY (instrument not reported)
Joshi *et al.* [30] (2011)	France, Germany, Netherlands, Portugal, UK (health care system)	CUA (model-based economic evaluation)	Unclear (discounting not performed)	- Treatment-related costs - Hospital care costs Valuation year: 2007/08	QALY (QoL weights taken from the literature)
Konski [31] (2004)	US (third-party payer)	CUA (model-based economic evaluation)	24 months (discounting not performed)	-Treatment-related costs -Hospital care costs Valuation year not reported	QALY (QoL weights taken from the literature)
McEwan *et al.* [32] (1994)	Canada (not reported)	CEA (trial-based economic evaluation)	Lifetime (discounting not performed)	-Treatment-related costs -Hospital care costs	Length of survival

				Valuation year: 1989	
Reed *et al.* [33] (2004)	US (societal)	CEA, CUA (trial-based economic evaluation)	15 months (discounting not performed)	-Treatment-related costs -Hospital care cost -Primary/community care costs Valuation year: 2000	- SAE avoided - QALY (EQ-5D-3L)
Ross *et al.* [34] (2004)	UK (health care perspective)	CEA (model-based economic evaluation)	4 years (discounting performed for the assessment of treatments for skeletal morbidity: 6% per year for costs, 1% per year for outcomes (SREs).	- Treatment-related costs - Hospital care costs - Primary and community care costs (only for the assessment of skeletal morbidity) Valuation year: 2000/2001	- LYG - SRE avoided
Snedecor *et al.* [35] (2012)	US (third-party payer)	CUA (model-based economic evaluation)	27 months (discounting performed at 3% per year)	- Treatment-related costs - Hospital care costs Valuation year: 2010	QALY (QoL weights taken from the literature)
Snedecor *et al.* [36] (2013)	US (third-party payer)	CUA (model-based economic evaluation)	27 months (discounting performed at 3% per year)	- Treatment-related costs - Hospital care costs Valuation year: 2010	QALY (QoL weights taken from the literature)
Stopeck *et al.* [37] (2012)	US (third-party payer)	CEA, CUA (model-based economic evaluation)	Lifetime (discounting performed at 3% per year)	-Treatment-related costs -Hospital care costs Valuation year: 2011	-SRE avoided -QALY (various including EQ-5D-3L and TTO exercises)
Van den Hout *et al.* [38] (2003)	UK (societal)	CUA (trial-based economic evaluation)	12 months for outcomes (discounting performed at 3% per year)	- Treatment-related costs - Hospital and specialist care costs - Primary/community care costs - Patient payments Valuation year: 2002	QALY (EQ-5D-3L)
Xie *et al.* [39] (2012)	US (third-party payer)	CEA (model-based economic evaluation)	12 months (discounting not applicable)	- Treatment-related costs - Hospital care costs Valuation year: 2011	- SRE avoided - Pathologic fracture avoided

Xie *et al*. [40] (2011)	US (third-party payer)	CEA (model-based economic evaluation)	12 months (discounting performed at 3% per year)	- Treatment-related costs - Hospital care costs - Terminal care costs Valuation year: 2012	SRE avoided
Yfantopoulos *et al.* [41] (2013)	Greece (health care system)	CUA (model-based economic evaluation)	14.5 months for breast cancer; 22.5 months for prostate cancer (discounting not performed); 9 months for other solid tumours (discounting not applicable)	- Treatment-related costs - Hospital care costs Valuation year: 2013	-QALY (QoL weights taken from the literature)
CBA: cost-benefit analysis; CCA: cost consequences analysis; CEA: cost-effectiveness analysis; CUA: cost-utility analysis; EQ-5D: EuroQol 5D; LYG: life-year gained; NICE: National Institute for Health and Care Excellence; SRE: skeletal-related event; QALY: quality-adjusted life year; QoL: quality of life; TTO: time trade-off elicitation method.					

Table 2. Summary of findings reported in the reviewed studies.

Study (year)	Type(s) of primary cancer investigated	Intervention(s) and comparator(s)	Main findings
Andronis *et al.* [18], James *et al.* [29] (2016)	Prostate	Interventions: ZA; Sr89 Comparators: No ZA; No Sr89	-ICER (ZA vs. no ZA): £8,005 per QALY -ZA is less costly and more effective than no ZA if the price of generic ZA is less than £31. -ICER (Sr89 vs. no Sr89): £16,884 per QALY gained.
Botteman *et al.* [19] (2006)	Breast	Interventions: ibandronate (oral or intravenous); ZA; pamidronate; clodronate (oral). Comparator(s): placebo	-ZA vs no therapy: cost savings of £2,267 and 0.205 additional QALYs. -Oral ibandronate vs. placebo: cost savings of £2,114 and 0.185 additional QALYs. - ICER (pamidronate vs. placebo): £584 per QALY gained. - ICER (intravenous ibandronate vs. placebo): £2,370 per QALY gained.
Botteman *et al.* [20] (2011)	Renal cancer	Intervention: ZA Comparator: placebo	- ZA vs placebo: cost savings and additional SREs avoided in all countries considered. - ZA vs placebo: cost savings and additional QALYs in all countries considered.
Carter *et al.* [21] (2011)	Prostate	Intervention: ZA Comparator(s): placebo	- ICER (France, ZA vs placebo): €36,007 per QALY gained. -ICER (Germany, ZA vs placebo): €23,582 per QALY gained. -ICER (Portugal, ZA vs placebo): €8,655 per QALY gained. -ICER (Netherlands, ZA vs placebo): €2,430 per QALY gained.
Collinson *et al.* [22] (2016)	Breast, prostate, lung	Intervention: single-fraction EBR Comparators: multi-fraction EBR; analgesia (in a secondary analysis)	Single-fraction EBR was less costly and more effective than multi-fraction EBR.
De Cock *et al.* [23] (2005)	Breast (patients receiving oral hormonal therapy)	Intervention(s): pamidronate (oral) Comparator(s): ZA (intravenous); pamidronate (generic, intravenous).	-Oral ibadronate vs. intravenous ZA: cost savings of £307and 0.018 additional QALYs. -Oral ibadronate vs. intravenous generic pamidronate: cost savings of £158 and 0.019 additional QALYs.
De Cock *et al.* [24] (2005)	Breast (patients receiving chemotherapy)	Intervention: pamidronate (oral) Comparators: ZA (intravenous); pamidronate (generic, intravenous)	-Oral ibadronate vs. intravenous ZA: cost savings of £386 and 0.019 additional QALYs. -Oral ibadronate vs. intravenous generic pamidronate: cost savings of £224 and 0.02 additional QALYs.
Dranitsaris and Hsu [25] (1999)	Breast	Intervention: pamidronate Comparator: placebo	ICER (pamidronate vs. placebo): CAN $18,700 per QALY gained.

Ford *et al.* [26] (2013)	Breast, prostate, lung, other solid tumours	Intervention: denosumab Comparator: ZA	*Breast cancer:* - ICER (denosumab vs ZA, without PAS): £245,264 per QALY gained. - Denosumab vs ZA (with PAS): cost savings and additional QALYs. *Prostate cancer:* - ICER (denosumab vs ZA, without PAS): £111,603 per QALY gained. - Denosumab vs ZA (with PAS): cost savings and additional QALYs. *Lung cancer:* - ICER (denosumab vs ZA, without PAS): £110,671 per QALY gained. - ICER (denosumab vs ZA, with PAS): £12,743 per QALY gained. *Other solid tumours:* - ICER (denosumab vs ZA, without PAS): £139,739 per QALY gained. - ICER (denosumab vs ZA, with PAS): £9,004 per QALY gained.
Gessner *et al.* [27] (2000)	Breast, multiple myeloma, other cancer types	Intervention(s): pamidronate 60mg Comparator(s): pamidronate 90mg	- Average total cost (for both treatments): ECU 12,060 +/- 4,380 - Change in pain intensity compared to baseline value (pamidronate 60mg): -36%. - Reduction in pain intensity compared to baseline value (pamidronate 90mg): -15%.
Hillner *et al.* [28] (2000)	Breast	Intervention: pamidronate (given with either hormonal systemic therapy or chemotherapy) Comparator: placebo	-ICER (pamidronate plus chemotherapy vs. placebo): US $3,940 per SRE avoided. - ICER (pamidronate plus chemotherapy vs. placebo): US $108,200 per QALY gained. -ICER (pamidronate plus hormonal systemic therapy vs. placebo): US $7,685 per SRE avoided. - ICER (pamidronate plus hormonal systemic therapy vs. placebo): US $305,300 per QALY gained.
Joshi *et al.* [30] (2011)	Lung	Intervention: ZA Comparator: placebo	- ZA vs placebo (Germany, UK and Portugal): costs savings and additional QALYs. - ICER (ZA vs placebo; France): €786 per QALY gained. -ICER (ZA vs placebo; Netherlands): €8278 per QALY gained.
Konski [31] (2004)	Prostate	Interventions: chemotherapy only (mitoxantrone plus prednisolone); single-fraction EBR; multi-fraction EBR. Comparator: BSC (pain medications only)	-ICER (single-fraction EBR vs. BSC): US $6857 per QALY gained. -ICER (multiple-fraction EBR vs. BSC): US $36,000 per QALY gained. -ICER (single-fraction EBR vs. multiple fraction EBR) (calculated)[a]: US $8,667 per QALY gained. -Chemotherapy is more costly and less effective than all other options.

McEwan *et al.* [32] (1994)	Prostate	Intervention: Sr89 (Metastron®) Comparator: placebo	-Cost per week survival (Metastron® vs. placebo): cost savings of CAN $209.
Reed *et al.* [33] (2004)	Prostate	Intervention: ZA Comparator: placebo	-ICER (ZA vs placebo): US $12,300 per SRE avoided. -ICER (ZA vs placebo): US $51,400 per additional patient free of SRE. -ICER (ZA vs placebo): US $159,200 per QALY gained.
Ross *et al.* [34] (2004)	Breast, multiple myeloma	Intervention(s): pamidronate (30mg, 60mg and 90mg); clodronate (1500mg); ZA (4mg and 8mg); ibandronate (2mg, 4mg, 6mg) Comparator(s): no bisphosphonate treatment	*Breast cancer:* - ICER (treatment of hypecalcaemia, ZA 8mg vs no bisphosphonate treatment): £17,100 per LYG - ICER (prevention of skeletal morbidity, ZA vs no bisphosphonate therapy): £250 per SRE avoided. *Multiple myeloma:* - ICER (prevention of skeletal morbidity, ZA vs no bisphosphonate therapy): £1,497 per SRE avoided.
Snedecor *et al.* [35] (2012)	Breast	Intervention: denosumab Comparator: ZA	-ICER (denosumab vs. ZA): US $697,499 per QALY gained.
Snedecor *et al.* [36] (2013)	Prostate	Intervention: denosumab Comparator(s): ZA	-ICER (denosumab vs. ZA): US $1,058,741 per QALY gained.
Stopeck *et al.* [37] (2012)	Prostate, breast, lung	Intervention: denosumab Comparator: ZA	*Prostate cancer* -ICER (denosumab vs ZA): US $49,405 per QALY gained. -ICER US $8,567 per SRE avoided. *Breast cancer* -ICER (denosumab vs ZA): US $78,915 per QALY gained. -ICER (denosumab vs ZA): US $13,557 per SRE avoided. *Lung cancer* - ICER (denosumab vs ZA): US $67,931 per QALY gained. - ICER (denosumab vs ZA): US $13,557 per SRE avoided.
Van den Hout *et al.* [38] (2003)	Breast, lung, prostate, other	Intervention: single-fraction EBR Comparator(s): multiple-fraction EBR (six fractions)	Single-fraction EBR was less costly and more effective than multi-fraction EBR.
Xie *et al.* [39] (2012)	Breast	Intervention: denosumab Comparator: ZA	-ICER (denosumab vs. ZA): US $114,628 per SRE avoided. -ICER (denosumab vs. ZA): US $290,136 per pathological fracture avoided.
Xie *et al*. [40] (2011)	Prostate	Intervention: denosumab Comparator: ZA	-ICER (denosumab vs. ZA, 12 months): US $71,027 per SRE avoided. -ICER (denosumab vs. ZA, 36 months): US $51,319 per SRE avoided.

Yfantopoulos *et al.* [41] (2013)	-Breast, prostate, other solid tumours (not specified)	Intervention: denosumab Comparator: ZA	*Breast cancer* -ICER (denosumab vs ZA): €56,818 per QALY gained. *Prostate cancer:* -ICER (denosumab vs ZA): €61,296 per QALY gained. Other solid tumours - ICER (denosumab vs ZA): €80,830 per QALY gained.

[a] Calculated on the basis of information given in the article.

BSC: best supportive care; EBR: external beam radiotherapy; ECU: European Currency Unit; ICER: incremental cost effectiveness ratio; LYG: life-year gained; NICE: National Institute for Health and Care Excellence; OST: other solid tumours; PAS: patient-access scheme; QALY: quality-adjusted life year; Sr89: strontium-89; TTO: time trade-Off elicitation method; ZA: zoledronic acid.

Table 3. Answers to the Consensus on Health Economic Criteria (CHEC) checklist [17]

Study	Item																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Andronis *et al.* [18]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Botteman *et al.* [19]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	N	N*	N
Botteman *et al.* [20]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N*	N
Carter *et al.* [21]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	N*	N
Collinson *et al.* [22]	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N*	N
De Cock *et al.* [23]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	N*	N
De Cock *et al.* [24]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
Dranitsaris & Hsu [25]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	Y	Y	N	N*	N
Ford *et al.* [26]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N*	N
Gessner *et al.* [27]	Y	Y	Y	U	N	Y	U	Y	Y	Y	Y	Y	N	N/A	U	Y	N	N*	N
Hillner *et al.* [28]	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	Y	N	Y	Y	N	Y	N
James *et al.* [29]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N*	N
Joshi *et al.* [30]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N*	N
Konski [31]	Y	Y	Y	Y	Y	Y	U	Y	U	U	U	Y	Y	N	Y	Y	N	N	Y
McEwan *et al.* [32]	Y	Y	Y	Y	Y	U	N	Y	Y	N	Y	Y	Y	N	N	Y	N	Y	N
Reed *et al.* [33]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	U	U	Y	Y	N*	N
Ross *et al.* [34]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Snedecor *et al.* [35]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N*	N
Snedecor *et al.* [36]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N*	N
Stopeck *et al.* [37]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N*	N
van den Hout *et al.* [38]	Y	Y	Y	U	U	Y	U	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	N
Xie *et al.* [40]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N*	N
Xie *et al.* [39]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N*	N
Yfantopoulos *et al.* [41]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	N*	N

Y: Yes; N: No; U: Unclear; N/A: Not applicable.
* Funding sources and potential conflicts of interests are acknowledged.

Item 1: Is the study population clearly described? Item 2: Are competing alternatives clearly described? Item 3: Is a well-defined research question posed in answerable form? Item 4: Is the economic study design appropriate to the stated objective? Item 5: Is the chosen time horizon appropriate to include relevant costs and consequences? Item 6: Is the actual perspective chosen appropriate? Item 7: Are all important and relevant costs for each alternative identified? Item 8: Are all costs measured appropriately in physical units? Item 9: Are costs valued appropriately? Item 10: Are all important and relevant outcomes for each alternative identified? Item 11: Are all outcomes measured appropriately? Item 12: Are outcomes valued appropriately? Item 13: Is an incremental analysis of costs and outcomes of alternatives performed? Item 14: Are all future costs and outcomes discounted appropriately? Item 15: Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis? Item 16: Do the conclusions follow from the data reported? Item 17: Does the study discuss the generalizability of the results to other settings and patient/ client groups? Item 18: Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)? Item 19: Are ethical and distributional issues discussed appropriately?