National Institute for Health and Care Excellence

Final

Hyperparathyroidism (primary): diagnosis, assessment and initial management

[G] Evidence review for calcimimetics

NICE guideline NG132

Intervention evidence review

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Final

This evidence review was developed by the National Guideline Centre

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1.1 Review question: What is the clinical and cost effectiveness of calcimimetics in people with primary hyperparathyroidism?

1.2 Introduction

Primary hyperparathyroidism (PHPT) results in inappropriately excessive secretion of parathyroid hormone (PTH) from the parathyroid gland. High PTH levels trigger various physiological processes to increase the amount of calcium in the blood, classically causing levels to rise above normal (hypercalcaemia); both raised PTH and calcium are responsible for the features of PHPT. Two of the most important long-term consequences of PHPT include loss of bone mineral with increased risk of fractures and an increased risk of kidney stones. [26] Calcimimetics reduce serum levels of PTH and calcium through their effect on the calcium-sensing receptor on parathyroid cells; however they do not directly stop bone loss or kidney problems due to PHPT. Currently the use of calcimimetics in PHPT is limited to the control of serum calcium in patients with symptomatic hypercalcaemia where surgery is indicated, but is not performed or has been unsuccessful. The aim of this review is to explore the clinical and cost effectiveness of calcimimetics in all people with PHPT.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults (18 years or over) with confirmed primary hyperparathyroidism Strata (the following groups are reported separately): • People with normocalcaemic PHPT • Previous parathyroidectomy • Pregnant women
Interventions	Oral calcimimetics (cinacalcet)
Comparisons	Placebo No treatment Bisphosphonates Surgery Combination treatment (calcimimetics and bisphosphonates)
Outcomes	Health-related quality of life; mortality; deterioration in renal function; fractures; occurrence of kidney stones; persistent hypercalcaemia; bone mineral density (lumbar spine and/or distal radius); cardiovascular events; adverse events; cancer incidence
Study design	RCTs and systematic reviews of RCTs (non-randomised studies will only be included in the absence of RCTs)

1.4 Clinical evidence

1.4.1 Included studies

A search was conducted for randomised controlled trials assessing the effectiveness of oral calcimimetics (cinacalcet) for treatment of people with primary hyperparathyroidism. The

calcimimetics were to be compared against the following: placebo, no treatment, bisphosphonates, surgery or combination treatment.

Three studies were included in the review.[10, 19, 25] These are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3). See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

All three studies compared oral cinacalcet tablets with placebo. All the participants in one of the studies[10] had met the criteria for parathyroid surgery but were unable to undergo parathyroidectomy. To be included, each participant had to have a diagnosis of primary hyperparathyroidism based on laboratory measurements of total corrected serum calcium of between 2.83 and 3.13 mmol/litre. In the other two studies, the minimum levels of serum calcium set for inclusion were lower (2.53 mmol/litre in Peacock 2005[19] and 2.62 mmol/litre in Shoback 2003[25]). The reference range for adjusted serum calcium is 2.2 to 2.6 mmol/litre. Therefore, all studies included people with hypercalcaemia and were analysed together. No studies were identified for the results strata of normocalcaemic PHPT, previous parathyroidectomy or pregnant women. No studies were identified reporting the protocol outcomes of deterioration in renal function, fractures, occurrence of kidney stone, cardiovascular events, or cancer incidence.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Follow-up	Outcomes
Khan 2015[10]	Cinacalcet versus placebo	n=67 • People with PHPT who met the criteria for parathyroid surgery but were unable to undergo parathyroidectomy • Total corrected serum calcium ≥ 2.85 mmol/L	28 weeks	• Health-related quality of life (PAS, MOS-CF, SF-36) • Mortality • Proportion of participants achieving normocalcaemia (corrected total serum calcium ≤2.575 mmol/L) • Treatment-associated adverse events • Serious adverse events
Peacock 2005[19]	Cinacalcet versus placebo	n=78 • Mild to moderate PHPT with disease severity ranging from asymptomatic to symptomatic • 23% with history of unsuccessful parathyroidectomy • Serum calcium 2.57–3.12 mmol/L	24 & 52 weeks	• Proportion of participants achieving normocalcaemia (serum calcium ≤2.57 mmol/L) with a minimum of 0.12 mmol/L reduction from baseline (follow-up 24 weeks) • Lumbar and distal radius BMDs (follow-up 52 weeks) • Withdrawals due to adverse events (follow-up 52 weeks) Data for people with unsuccessful surgery has been analysed in the failed surgery evidence review.
Shoback	Cinacalcet	n=22	22 days	• Adverse events

Study	Intervention and comparison	Population	Follow-up	Outcomes
2003[25]	versus placebo	• Mild to moderate PHPT with disease severity ranging from asymptomatic to symptomatic • 18% with history of unsuccessful parathyroidectomy • Serum calcium 2.62 – 3.13 mmol/L		

PAS = Parathyroid assessment of symptoms; MOS-CF = Medical outcomes study – cognitive functioning; SF-36 = Short-form 36 questionnaire

See appendix D for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: cinacalcet versus placebo

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Cinacalcet
QOL SF-36 physical component Scale from: 0 to 100 follow up: 28 weeks	67 (1 RCT)	VERY LOW [a,b,c]	-	The mean change in SF-36 physical component was 0.4	MD 2.9 higher mean change score (0.29 lower to 6.09 higher)
QOL SF-36 mental component Scale from: 0 to 100 follow up: 28 weeks	67 (1 RCT)	VERY LOW [a,b,c]	-	The mean change in SF-36 mental component was -2.7	MD 4.3 higher mean change score (0 to 8.6 higher)
QOL MOS-CF Scale from: 0 to 100 follow up: 28 weeks	67 (1 RCT)	VERY LOW [a,b]	-	The mean change in MOS-CF was -1.6	MD 8.7 higher mean change score (0.59 lower to 17.99 higher)
QOL PAS Scale from: 0 to 1300 follow up: 28 weeks	67 (1 RCT)	VERY LOW [a,b]	-	The mean change in PAS was -59	MD 32 lower mean change score (132.23 lower to 68.23 higher)
Mortality follow up: 28 weeks[d]	67 (1 RCT)	VERY LOW [a,b]	Peto OR 7.62 (0.15 to 384.01)	Moderate	
				0 per 1,000	30 more per 1,000 (50 fewer to 110 more)
Achieving normocalcaemia follow up: range 24 weeks to 28 weeks	145 (2 RCTs)	LOW [a]	RR 21.28 (6.29 to 71.99)	Moderate	
				26 per 1,000	527 more per 1,000 (138 more to 1000 more)
Lumbar spine BMD Z-score follow up: 52 weeks	78 (1 RCT)	VERY LOW [a,b]	-	The mean change in lumbar spine BMD Z-score was 0.03	MD 0.03 lower mean change score (0.14 lower to 0.08 higher)
Distal radius BMD Z-score follow up: 52 weeks	78 (1 RCT)	VERY LOW [a,b]	-	The mean change in distal radius BMD Z-score was -0.01	MD 0.04 lower mean change score

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Cinacalcet
					(0.19 lower to 0.11 higher)
Adverse events at <6 months follow up: 22 days	22 (1 RCT)	VERY LOW[a,b]	RR 0.84 (0.41 to 1.72)	Moderate	
				667 per 1,000	107 fewer per 1,000 (394 fewer to 480 more)
Adverse events at ≥6 months follow up: range 28 weeks to 52 weeks [e]	145 (2 RCTs)	VERY LOW[a,b]	RR 1.36 (0.98 to 1.90)	Moderate	
				373 per 1,000	134 more per 1,000 (7 fewer to 336 more)
Serious adverse events at ≥6 months follow up: 28 weeks	67 (1 RCT)	VERY LOW[a,b]	RR 0.77 (0.19 to 3.19)	Moderate	
				118 per 1,000	27 fewer per 1,000 (95 fewer to 258 more)

a. Downgraded by one increment if the majority of the evidence was at high risk of bias and downgraded by two increments if the majority of the evidence was a very high risk of bias
b. Downgraded by one increment if the confidence interval crossed one MID and downgraded by two increments if the confidence interval crossed both MIDs
c. Established MIDs used for SF36
d. Fatal event in the study was considered as unrelated to the intervention. One patient died due to decreased appetite (anorexia). The patient had a history of dementia and was taking concurrent medications including haloperidol.
e. Actual outcome reported in one study was the number of people withdrawing due to adverse events (not the total number of people having adverse events). The other study reported the total number of people having adverse events, with the most frequent events being nausea and muscle spasms.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.5.3 Unit costs

The cost of cinacalcet was presented to the committee for consideration of cost effectiveness. Cinacalcet is the only calcimimetic currently available for the treatment of PHPT in the UK.

Table 4: Cost of cinacalcet

Drug	Daily dose (or unit or total)	Cost – per month	Cost – annual (or per course)
Cinacalcet	60 mg (30 mg twice daily)	£273	£3,278

Source: BNF – September 2017[9]

1.5.4 Economic considerations

Due to a lack of economic evidence a simple estimate of the cost effectiveness of calcimimetics was undertaken. This was calculated with an assumed population of 1,000 patients who are given either cinacalcet or placebo, with the outcome measured by whether normocalcaemia is achieved. The absolute values for outcomes were taken from the clinical review to determine the number of people in each arm that would achieve normocalcaemia.

Utility values of 0.8 and 0.6 were applied to those achieving normocalcaemia and those who do not, respectively. Due to a lack of quality of life data for these populations, these were estimated based on the quality of life outcomes from the clinical review and with committee consideration and the difference in quality of life between the two health states was considered to be a generous estimate.

All people in the cinacalcet arm incurred the cost of treatment with cinacalcet. The cost of a pack of 28 tablets (30 mg per tablet) was £125.75. Assuming an average dose of 60 mg per day (30 mg twice daily), this will cost £3,278 per year. For simplicity the cost of placebo was assumed to be zero.

A time horizon of 6 months was used to maintain consistency with the length of time for the clinical outcome used. It was agreed that as the effectiveness of calcimimetics does not diminish over time, and will remain effective as long as it continues to be taken. Therefore 6 months was considered to be sufficient for the purpose of this calculation.

The analysis showed the ICER to be £31,105. This is not cost effective at the £20,000 per QALY threshold, but is borderline cost effective at the £30,000 per QALY threshold.

The incremental effectiveness of 0.2 is considered to be a generous estimate as it is unclear whether patients included in the studies are symptomatic, and if so, to what extent. People who are severely symptomatic prior to treatment are likely to experience a greater improvement in quality of life; therefore this utility gain could be reflective, further reducing the likelihood of cinacalcet being cost effective.

1.6 Resource impact

The recommendations made by the committee based on this review are not expected to have a substantial impact on resources.

1.7 Evidence statements

1.7.1 Clinical evidence statements

1.7.1.1 Cinacalcet versus placebo

There was a clinically important benefit of cinacalcet for achieving normocalcaemia (2 studies, n=145; Low quality); short-term adverse events < 6 months (1 study, n=22; follow up 22 days; Very Low quality); QOL (SF-36 physical component; SF-36 mental component; MOS-CF; PAS) (1 study, n=67; follow up 28 weeks; Very Low quality). There was a clinical harm of calcimimetics for the outcome of long-term adverse events ≥6 months (2 studies, n=145; follow up 24 to 28 weeks; Very Low quality).There was no difference between cinacalcet and placebo for Lumbar spine BMD Z-score; distal radius BMD Z-score (1 study, n=78; follow up 52 weeks; Very Low quality). There was no difference between cinacalcet and placebo for mortality and serious adverse events ≥6 months (1 study, n=67; follow up 28 weeks; Very Low quality). No evidence was identified for the outcomes of deterioration in renal function, fractures, occurrence of kidney stones, cardiovascular events or cancer incidence.

1.7.1.2 Calcimimetics versus surgery

No evidence was identified

1.7.1.3 Calcimimetics versus bisphosphonates

No evidence was identified

1.7.1.4 Calcimimetics versus combination treatment (calcimimetics and bisphosphonates)

No evidence was identified

1.7.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.8 The committee's discussion of the evidence

1.8.1 Interpreting the evidence

1.8.1.1 The outcomes that matter most

The committee considered the outcomes of health-related quality of life and mortality as critical outcomes for decision making. Other important outcomes included renal function, fractures, kidney stones, persistent hypercalcaemia, bone mineral density (lumbar spine and/or distal radius), cardiovascular events, cancer incidence and adverse events. The committee was interested in cardiovascular and cancer outcomes, as there is some observational evidence to suggest that the risk of these future events is higher in untreated primary hyperparathyroidism.

No evidence was identified for the outcomes of deterioration in renal function, fractures, occurrence of kidney stones, cardiovascular events or cancer incidence.

1.8.1.2 The quality of the evidence

There was evidence from 3 studies comparing cinacalcet versus placebo. Cinacalcet is an oral calcimimetic used in the management of primary hyperparathyroidism. No evidence was

available for comparison of calcimimetics with surgery, bisphosphonates or combination treatment (calcimimetics and bisphosphonates).

For the comparison of cinacalcet with placebo, the majority of the evidence was of Very Low quality due to risk of bias and imprecision. This decreases our confidence in the estimate of effect of cinacalcet.

All studies included people with hypercalcaemia. No evidence was identified for the results strata of normocalcaemic primary hyperparathyroidism or pregnant women.

1.8.1.3 Benefits and harms

Of the three included studies, two studies included patients with mild to moderately severe primary hyperparathyroidism (serum calcium 2.62 – 3.13 mmol/litre) and in one study all the participants had met the criteria for parathyroid surgery (total adjusted serum calcium ≥ 2.85 mmol/litre) but were unable to undergo parathyroidectomy. The committee discussed that the population in the latter study reflected the current licenced indications for cinacalcet in primary hyperparathyroidism. It is also the population considered in a recent NHS England clinical commissioning document for 'Cinacalcet for complex primary hyperparathyroidism in adults'. [26]

The evidence suggested that the clinical benefits of cinacalcet outweigh the harms. The committee noted the clinical benefit of cinacalcet for the outcomes of quality of life, achieving normocalcaemia, and short-term adverse events. There was a clinical harm of cinacalcet for the outcome of long-term adverse events. The evidence for mortality was only based on one event and the fatal event in the study was considered as unrelated to the intervention. For this reason, the committee did not consider the evidence for the critical outcome of mortality. No clinical difference was found for the outcomes of serious adverse events, BMD of the lumbar spine and the distal radius.

Evidence was also available from a small sub-set of the population who had undergone previous unsuccessful surgery. The committee noted that there was a clinical benefit of using cinacalcet for the achievement of normocalcaemia. No evidence was available for any other outcomes for this population.

Cinacalcet acts to decrease serum calcium and therefore the committee considered the largest benefit would be in people with an adjusted serum calcium level above the reference range. Therefore, most benefit will be achieved in people with a high serum calcium level and symptoms resulting from their hypercalcaemia. It would also lower the risk of end organ damage. The committee however noted that cinacalcet should be an option in people who are unable to undergo surgery only and not as an alternative to surgery, as parathyroidectomy is the only definitive treatment option in people with primary hyperparathyroidism without surgical contraindication. Cinacalcet does not directly stop bone loss or kidney problems due to primary hyperparathyroidism.

The committee from their experience discussed that there is a group of patients who will not undergo surgery either because of patient choice or because they are unsuitable for surgery. In such cases cinacalcet can decrease their serum calcium levels and avoid episodes of hypercalcaemic crisis. The committee also noted that there is a small group of patients who have primary hyperparathyroidism after single/multiple unsuccessful surgeries who tend to benefit from cinacalcet. Often there are very few other options for these people and they can report an improvement in general wellbeing. Hence the committee recommended that cinacalcet should be considered in these groups of people with primary hyperparathyroidism.

The committee agreed to make recommendations specifically for cinacalcet as the evidence was available only for this type of calcimimetic. They also considered that if another calcimimetic was to be available in the future for use in primary hyperparathyroidism, the

criteria for its use may be different. Hence they agreed that these recommendations should be applicable to cinacalcet only.

The committee discussed the cut-off values for hypercalcaemia and use of cinacalcet. The clinical benefit in quality of life in this review was judged to be in people with an adjusted serum calcium level above 2.85 mmol/litre. Therefore, the cut-off was set at 2.85 mmol/litre for people with symptoms of hypercalcaemia. For the cut-off to define hypercalcaemia in the presence or absence of symptoms, the committee agreed from clinical experience that this should be set at above 3.0 mmol/litre, largely due to the increased risk of hypercalcaemic crises that may be seen with this degree of hypercalcaemia. In the absence of evidence, the committee was unable to make a recommendation for people with normocalcaemia.

The committee discussed that for people with an initial albumin-adjusted serum calcium level below 3.0 mmol/litre, continuation of treatment should be based on reduction in symptoms. For people with initial albumin-adjusted serum calcium level 3.0 mmol/litre or above, continuation of treatment should be based on either reduction in serum calcium or reduction in symptoms. This distinction was again made largely due to the increased risk of hypercalcaemic crises that may be seen with this degree of hypercalcaemia.

The committee noted that albumin-adjusted serum calcium level should be measured before initiation of cinacalcet treatment and within 1 week after starting treatment or adjusting the dose. It was recognised that the dose of cinacalcet may be titrated up to achieve optimum effect in lowering serum calcium and potentially improving patients' symptoms. They agreed that albumin-adjusted serum calcium level should be measured every 2–3 months, as stated in the British National Formulary (BNF). The committee in accordance with the BNF view felt that continued biochemical monitoring should occur irrespective of symptoms. The committee from their experience stated that if there is any improvement and return to the adjusted serum calcium reference range with cinacalcet, treatment should be continued at the minimum effective dose to maintain that state, as discontinuation of the cinacalcet will lead to raised calcium and the symptoms are likely to return. If cinacalcet is deemed effective, it would become potentially chronic therapy.

The committee discussed from clinical experience that cinacalcet is unlikely to have a beneficial effect on bone disease or kidney stones, as they do not act directly to reduce calcium excretion or bone loss. Hence they agreed that there was no benefit in prescribing cinacalcet if there are symptoms of end organ damage.

1.8.2 Cost effectiveness and resource use

No economic evidence was identified for this question.

Cinacalcet is the only calcimimetic currently licensed for PHPT in the UK. It is an expensive drug costing around £3,278 per patient per year, at an average dose of 60 mg per day (30 mg twice daily).

It was noted in the clinical review that there is a trade-off in cases where an intervention is more effective, and has more adverse events. However, the adverse events noted in the studies were nausea, headache, muscle spasm, and paresthesia. Such adverse events are not uncommon to many other pharmacological treatments, and the committee considered that the benefits of treatment outweigh the potential adverse events.

However, cinacalcet is an expensive treatment and the cost effectiveness of treatment for this population is highly uncertain.

A simple calculation using the outcome of those achieving normocalcaemia was undertaken to estimate cost effectiveness. The example assumed a population of 1000, with each subject given either cinacalcet or placebo, and outcomes are measured by whether normocalcaemia is achieved. The absolute values for outcomes were taken from the clinical

review. Assumptions for utility values were 0.8 and 0.6 for those achieving normocalcaemia and those who do not, respectively. A time horizon of 6 months was used to maintain consistency with length of time for the clinical outcome used.

The committee discussed that patients usually take cinacalcet for more than 6 months, which was the maximum duration of some of the trials in the clinical review. However, given that cinacalcet continues to be effective as long as it is being taken, for the purpose of this calculation a 6-month time horizon is considered to be sufficient, as the ratio between cost and effectiveness is likely to remain proportional thereafter. Only the cost of cinacalcet (at 60 mg per day) was included; the cost of placebo was assumed to be zero.

The analysis outlined above generated an ICER of around £31,000. This is borderline cost effective at the higher NICE threshold. However, it should be noted that the incremental quality of life estimates of 0.2 between a normocalcaemic and non-normocalcaemic patient is considered generous. It is unclear if patients included in the studies are symptomatic and if so, to what extent. If the true quality of life difference was smaller, the ICER will be higher than that estimated above.

The committee noted that side effects from cinacalcet are also likely to affect quality of life. Where people experience side effects as a result of taking cinacalcet, their actual improvement in quality of life is likely to be lower than that estimated in the above calculations. Additionally, if such side effects require use of health care resources – for example hospitalisation – then the incremental cost of calcimimetics may potentially be higher than estimated above. However, as mentioned above the adverse events reported in the studies are unlikely to cause a significant disutility to patients or incur significant additional costs.

The committee also discussed that the above calculation does not account for changes in resource use for those receiving no treatment. The committee noted that the cost of no treatment would be higher in current practice due to the cost of rehydration as a result of hypercalcaemia, which often requires hospital admission for intravenous fluids to be delivered, and treatment for the symptoms and further consequences of hypercalcaemia. Furthermore, there is a potential for long-term reduction in resource use following successful treatment with calcimimetics due to reducing symptoms of hypercalcemia and a reduced number of blood tests and GP appointments, as well as preventing possible end organ disease such as renal stones and fragility fractures.

In addition, the committee noted that patients with untreated hypercalcaemia are at a higher risk of hypercalcaemic crisis. This requires urgent hospitalisation and consequently leads to very high levels of healthcare resource use, as well as a significant decrement in quality of life, along with a high risk of mortality. While it was indicated that this is a rare occurrence, the high associated costs, and decrement in QALYs from hypercalcaemic crisis increases the likelihood of cinacalcet being cost effective. Therefore, overall, this is likely to lower the incremental cost and QALY difference between drug and placebo, hence reducing the ICER, and making cinacalcet more likely to be cost effective.

Overall, the cost effectiveness of calcimimetics is highly uncertain, due to the Low quality clinical review evidence. However, the committee noted that for patients who are unable to have surgery, calcimimetics would likely be their last remaining option in managing primary hyperparathyroidism and controlling their hypercalcaemia and avoiding potentially serious events that incur high healthcare resource use. Hence, despite the fact that the cost effectiveness of calcimimetics is highly uncertain, they should still be considered for people where appropriate.

The committee noted that the recommendations made were in line with current practice according to NHS England clinical commissioning policy and therefore do not expect a significant resource impact.

1.8.3 Other factors the committee took into account

The committee discussed that cinacalcet was granted a marketing authorisation initially for management of secondary hyperparathyroidism in renal failure and for management of hypercalcaemia in parathyroid carcinoma. It was later approved for use in patients with primary hyperparathyroidism, who meet hypercalcaemia criteria for parathyroidectomy but who refuse or cannot undergo surgery. [26]

The lay members in the committee pointed out that there is concern among patients that cinacalcet is being offered as an alternative when surgery should be used. As cinacalcet treats the symptoms and not the cause, many patients are concerned about the long term consequences of primary hyperparathyroidism if the underlying cause is not treated.

The committee discussed whether a validated objective assessment of symptoms was necessary but it was decided that the potential benefit was minimal compared to the time it would take to administer a questionnaire. The committee noted that the number of people who cannot have surgery has reduced with advances in surgical practice and anaesthesia.

While the committee acknowledged that the cost-effectiveness of cinacalcet is unclear, in many cases intervention using cinacalcet is the only option available to patients who are unable to have surgery.

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Appendices

Appendix A: Review protocols

Table 5: Review protocol: Calcimimetics

Field	Content
Review question	What is the clinical and cost effectiveness of calcimimetics in people with primary hyperparathyroidism?
Type of review question	Intervention
Objective of the review	To assess the effectiveness of calcimimetics in people with primary hyperparathyroidism
Eligibility criteria – population	Adults (18 years or over) with confirmed primary hyperparathyroidism Strata: • People with normocalcaemic PHPT (serum adjusted calcium ≤2.6 mmol/L and an elevated PTH that cannot be explained by abnormal renal function or low 25OHD) • Previous parathyroidectomy • Pregnant women Exclude people: • with secondary and tertiary HPT • with multiple endocrine neoplasia (MEN) • with familial hyperparathyroidism • with parathyroid carcinoma • people on medications interfering with calcium metabolism (for example, lithium). Studies including mixed populations of people with primary and secondary or tertiary hyperparathyroidism will be excluded unless subgroups are reported separately by type of hyperparathyroidism.
Eligibility criteria – intervention(s)	Oral calcimimetics (cinacalcet)
Eligibility criteria – comparator(s)	• Placebo • No treatment (surveillance/conservative management) • Surgery (see protocol in evidence report C) • Bisphosphonates • Combination treatment (calcimimetics and bisphosphonates) The above comparators will not be pooled in the analysis
Outcomes and prioritisation	**Report all outcomes separately for <6 months and ≥6 months** **Critical outcomes:** • HRQOL (continuous outcome) • Mortality (dichotomous outcome) **Important outcomes:** • Deterioration in renal function (dichotomous - study may also report renal

	replacement) • Fractures (vertebral or long bone) (dichotomous outcome) • Occurrence of kidney stones (dichotomous outcome) • Persistent hypercalcaemia (dichotomous outcome) • BMD (continuous) of the distal radius or the lumbar spine • Cardiovascular events (dichotomous outcome) • Adverse events (to include discontinuation due to side effects; dichotomous outcome) • Cancer incidence (dichotomous outcome)
Eligibility criteria – study design	RCTs and systematic reviews of RCTs In the absence of RCT evidence NRSs will be included (only if the following key confounders are matched for or adjusted for in the analysis) Key confounders: • Age • Absence/presence of end-organ effects • Adjusted serum calcium level
Other inclusion exclusion criteria	• Non-English language articles • Conference abstracts
Proposed sensitivity / subgroup analysis, or meta-regression	Subgroups will be investigated in the following order if there is heterogeneity in the data: • Adjusted serum calcium ≥2.85 mmol/L and <2.85 mmol/L) • People with end-organ effects versus absence of end-organ effects (end organ effects defined as kidney stones, history of fragility fractures or osteoporosis [BMD T-score <-2.5 at any site])
Selection process – duplicate screening / selection / analysis	• Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol.
Data management (software)	• Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). • GRADEpro was used to assess the quality of evidence for each outcome. • Endnote for bibliography, citations, sifting and reference management • Data extractions performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
Information sources – databases and dates	Clinical search databases to be used: Medline, Embase, Cochrane Library, CINAHL, PsycINFO Date: all years Health economics search databases to be used: Medline, Embase, NHSEED, HTA Date: Medline, Embase from 2002 NHSEED, HTA – all years Language: Restrict to English only Supplementary search techniques: backward citation searching Key papers: Not known

Identify if an update	N/A
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10051
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Jonathan Mant in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC 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.
Sources of funding / support	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of	The NGC is funded by NICE and hosted by the Royal College of Physicians.

sponsor	
Roles of sponsor	NICE funds the NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 6: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations (recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered). • Unpublished reports will not be considered unless submitted as part of a call for evidence. Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[16] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological

Review question	All questions – health economic evidence
	limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2002 or later but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'. • Studies published before 2002 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017 https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 7: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 06 August 2018	Exclusions
Embase (OVID)	1974 – 06 August 2018	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2018 Issue 8 of 12 CENTRAL to 2018 Issue 7 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None
CINAHL, Current Nursing and Allied Health Literature (EBSCO)	Inception – 06 August 2018	Exclusions
PsycINFO (ProQuest)	Inception – 06 August 2018	Exclusions

Medline (Ovid) search terms

1.	hyperparathyroidism/ or hyperparathyroidism, primary/
2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)).ti,ab.
3.	PHPT.ti,ab.
4.	Parathyroid Neoplasms/
5.	(parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language

Embase (Ovid) search terms

1.	hyperparathyroidism/ or primary hyperparathyroidism/
2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or

	hyperparathyroidis*)).ti,ab.
3.	PHPT.ti,ab.
4.	parathyroid tumor/ or parathyroid adenoma/ or parathyroid carcinoma/
5.	(parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	Case report/ or Case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	Nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental animal/
19.	Animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Hyperparathyroidism] explode all trees
#2.	MeSH descriptor: [Hyperparathyroidism, Primary] explode all trees
#3.	((primary or asymptomatic or symptomatic or mild or familial or maternal) near/6 (HPT or hyperparathyroidis*)):ti,ab
#4.	PHPT:ti,ab
#5.	MeSH descriptor: [Parathyroid Neoplasms] explode all trees
#6.	(parathyroid* near/3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)):ti,ab
#7.	(or #1-#6)

CINAHL (EBSCO) search terms

S1.	(MH "Hyperparathyroidism")
S2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) n6 HPT) OR ((primary or asymptomatic or symptomatic or mild or familial or maternal) n6 hyperparathyroidis*)
S3.	PHPT
S4.	(MH "Parathyroid Neoplasms")
S5.	(parathyroid* n3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumor* or tumour* or cancer* or metasta* or hypercalcemi* or hypercalcaemi*))
S6.	S1 OR S2 OR S3 OR S4 OR S5
S7.	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or

	PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT "questions and answers" or PT response or PT software or PT teaching materials or PT website
S8.	S6 NOT S7

PsycINFO (ProQuest) search terms

1.	su.Exact("parathyroid neoplasms" OR "hyperparathyroidism" OR "hyperparathyroidism, primary")
2.	PHPT
3.	((primary or asymptomatic or symptomatic or mild or familial or maternal) Near/6 (HPT or hyperparathyroidis*))
4.	(parathyroid* near/3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumor* or tumour* or cancer* or metasta* or hypercalcaemi* or hypercalcemi*))
5.	1 or 2 or 3 or 4
6.	(su.exact.explode("rodents") or su.exact.explode("mice") or (su.exact("animals") not (su.exact("human males") or su.exact("human females"))) or ti(rat or rats or mouse or mice))
7.	(s1 or s2 or s3 or s4) NOT (su.exact.explode("rodents") or su.exact.explode("mice") or (su.exact("animals") not (su.exact("human males") or su.exact("human females"))) or ti(rat or rats or mouse or mice))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to primary hyperparathyroidism population in the NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. The NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics papers published since 2002.

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2002 – 06 August 2018	Exclusions Health economics studies
Embase	2002 – 06 August 2018	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 06 August 2018 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	hyperparathyroidism/ or hyperparathyroidism, primary/
2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)).ti,ab.
3.	PHPT.ti,ab.
4.	Parathyroid Neoplasms/
5.	(parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/

9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	26 and 43

Embase (Ovid) search terms

1.	hyperparathyroidism/ or primary hyperparathyroidism/
2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)).ti,ab.
3.	PHPT.ti,ab.
4.	parathyroid tumor/ or parathyroid adenoma/ or parathyroid carcinoma/
5.	(parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)).ti,ab.

6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	Case report/ or Case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	Nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental animal/
19.	Animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	24 and 38

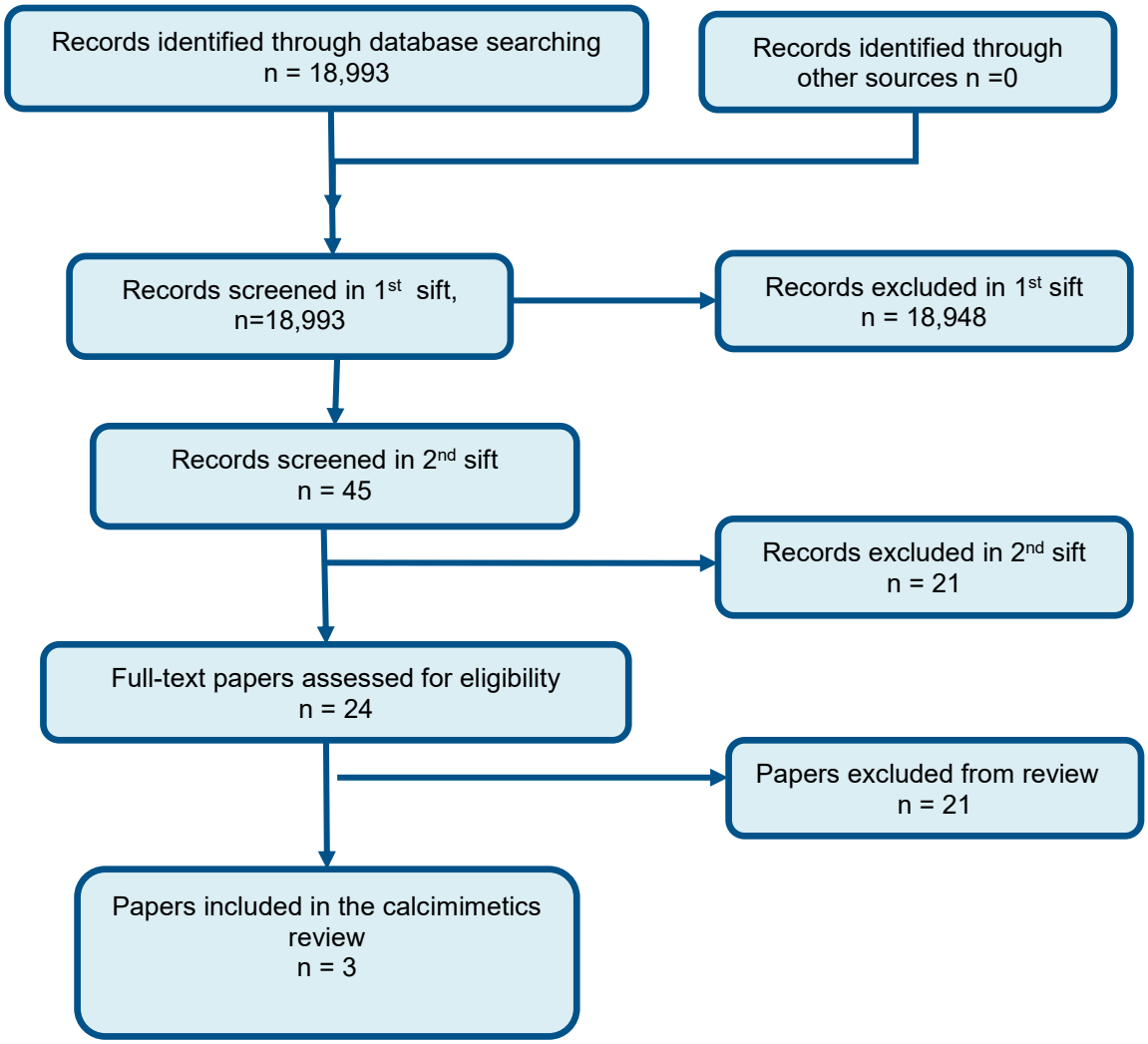
NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Hyperparathyroidism EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Hyperparathyroidism, Primary EXPLODE ALL TREES
#3.	(((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)))
#4.	(PHPT)

#5.	MeSH DESCRIPTOR Parathyroid Neoplasms EXPLODE ALL TREES
#6.	((parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)))
#7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8.	* IN NHSEED
#9.	* IN HTA
#10.	#7 AND #8
#11.	#7 AND #9

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of pharmacological management (sifted for both calcimimetics and bisphosphonates reviews)



Appendix D: Clinical evidence tables

Study	Khan 2015[10]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=67)
Countries and setting	Conducted in Multiple countries
Line of therapy	Mixed line
Duration of study	Intervention time: 28 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of PHPT was based on laboratory measurements of total corrected serum calcium >11.3 mg/dL (2.83 mmol/L) and ≤12.5 mg/dL (3.13 mmol/L) as determined on 2 separate occasions at least 7 days apart within the last 6 months before entry.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age ≥18 years; diagnosis of PHPT (as previously defined in the guideline condition assessment method); plasma PTH >55 pg/mL as determined on 2 separate occasions at least 7 days apart within the last 6 months and confirmed during screening. In addition, at least one of the following criteria to be met: failed parathyroidectomy; cardiovascular or other co-morbid conditions contraindicating parathyroidectomy, or parathyroidectomy not considered appropriate/feasible by primary physician; failure to find the parathyroid gland for removal; or ectopic parathyroid gland.
Exclusion criteria	Symptoms attributable to hypercalcaemia requiring immediate medical intervention; unstable medical condition or hospitalisation within 30 days before the date of informed consent; administration of thiazide diuretics or lithium, or other drugs influencing serum calcium measurements; initiated/changed dose of bisphosphonate within 12 weeks before study randomisation; known hypersensitivity to or inability to tolerate cinacalcet; prior treatment with cinacalcet within the last 60 days; family history of diagnosis of familial benign hypocalciuric hypercalcaemia; pregnancy/lactation
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (SD): 72.3 (11.4). Gender (M:F): 15:52. Ethnicity: White or Caucasian = 61/67 (91.0%)

Further population details	1. Adjusted serum calcium: ≥2.85 mmol/L 2. Presence of end-organ effects (end organ effects defined as kidney stones, history of fragility fractures or osteoporosis [BMD T-score <-2.5 at any site]): Not stated / Unclear (all people included in the study were eligible for surgery but not specifically stated that all people had end-organ effects of PHPT)
Extra comments	Individuals with PHPT who met the criteria for parathyroid surgery but were unable to undergo parathyroidectomy.
Indirectness of population	No indirectness
Interventions	(n=33) Intervention 1: Calcimimetics - Cinacalcet. To start with, 30 mg twice daily. The dose was titrated once every 3 weeks (up to 12 weeks during the titration phase) and could be sequentially increased to 60 mg twice daily, 90 mg twice daily or 90 mg thrice daily. Then, during the efficacy assessment phase (between week 12 and week 28), the cinacalcet dose could be increased or decreased once every 4 weeks as needed to maintain a serum calcium concentration within the normal range. Duration 28 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=34) Intervention 2: Conservative management. 30 mg twice a day. Duration 28 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Study funded by industry (Amgen, Inc.)

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

Protocol outcome 1: Quality of life
- Actual outcome: Least squares mean change in medical outcome scores - cognitive functioning (MOS-CF) at 28 weeks; Group 1: mean 7.1 Least squares mean change (SD 19.53); n=33, Group 2: mean -1.6 Least squares mean change (SD 19.24); n=34; Medical outcome scores - cognitive functioning 0 - 100 Top=High is good outcome; Comments: p = 0.066. The standard deviations have been calculated from the standard errors of mean reported in the study.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - The mean age and age range were lower in the cinacalcet group (69.5, 29-89) than in the placebo group (75.0, 62-90). The median intact parathyroid hormone [Q1, Q3] was lower in the cinacalcet group (157.5 [121.0, 186.0]) than in the placebo group (167.0 [136.0, 248.0]). The mean parathyroid assessment score [SD] was higher in the cinacalcet group (321.4 [211.8]) than in the placebo group (284.8 [237.5]); Indirectness of outcome: No indirectness; Baseline details: The baseline characteristics were comparable for both groups in most factors except for age, level of intact parathyroid hormone, and parathyroid assessment score (see comments for more detail); Group 1 Number missing: 6, Reason: Adverse event (n=2); consent withdrawn (n=2); lost to follow-up (n=1); calcium >12.5 mg/dL on 2 consecutive occasions (n=1); Group 2 Number missing: 6, Reason: Adverse event (n=2); consent withdrawn (n=2); calcium >12.5 mg/dL on 2 consecutive occasions (n=1); other (n=1)
- Actual outcome: Least squares mean change in short form - 36 questionnaire (SF-36) physical components at 28 weeks; Group 1: mean 3.3 Least squares mean change (SD 6.89); n=33, Group 2: mean 0.4 Least squares mean change (SD 6.41); n=34; Short form - 36 (SF-36) 0 - 100 Top=High is good outcome; Comments: p = 0.071. The standard deviations have been calculated from standard errors of mean reported in the study.

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - The mean age and age range were lower in the cinacalcet group (69.5, 29-89) than in the placebo group (75.0, 62-90). The median intact parathyroid hormone [Q1, Q3] was lower in the cinacalcet group (157.5 [121.0, 186.0]) than in the placebo group (167.0 [136.0, 248.0]). The mean parathyroid assessment score [SD] was higher in the cinacalcet group (321.4 [211.8]) than in the placebo group (284.8 [237.5]); Indirectness of outcome: No indirectness; Baseline details: The baseline characteristics were comparable for both groups in most factors except for age, level of intact parathyroid hormone, and parathyroid assessment score (see comments for more detail); Group 1 Number missing: 6, Reason: Adverse event (n=2); consent withdrawn (n=2); lost to follow-up (n=1); calcium >12.5 mg/dL on 2 consecutive occasions (n=1); Group 2 Number missing: 6, Reason: Adverse event (n=2); consent withdrawn (n=2); calcium >12.5 mg/dL on 2 consecutive occasions (n=1); other (n=1)
- Actual outcome: Least squares mean change in parathyroid assessment of symptoms (PAS) score at 28 weeks; Group 1: mean -91 Least squares mean change (SD 213.12); n=33, Group 2: mean -59 Least squares mean change (SD 205.25); n=34; Parathyroid assessment of symptoms (PAS) score 0 - 1300 Top=High is poor outcome; Comments: p = 0.515. The standard deviations have been calculated from standard errors of mean reported in the study.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - The mean age and age range were lower in the cinacalcet group (69.5, 29-89) than in the placebo group (75.0, 62-90). The median intact parathyroid hormone [Q1, Q3] was lower in the cinacalcet group (157.5 [121.0, 186.0]) than in the placebo group (167.0 [136.0, 248.0]). The mean parathyroid assessment score [SD] was higher in the cinacalcet group (321.4 [211.8]) than in the placebo group (284.8 [237.5]); Indirectness of outcome: No indirectness; Baseline details: The baseline characteristics were comparable for both groups in most factors except for age, level of intact parathyroid hormone, and parathyroid assessment score (see comments for more detail); Group 1 Number missing: 6, Reason: Adverse event (n=2); consent withdrawn (n=2); lost to follow-up (n=1); calcium >12.5 mg/dL on 2 consecutive occasions (n=1); Group 2 Number missing: 6, Reason: Adverse event (n=2); consent withdrawn (n=2); calcium >12.5 mg/dL on 2 consecutive occasions (n=1); other (n=1)
- Actual outcome: Least squares mean change in short form - 36 questionnaire (SF-36) mental components at 28 weeks; Group 1: mean 1.6 Least squares mean change (SD 9.19); n=33, Group 2: mean -2.7 Least squares mean change (SD 8.75); n=34; Comments: p = 0.515. The standard deviations have been calculated from standard errors of mean reported in the study.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - The mean age and age range were lower in the cinacalcet group (69.5, 29-89) than in the placebo group (75.0, 62-90). The median intact parathyroid hormone [Q1, Q3] was lower in the cinacalcet group (157.5 [121.0, 186.0]) than in the placebo group (167.0 [136.0, 248.0]). The mean parathyroid assessment score [SD] was higher in the cinacalcet group (321.4 [211.8]) than in the placebo group (284.8 [237.5]).; Indirectness of outcome: No indirectness; Baseline details: The baseline characteristics were comparable for both groups in most factors except for age, level of intact parathyroid hormone, and parathyroid assessment score (see comments for more detail); Group 1 Number missing: 6, Reason: Adverse event (n=2); consent withdrawn (n=2); lost to follow-up (n=1); calcium >12.5 mg/dL on 2 consecutive occasions (n=1); Group 2 Number missing: 6, Reason: Adverse event (n=2); consent withdrawn (n=2); calcium >12.5 mg/dL on 2 consecutive occasions (n=1); other (n=1)

Protocol outcome 2: Mortality
- Actual outcome: Fatal event at 28 weeks; Group 1: 1/33, Group 2: 0/34; Comments: One fatal event in the cinacalcet group was reported by the investigator as due to decreased appetite (anorexia), which the investigator did not consider to be related to the investigational product or to hypercalcaemia.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - The mean age and age range were lower in the cinacalcet group (69.5, 29-89) than in the placebo group (75.0, 62-90). The

median intact parathyroid hormone [Q1, Q3] was lower in the cinacalcet group (157.5 [121.0, 186.0]) than in the placebo group (167.0 [136.0, 248.0]). The mean parathyroid assessment score [SD] was higher in the cinacalcet group (321.4 [211.8]) than in the placebo group (284.8 [237.5]); Indirectness of outcome: No indirectness; Baseline details: The baseline characteristics were comparable for both groups in most factors except for age, level of intact parathyroid hormone, and parathyroid assessment score (see comments for more detail); Group 1 Number missing: 6, Reason: Adverse event (n=2); consent withdrawn (n=2); lost to follow-up (n=1); calcium >12.5 mg/dL on 2 consecutive occasions (n=1); Group 2 Number missing: 6, Reason: Adverse event (n=2); consent withdrawn (n=2); calcium >12.5 mg/dL on 2 consecutive occasions (n=1); other (n=1)

Protocol outcome 3: Persistent hypercalcaemia
- Actual outcome: Number of participants achieving normal serum calcium by 28 weeks at 28 weeks; Group 1: 25/33, Group 2: 0/34; Comments: Normal serum calcium: ≤10.3 mg/dL (2.575 mmol/L). Group difference: p<0.001. Logistic regression (bisphosphonate stratification as a covariate & adjusted for baseline calcium): OR (95% CI) = 119.22 (18.20 to infinity); p<0.001.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - The mean age and age range were lower in the cinacalcet group (69.5, 29-89) than in the placebo group (75.0, 62-90). The median intact parathyroid hormone [Q1, Q3] was lower in the cinacalcet group (157.5 [121.0, 186.0]) than in the placebo group (167.0 [136.0, 248.0]). The mean parathyroid assessment score [SD] was higher in the cinacalcet group (321.4 [211.8]) than in the placebo group (284.8 [237.5]); Indirectness of outcome: No indirectness; Baseline details: The baseline characteristics were comparable for both groups in most factors except for age, level of intact parathyroid hormone, and parathyroid assessment score (see comments for more detail); Group 1 Number missing: 6, Reason: Adverse event (n=2); consent withdrawn (n=2); lost to follow-up (n=1); calcium >12.5 mg/dL on 2 consecutive occasions (n=1); Group 2 Number missing: 6, Reason: Adverse event (n=2); consent withdrawn (n=2); calcium >12.5 mg/dL on 2 consecutive occasions (n=1); other (n=1)

Protocol outcome 4: Adverse events (including discontinuation due to side effects)
- Actual outcome: Treatment-associated adverse events at 28 weeks; Group 1: 27/33, Group 2: 20/34; Comments: The most frequent adverse events were nausea (30% cinacalcet versus 18% placebo) and muscle spasms (18% cinacalcet versus 0% placebo). No hypocalcaemic events were recorded in either group.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - The mean age and age range were lower in the cinacalcet group (69.5, 29-89) than in the placebo group (75.0, 62-90). The median intact parathyroid hormone [Q1, Q3] was lower in the cinacalcet group (157.5 [121.0, 186.0]) than in the placebo group (167.0 [136.0, 248.0]). The mean parathyroid assessment score [SD] was higher in the cinacalcet group (321.4 [211.8]) than in the placebo group (284.8 [237.5]); Indirectness of outcome: No indirectness; Baseline details: The baseline characteristics were comparable for both groups in most factors except for age, level of intact parathyroid hormone, and parathyroid assessment score (see comments for more detail); Group 1 Number missing: 6, Reason: Adverse event (n=2); consent withdrawn (n=2); lost to follow-up (n=1); calcium >12.5 mg/dL on 2 consecutive occasions (n=1); Group 2 Number missing: 6, Reason: Adverse event (n=2); consent withdrawn (n=2); calcium >12.5 mg/dL on 2 consecutive occasions (n=1); other (n=1)
- Actual outcome: Serious adverse events at 28 weeks; Group 1: 3/33, Group 2: 4/34; Comments: No description for serious adverse events was given.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - The mean age and age range were lower in the cinacalcet group (69.5, 29-89) than in the placebo group (75.0, 62-90). The median intact parathyroid hormone [Q1, Q3] was lower in the cinacalcet group (157.5 [121.0, 186.0]) than in the placebo group (167.0 [136.0, 248.0]). The mean parathyroid assessment score [SD] was higher in the cinacalcet group (321.4 [211.8]) than in the placebo group (284.8 [237.5]); Indirectness of outcome: No indirectness; Baseline details: The baseline characteristics were comparable for both groups in most factors except for age, level of intact

parathyroid hormone, and parathyroid assessment score (see comments for more detail); Group 1 Number missing: 6, Reason: Adverse event (n=2); consent withdrawn (n=2); lost to follow-up (n=1); calcium >12.5 mg/dL on 2 consecutive occasions (n=1); Group 2 Number missing: 6, Reason: Adverse event (n=2); consent withdrawn (n=2); calcium >12.5 mg/dL on 2 consecutive occasions (n=1); other (n=1)	
Protocol outcomes not reported by the study	Deterioration in renal function; Fractures (vertebral or long bone); Occurrence of kidney stones; Bone mineral density (BMD; distal radius or lumber spine); Cardiovascular events; Cancer

Study	Peacock 2005[19]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 n=78)
Countries and setting	Conducted in USA
Line of therapy	Mixed line
Duration of study	Intervention time: 52 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: See inclusion criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Serum calcium concentration between 10.3 mg/dL (2.57 mmol/L) and 12.5 mg/dL (3.12 mmol/L), and plasma PTH concentration >45 pg/mL. Parathyroid hormone was measured on ≥2 occasions ≥7 days apart during the 12-month before baseline.
Exclusion criteria	Pregnancy; creatinine clearance < 50 ml/min; treatment with bisphosphonates/fluoride within 90 days before baseline; familial hypocalciuric hypercalcaemia; fasting urine calcium/creatinine in mg (molar) ratio less than 0.05 (0.14); requirement for drugs which are metabolised by P450 2D6 (CYP2D6) and have a narrow therapeutic index (e.g. flecainide, thioridazine, tricyclic antidepressants).
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (range): 62 (27 - 83). Gender (M:F): 21:57. Ethnicity: Not reported
Further population details	1. Adjusted serum calcium: Not stated / Unclear (See inclusion criteria). 2. Presence of end-organ effects (end organ effects defined as kidney stones, history of fragility fractures or osteoporosis [BMD T-score <-2.5 at any site]): Not stated / Unclear
Extra comments	Adults with PHPT. Women on stable doses of selective oestrogen receptor modulators or oestrogen replacement therapy were eligible. Usually, similar studies exclude people who are on hormone replacement therapy.
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Calcimimetics - Cinacalcet. 30 mg twice daily, but if patients were still hypercalcaemic (serum calcium > 10.3 mg/dL) then the dose was increased to 40 mg twice daily at Week 4 and increased to 50 mg twice daily at Week 8. Duration 52 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=38) Intervention 2: Conservative management. 30 mg twice daily, but if the patients were still hypercalcaemic the dose was increased to 40 mg twice daily at Week 4 and 50 mg twice daily at Week 8.

	Duration 52 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Study funded by industry (Amgen Inc.)

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

Protocol outcome 1: Persistent hypercalcaemia
- Actual outcome: Proportion of participants who achieved a mean serum calcium of ≤10.3 mg/dL (2.57 mmol/L) and a reduction from baseline of ≥0.5 mg/dL (0.12 mmol/L) at 24 weeks; Group 1: 29/40, Group 2: 2/38; Comments: In the study, this is reported as cinacalcet group, 73% (29/40), and in the placebo group, 5% (2/38) achieved the primary endpoint (p<0.001).
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some difference in baseline mean plasma parathyroid hormone (SD) was observed: Cinacalcet 105 (36) versus Placebo 120 (54) pg/mL; Group 1 Number missing: 8, Reason: Due to unspecified adverse events; Group 2 Number missing: 6, Reason: Due to unspecified adverse events

Protocol outcome 2: Bone mineral density (BMD; distal radius or lumber spine)
- Actual outcome: Lumbar spine BMD - mean change in Z score from baseline to Week 24; Group 1: mean -0.08 (SD 0.2); n=40, Group 2: mean 0.05 (SD 0.23); n=38
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some difference in baseline mean plasma parathyroid hormone (SD) was observed: Cinacalcet 105 (36) versus Placebo 120 (54) pg/mL; Group 1 Number missing: 8, Reason: Due to unspecified adverse events; Group 2 Number missing: 6, Reason: Due to unspecified adverse events
- Actual outcome: Total femur BMD - mean change in Z score from baseline to Week 24; Group 1: mean -0.03 (SD 0.28); n=40, Group 2: mean 0.03 (SD 0.16); n=38
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some difference in baseline mean plasma parathyroid hormone (SD) was observed: Cinacalcet 105 (36) versus Placebo 120 (54) pg/mL; Group 1 Number missing: 8, Reason: Due to unspecified adverse events; Group 2 Number missing: 6, Reason: Due to unspecified adverse events
- Actual outcome: Distal radius BMD - mean change in Z score from baseline to Week 24; Group 1: mean 0.01 (SD 0.17); n=40, Group 2: mean 0.02 (SD 0.24); n=38
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some difference in baseline mean plasma parathyroid hormone (SD) was observed: Cinacalcet 105 (36) versus Placebo 120 (54) pg/mL; Group 1 Number missing: 8, Reason: Due to unspecified adverse events; Group 2 Number missing: 6, Reason: Due to unspecified adverse events
- Actual outcome: Lumbar spine BMD - mean change in Z score from baseline to Week 52; Group 1: mean 0 (SD 0.21); n=40, Group 2: mean 0.03 (SD 0.29); n=38
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some difference in baseline mean plasma parathyroid hormone (SD) was

observed: Cinacalcet 105 (36) versus Placebo 120 (54) pg/mL.; Group 1 Number missing: 8, Reason: Due to unspecified adverse events; Group 2 Number missing: 6, Reason: Due to unspecified adverse events - Actual outcome: Total femur BMD - mean change in Z score from baseline to Week 52; Group 1: mean -0.01 (SD 0.22); n=40, Group 2: mean -0.02 (SD 0.18); n=38 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some difference in baseline mean plasma parathyroid hormone (SD) was observed: Cinacalcet 105 (36) versus Placebo 120 (54) pg/mL; Group 1 Number missing: 8, Reason: Due to unspecified adverse events; Group 2 Number missing: 6, Reason: Due to unspecified adverse events - Actual outcome: Distal radius BMD - mean change in Z score from baseline to Week 52; Group 1: mean -0.05 (SD 0.32); n=40, Group 2: mean -0.01 (SD 0.36); n=38 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some difference in baseline mean plasma parathyroid hormone (SD) was observed: Cinacalcet 105 (36) versus Placebo 120 (54) pg/mL; Group 1 Number missing: 8, Reason: Due to unspecified adverse events; Group 2 Number missing: 6, Reason: Due to unspecified adverse events Protocol outcome 3: Adverse events (including discontinuation due to side effects) - Actual outcome: Number of participants who withdrew from the study due to adverse events at 52 weeks; Group 1: 8/40, Group 2: 6/38; Comments: The two most common adverse events were nausea (28% cinacalcet versus 16% placebo) and headache (23% cinacalcet versus 41% placebo). Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: It does not provide a full picture of adverse events.; Baseline details: Some difference in baseline mean plasma parathyroid hormone (SD) was observed: Cinacalcet 105 (36) versus Placebo 120 (54) pg/mL; Group 1 Number missing: 8, Reason: Due to unspecified adverse events; Group 2 Number missing: 6, Reason: Due to unspecified adverse events	
Protocol outcomes not reported by the study	Quality of life; Mortality; Deterioration in renal function; Fractures (vertebral or long bone); Occurrence of kidney stones; Cardiovascular events; Cancer

Study	Shoback 2003[25]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=22)
Countries and setting	Conducted in USA
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 15 days of treatment + 7 days of follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: PHPT was defined as parathyroid hormone concentration ≥45 pg/mL on ≥2 occasions during the 12 months before the first dose of study medication and 2 serum calcium concentrations between 10.3 and 12.5 mg/dL.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Medically stable adults (≥18 years) with PHPT. In addition, acceptable hepatic (serum aspartate aminotransferase, alanine aminotransferase, and total bilirubin ≤2 times the upper limit of normal) and renal (estimated glomerular filtration rate ≥50 ml/min based on 24-hour urine for creatinine clearance) functions were required for entry.
Exclusion criteria	History of seizures, malignancy, myocardial infarction, or diseases other than PHPT known to cause hypercalcaemia.
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (range): Cinacalcet = 61 (36-79) versus Placebo = 64 (44-79). Gender (M:F): 9:13. Ethnicity: Not reported
Further population details	1. Adjusted serum calcium: Not applicable (see diagnostic criteria used). 2. Presence of end-organ effects (end organ effects defined as kidney stones, history of fragility fractures or osteoporosis [BMD T-score <-2.5 at any site]): Not stated / Unclear
Extra comments	No limitations were placed on dietary calcium intake during the course of the study.
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Calcimimetics - Cinacalcet. Twice daily doses of 30 mg (n=5), 40 mg (n=6) or 50 mg (n=5), 12 hours between each dose. Duration 15 days. Concurrent medication/care: No limitations were placed on dietary calcium intake during the course of the study. Indirectness: No indirectness; Indirectness comment: within the intervention group, participants were allocated different dosages. In other comparable studies, doses were titrated for individuals and so it is likely that the dosages were different between participants in those studies (even if the starting dose was the same for all participants). Therefore, no change has been made to the assessment of indirectness.

	(n=6) Intervention 2: Conservative management. "Matching placebo capsules were provided." Duration 15 days. Concurrent medication/care: No limitations were placed on dietary calcium intake during the course of the study. Indirectness: No indirectness
Funding	Study funded by industry (Amgen Inc.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CINACALCET versus PLACEBO Protocol outcome 1: Adverse events (including discontinuation due to side effects) - Actual outcome: Number of participants reporting adverse events at 22 days (15 days of treatment + 7 days of follow-up); Group 1: 9/16, Group 2: 4/6; Comments: The most common adverse event was paraesthesia (cinacalcet = 3 versus placebo = 2). No severe adverse events occurred and none withdrew due to adverse events. Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - The study reports that one patient was withdrawn before completing the study because of inadequate vascular access for phlebotomy, however, it does not specify when they withdrew or whether this patient belonged to the cinacalcet or placebo group. High risk of bias was given for incomplete outcome data taking into consideration the small number of participants (n=22); Indirectness of outcome: No indirectness; Group 1 Number missing: 1, Reason: Inadequate vascular access for phlebotomy; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Mortality; Deterioration in renal function; Fractures (vertebral or long bone); Occurrence of kidney stones; Persistent hypercalcaemia; Bone mineral density (BMD; distal radius or lumber spine); Cardiovascular events; Cancer

Appendix E: Forest plots

E.1 Cinacalcet versus placebo in primary hyperparathyroidism

Figure 2: SF-36 physical component

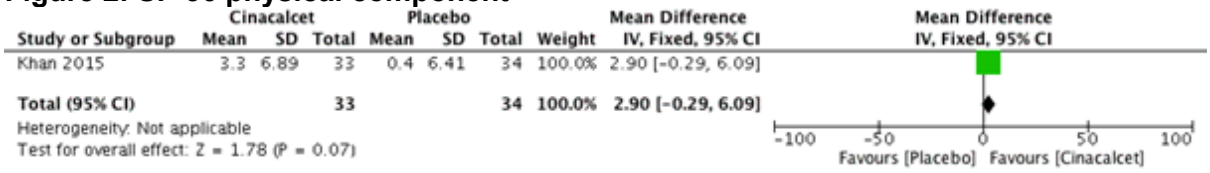


Figure 3: SF-36 mental component

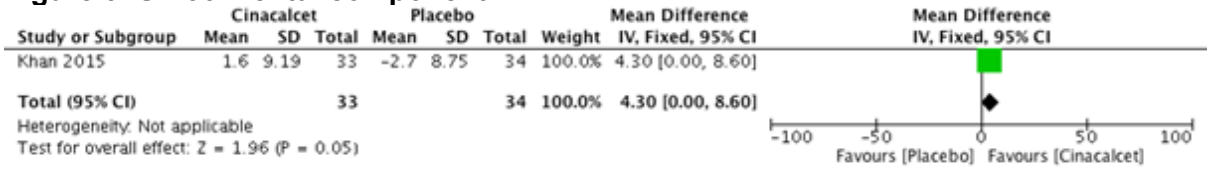


Figure 4: MOS-CF scores

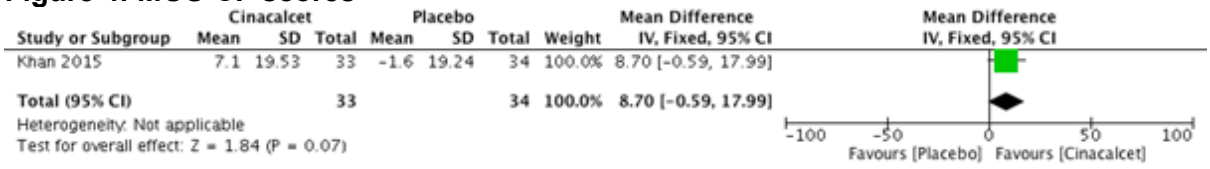


Figure 5: PAS scores

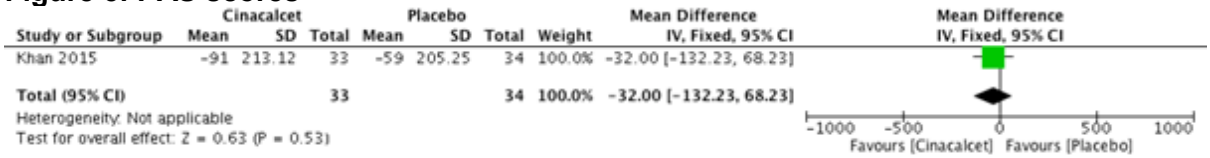
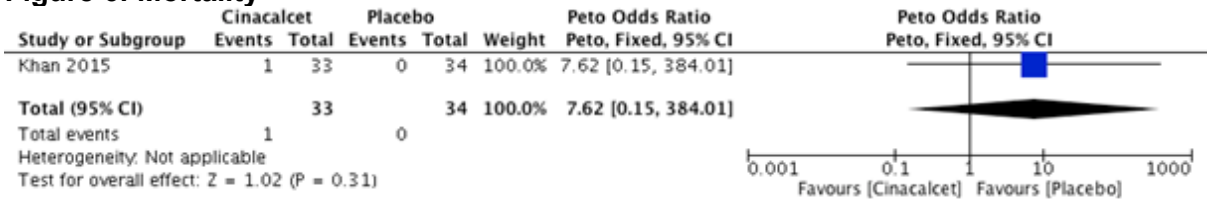


Figure 6: Mortality



Fatal event in the study was considered as unrelated to the intervention. One patient died due to decreased appetite (anorexia). The patient had a history of dementia and was taking concurrent medications including haloperidol

Figure 7: Achieving normocalcaemia

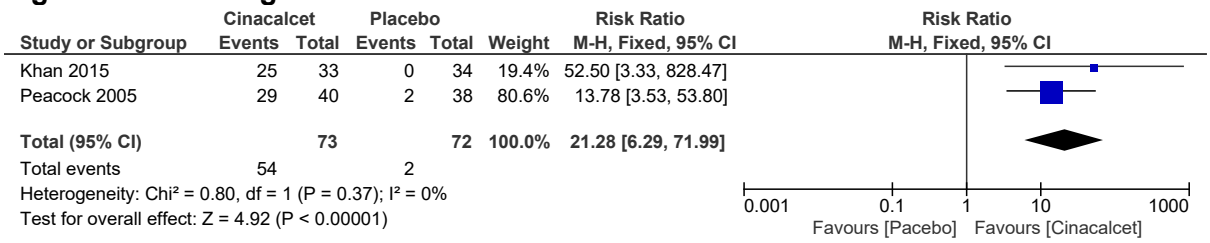


Figure 8: Lumbar spine BMD Z-score

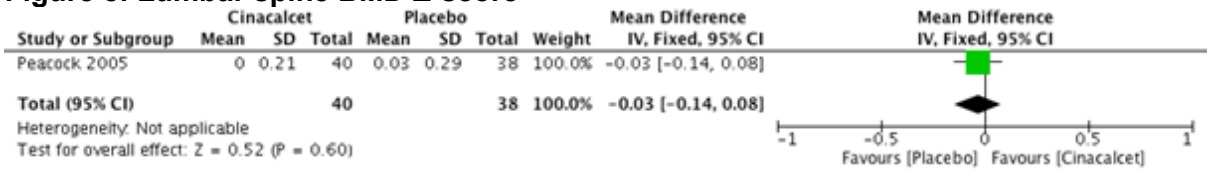


Figure 9: Distal radius BMD Z-score

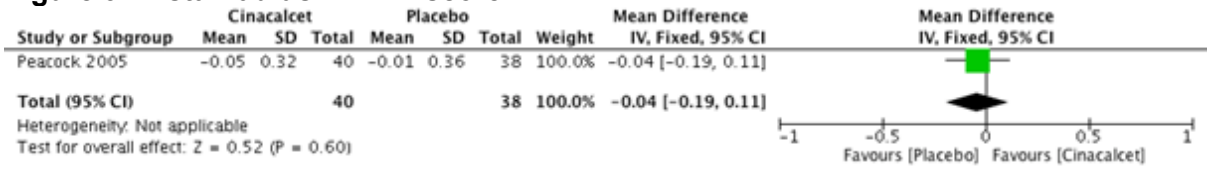


Figure 10: Adverse events at <6 months

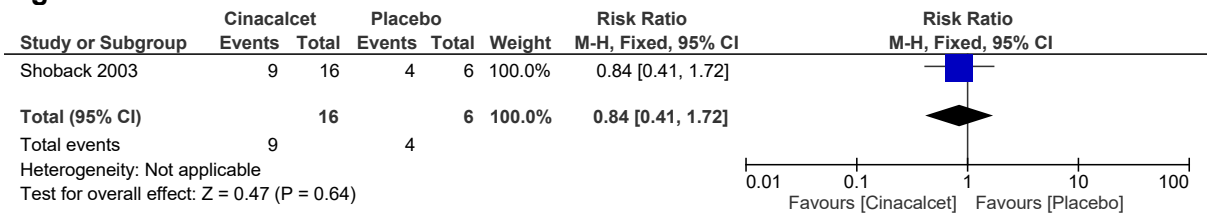
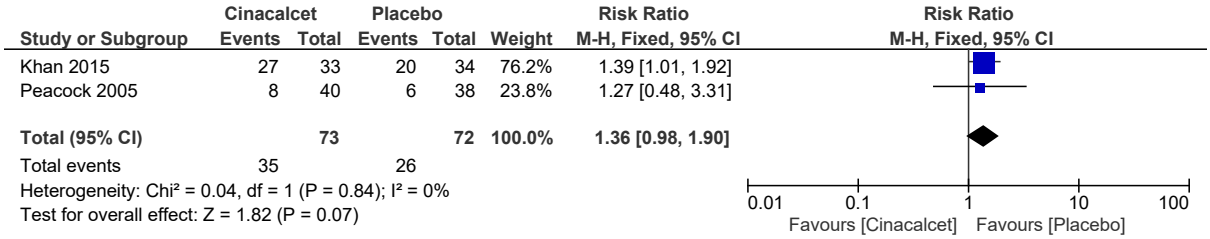
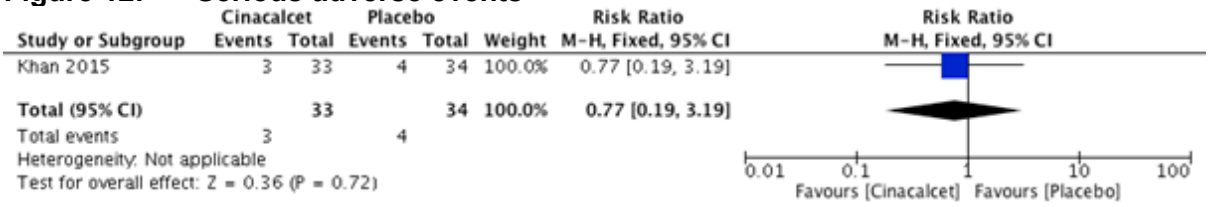


Figure 11: Adverse events at ≥6 months



Actual outcome reported in one study was the number of people withdrawing due to adverse events (not the total number of people having adverse events). The other study reported the total number of people having adverse events, with the most frequent events being nausea and muscle spasms

Figure 12: Serious adverse events



Appendix F: GRADE tables

Table 9: Clinical evidence profile: Cinacalcet versus placebo

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cinacalcet	Placebo	Relative (95% CI)	Absolute (95% CI)		
SF-36 physical component (follow up: 28 weeks; Scale from: 0 to 100 higher scores indicate better outcomes; change score)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,c]	none	33	34	-	MD **2.9 higher** (0.29 lower to 6.09 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 mental component (follow up: 28 weeks; Scale from: 0 to 100 higher scores indicate better outcomes; change score)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,c]	none	33	34	-	MD **4.3 higher** (0 to 8.6 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MOS-CF (follow up: 28 weeks; Scale from: 0 to 100 higher scores indicate better outcomes; change score)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	33	34	-	MD **8.7 higher** (0.59 lower to 17.99 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cinacalcet	Placebo	Relative (95% CI)	Absolute (95% CI)		
PAS (follow up: 28 weeks; Scale from: 0 to 1300 higher scores indicate poorer outcomes; change score)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	33	34	-	MD **32 lower** (132.23 lower to 68.23 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality (follow up: 28 weeks)[d]												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	1/33 (3.0%)	0.0%	Peto OR 7.62 (0.15 to 384.01)	**30 more per 1000** (from 50 fewer to 110 more)	⨁◯◯◯ VERY LOW	CRITICAL
Achieving normocalcaemia (follow up: range 24 weeks to 28 weeks)												
2	randomised trials	very serious [a]	not serious	not serious	not serious	none	54/73 (74.0%)	2.6%	**RR 21.28** (6.29 to 71.99)	**527 more per 1,000** (from 138 more to 1,000 more)	⨁⨁◯◯ LOW	IMPORTANT
Lumbar spine BMD Z-score (follow up: 52 weeks; change score)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	40	38	-	MD **0.03 lower** (0.14 lower to 0.08 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

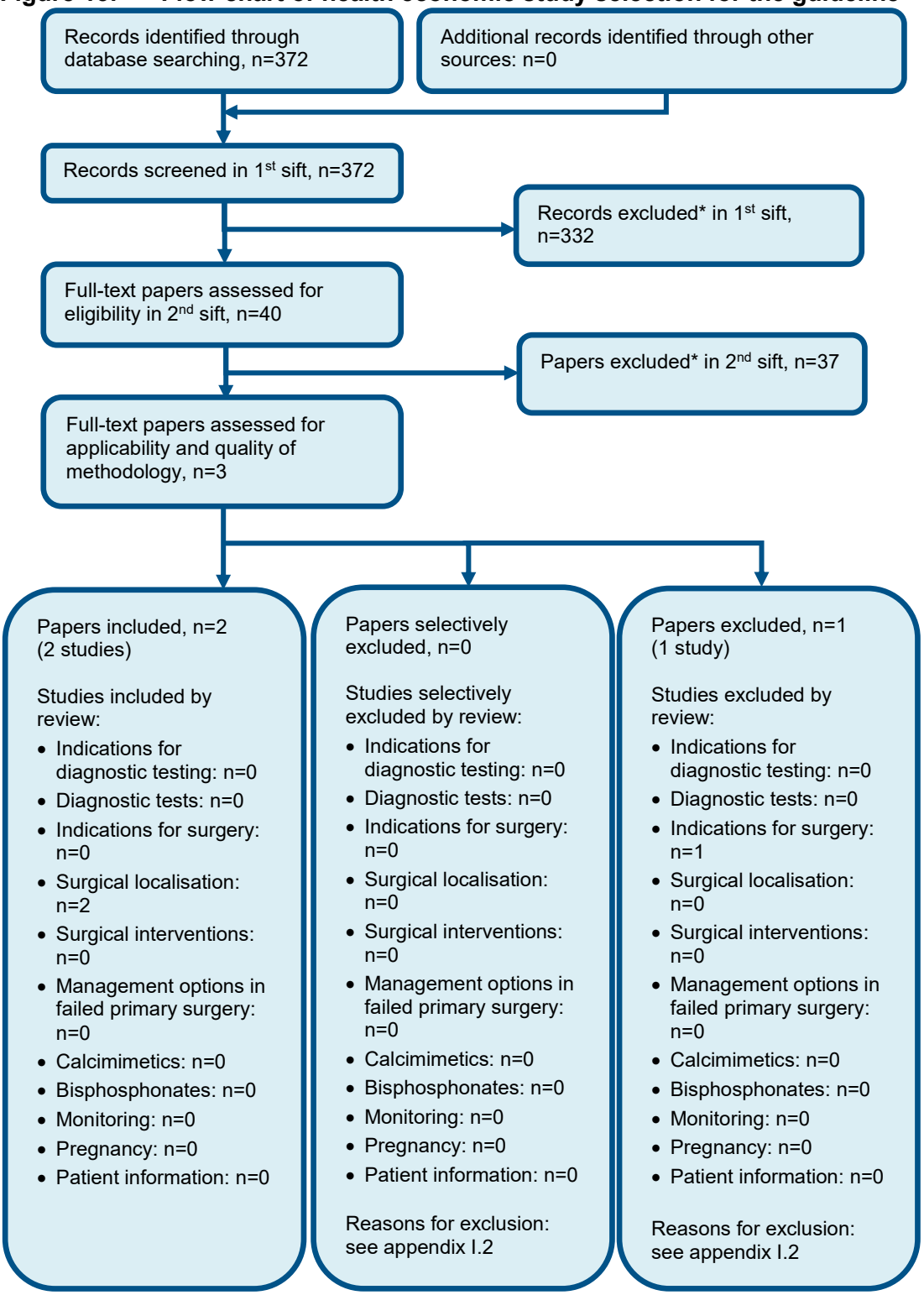
Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cinacalcet	Placebo	Relative (95% CI)	Absolute (95% CI)		
Distal radius BMD Z-score (follow up: 52 weeks; change score)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	40	38	-	MD **0.04 lower** (0.19 lower to 0.11 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Adverse events at <6 months (follow up: 22 days)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	9/16 (56.3%)	66.7%	**RR 0.84** (0.41 to 1.72)	**107 fewer per 1,000** (from 394 fewer to 480 more)	⨁◯◯◯ VERY LOW	
Adverse events (follow up: range 28 weeks to 52 weeks)[e]												
2	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	35/73 (47.9%)	37.3%	**RR 1.36** (0.98 to 1.90)	**134 more per 1,000** (from 7 fewer to 336 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events (follow up: 28 weeks)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cinacalcet	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	3/33 (9.1%)	11.8%	**RR 0.77** (0.19 to 3.19)	**27 fewer per 1,000** (from 95 fewer to 258 more)	⨁◯◯◯ VERY LOW	IMPORTANT

a. Downgraded by one increment if the majority of the evidence was at high risk of bias and downgraded by two increments if the majority of the evidence was at very high risk of bias
b. Downgraded by one increment if the confidence interval crossed one MID and downgraded by two increments if the confidence interval crossed both MIDs
c. Established MIDs used for SF36
d. Fatal event in the study was considered as unrelated to the intervention. One patient died due to decreased appetite (anorexia). The patient had a history of dementia and was taking concurrent medications including haloperidol.
e. Actual outcome reported in one study was the number of people withdrawing due to adverse events (not the total number of people having adverse events). The other study reported the total number of people having adverse events, with the most frequent events being nausea and muscle spasms.

Appendix G: Health economic evidence selection

Figure 13: Flow chart of health economic study selection for the guideline



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

Appendix H: Health economic evidence tables

No relevant health economic studies were identified.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 10: Studies excluded from the clinical review

Study	Exclusion reason
Akbaba 2013[1]	Incorrect comparator
Brardi 2015[2]	Incorrect interventions
Casez 2003[3]	Incorrect interventions
Cesareo 2017[4]	Incorrect interventions (bisphosphonates)
Chow 2003[5]	Incorrect interventions (bisphosphonates)
Hamdy 1987[6]	Incorrect interventions (bisphosphonates)
Hassani 2001[7]	Incorrect interventions (bisphosphonates)
Horiuchi 2002[8]	Incorrect interventions (bisphosphonates)
Khan 2004[13]	Incorrect interventions (bisphosphonates)
Khan 2009[12]	Incorrect interventions (bisphosphonates)
Khan 2014[11]	Conference abstract
Martin 2010[14]	Conference abstract
Narayan 2007[15]	Incorrect population (end stage renal disease)
Parker 2002[17]	Incorrect interventions (bisphosphonates)
Peacock 2009[20]	Open label non-comparative extension study of an RCT
Peacock 2011[18]	Pooled analysis of 3 clinical trials checked for references
Reasner 1993[21]	Dose study
Rossini 2001[22]	Incorrect interventions (bisphosphonates)
Sankaran 2010[23]	Non-systematic literature review
Schwarz 2014[24]	Non-comparative observational study (PRIMARA study)
Szczech 2004[27]	Non-systematic literature review

I.2 Excluded health economic studies

None.